Report on the Deliberation Results

August 5, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Rinvoq Tablets 7.5 mg Rinvoq Tablets 15 mg Rinvoq Tablets 30 mg
Non-proprietary Name	Upadacitinib Hydrate (JAN*)
Applicant	AbbVie GK
Date of Application	October 28, 2020

Results of Deliberation

In its meeting held on July 30, 2021, the Second Committee on New Drugs concluded that the partial change approval application for Rinvoq Tablets 7.5 mg and 15 mg and the approval application for Rinvoq Tablets 30 mg may be approved, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

Rinvoq Tablets 30 mg is not classified as a biological product or a specified biological product. The drug product is classified as a powerful drug. The re-examination period for Rinvoq Tablets 7.5 mg, 15 mg, and 30 mg is the remainder of the re-examination period for the initial approval of the product (until January 22, 2028).

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

July 19, 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	(a) Rinvoq Tablets 7.5 mg (b) Rinvoq Tablets 15 mg (c) Rinvoq Tablets 30 mg
Non-proprietary Name	Upadacitinib Hydrate
Applicant	AbbVie GK
Date of Application	October 28, 2020
Dosage Form/Strength	Tablets: Each tablet contains 7.7 mg, 15.4 mg, or 30.7 mg of upadacitinib hydrate (7.5 mg, 15.0 mg, or 30.0 mg of upadacitinib, respectively).
Application Classification	(a) (b): Prescription drugs, (4) Drugs with new indications, (6) Drugs with new dosage (c): Prescription drug, (4) Drug with new indications, (6) Drug with new dosage, (8) Drug in an additional dosage form
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with atopic dermatitis who have an inadequate response to conventional treatments, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following approval condition. The safety and efficacy of the product in clinical use should be further investigated in the post-marketing surveillance.

Indications (a) (b) The following diseases that have an inadequate response to conventional treatments:
Rheumatoid arthritis (including prevention of structural joint damage)
Psoriatic arthritis
Atopic dermatitis

(c) The following disease that has an inadequate response to conventional treatments:
Atopic dermatitis

(Underline denotes additions.[1])

Dosage and Administration

(a) (b) Rheumatoid arthritis

The usual adult dosage is 15 mg of upadacitinib administered orally once daily. The dose may be changed to 7.5 mg once daily according to the patient's condition.

Psoriatic arthritis

The usual adult dosage is 15 mg of upadacitinib administered orally once daily.

Atopic dermatitis

The usual adult dosage is 15 mg of upadacitinib administered orally once daily. The dose may be changed to 30 mg once daily according to the patient's condition.

The usual dosage in pediatric patients aged ≥12 years weighing ≥30 kg is 15 mg of upadacitinib administered orally once daily.

(c) Atopic dermatitis

The usual adult dosage is 15 mg of upadacitinib administered orally once daily. The dose may be changed to 30 mg once daily according to the patient's condition.

The usual dosage in pediatric patients aged ≥12 years weighing ≥30 kg is 15 mg of upadacitinib administered orally once daily.

(Underline denotes additions.[1])

Approval Condition

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

[1] The dotted-line part indicates addition pursuant to the approval of the partial change dated May 27, 2021.

Attachment

Review Report (1)

June 24, 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	(a) Rinvoq Tablets 7.5 mg (b) Rinvoq Tablets 15 mg (c) Rinvoq Tablets 30 mg
Non-proprietary Name	Upadacitinib Hydrate
Applicant	AbbVie GK
Date of Application	October 28, 2020
Dosage Form/Strength	Tablets: Each tablet contains 7.7 mg, 15.4 mg, or 30.7 mg of upadacitinib hydrate (7.5 mg, 15.0 mg, or 30.0 mg of upadacitinib, respectively).
Proposed Indications	(a) (b) <u>The following diseases</u> that have an inadequate response to conventional treatments: Rheumatoid arthritis (including prevention of structural joint damage) <u>Atopic dermatitis</u> (c) <u>The following disease that has an inadequate response to conventional treatment:</u> <u>Atopic dermatitis</u>

(Underline denotes additions.)

Proposed Dosage and Administration

(a) (b) <u>Rheumatoid arthritis</u>

The usual adult dosage is 15 mg of upadacitinib administered orally once daily. The dose may be changed to 7.5 mg once daily according to the patient's condition.

<u>Atopic dermatitis</u>

<u>The usual dosage in patients aged ≥18 years is 15 mg or 30 mg of upadacitinib administered orally once daily.</u>

<u>The usual dosage in patients aged ≥12 and <18 years weighing ≥40 kg is 15 mg of upadacitinib administered orally once daily.</u>

(c) Atopic dermatitis

The usual dosage in patients aged ≥18 years is 15 mg or 30 mg of upadacitinib administered orally once daily.

The usual dosage in patients aged ≥12 and <18 years weighing ≥40 kg is 15 mg of upadacitinib administered orally once daily.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

Upadacitinib hydrate (hereinafter referred to as upadacitinib), the active ingredient of "Rinvoq Tablets 7.5 mg, Rinvoq Tablets 15 mg, Rinvoq Tablets 30 mg" is a Janus kinase (JAK) inhibitor discovered by AbbVie Inc. (the US). In Japan, upadacitinib was approved in January 2020 with the indication for rheumatoid arthritis and, in May 2021, approved with the additional indication for psoriatic arthritis.

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by pruritic eczema with recurrent aggravation and remission. For the drug therapy of AD, a stepwise treatment dependent on the disease severity is recommended. The basic treatment is control of the disease with topical anti-inflammatory drugs such as topical corticosteroids (TCS) and topical calcineurin inhibitor (TCI) with continuous use of topical skin moisturizer. If these topical treatments are not adequately effective, systemic treatments with oral drugs such as cyclosporine are used. Because of the safety concerns in the long-term use of oral cyclosporine, a short-period or intermittent administration is recommended (Guideline for Management of Atopic Dermatitis 2018 [in Japanese], edited by Japanese Dermatological Association/Japanese Society for Allergology [Clinical Practice Guidelines for AD 2018]). In recent years, dupilumab (genetical recombination), which is an antibody against interleukin (IL)-4 receptor α subunit, and a JAK inhibitor baricitinib have been approved with indication for atopic dermatitis that have an inadequate response to conventional treatments, providing new options of systemic therapies.

Multiple cytokines such as IL-4, IL-13, IL-22, IL-31, thymic stromal lymphopoietin, and interferon (IFN)-γ are involved in the pathogenic mechanism of AD (*Acta Derm Venereol.* 2012;92:24-8, *Autoimmun Rev*. 2014;13:615-20, *The Medical Association of Nippon Medical School.* 2017;13:8-21). Since upadacitinib inhibits JAK-signal transducer and activator of transcription (STAT) signaling pathway involved in the signal transduction of these cytokines, development of upadacitinib was undertaken in expectation of the treatment effect for AD.

The clinical development of upadacitinib for AD was initiated in October 2016. Recently, a partial change application was submitted, based on the data obtained from global studies including Japan and from Japanese clinical studies. Overseas, as of June 2021, upadacitinib is under review as a therapeutic agent for AD in the US and Europe.

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

The present application relates to new indications and a new dosage. The application for Rinvoq Tablets 30 mg is for an additional dosage form, submitted with data on the quality and bioequivalence. In this report only matters related to the new indications and the new dosage are described, and PMDA's review on the additional dosage form did not reveal any significant problem.

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

The present application relates to new indications and a new dosage. Since non-clinical pharmacology of upadacitinib was evaluated during the review process for the initial approval, no new study data on non-clinical pharmacology were submitted.

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

The present application relates to new indications and a new dosage. Since non-clinical pharmacokinetics of upadacitinib was evaluated during the review process for the initial approval, no new study data on non-clinical pharmacokinetics were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application relates to new indications and a new dosage. Since toxicity of upadacitinib was evaluated during the review process for the initial approval, no new study data on toxicity were submitted.

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

6.1 Biopharmaceutic studies and associated analytical methods

The applicant submitted data of relative bioavailability as reference data, which had already been reviewed (see Review Report "Rinvoq Tablets 7.5 mg, etc." dated April 9, 2021) and are omitted from the description in this review report.

Plasma upadacitinib concentration was measured by liquid chromatography/tandem mass spectrometry (lower limit of quantitation 0.0503 ng/mL).

6.2 Clinical pharmacology

The applicant submitted results of population pharmacokinetic analysis as evaluation data. The dose of Rinvoq is expressed in the dose of upadacitinib unless specified otherwise.

6.2.1 Population pharmacokinetic analysis (CTD 5.3.3.5-1)

A population pharmacokinetic analysis (NONMEM version 7.4.4) was conducted using the data of plasma upadacitinib concentration (4,161 measuring time points in 911 subjects) obtained from Studies M16-048 [see Section 7.1.1], M16-045 [see Section 7.2.1] , M16-047 [see Section 7.2.2] , M17-377 [see Section 7.2.3] , and M18-891[2)] in patients with AD and from Study M14-680 in healthy subjects (see Review Report "Rinvoq Tablets 7.5 mg, etc." dated November 14, 2019).

The pharmacokinetics of upadacitinib in patients with AD was described by a 2-compartment model with zero and first order mixed absorption process containing a lag time. Covariates identified for CL/F were presence or absence of disease (patients with AD, healthy subjects), sex, and creatinine clearance.[3)] Table 1 shows pharmacokinetic parameters of upadacitinib at steady state following multiple administration of upadacitinib to Japanese and non-Japanese patients with AD, estimated from the final model.

---

2) Foreign phase III study conducted in a similar design as that of Study M16-045

3) The following parameters were investigated as candidate covariates for CL/F and Vc/F: Age, age group (<18 years, ≥18 years), body weight, region (Japan, other), presence or absence of disease (patients with AD, healthy subjects), sex, race (Caucasians, Blacks, Asians, other), ethnicity (Hispanic, other than Hispanic), region (US/Puerto Rico/Canada, Japan, China/Hong Kong), baseline serum bilirubin, baseline AST, baseline ALT, baseline Eczema area and severity index (EASI) score, creatinine clearance, and concomitant drugs [use or non-use of antacids, H2-receptor antagonist, proton pump inhibitors, pH regulators, and/or cytochrome P450 (CYP)3A4 inhibitors]).

Table 1. Pharmacokinetic parameters of upadacitinib at steady state, estimated by population pharmacokinetic model

Dosage regimen	Race	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
7.5 mg Once daily	Japanese	5.7 [4.1, 7.4]	15.1 [14.2, 16.0]	1.6 [0.6, 2.5]
	Non-Japanese	7.2 [4.6, 11.2]	17.3 [12.3, 21.4]	1.9 [0.7, 9.1]
15 mg Once daily	Japanese	15.4 [9.6, 22.3]	34.8 [24.9, 43.4]	4.3 [1.6, 14.4]
	Non-Japanese	14.6 [9.5, 29.2]	35.5 [25.6, 44.0]	3.7 [1.6, 23.8]
30 mg Once daily	Japanese	26.8 [17.6, 47.2]	72.6 [57.6, 85.2]	6.06 [2.55, 35.4]
	Non-Japanese	29.5 [19.7, 53.4]	71.5 [54.4, 87.8]	7.69 [3.21, 43.5]

Median [5 percentile, 95 percentile]

6.2.2 Exposure-response analysis (CTD 5.3.5.4-2)

An exposure-response analysis was conducted using efficacy and safety data obtained from Studies M16-048 [see Section 7.1.1], M16-045 [see Section 7.2.1], M16-047 [see Section 7.2.2], and M17-377 [see Section 7.2.3], and individual C_{avg} estimates based on the population pharmacokinetic analysis [see Section 6.2.1].

Table 2 shows the results of the primary efficacy endpoints at Week 16, by quartile of the exposure to upadacitinib (C_{avg}). In upadacitinib monotherapy, all endpoints showed a tendency of exposure-dependent increase in the achievement rate. In the co-administration with TCS, rates of achieving Eczema area and severity index (EASI)-90 and validated investigator global assessment for atopic dermatitis (vIGA-AD) (0, 1) tended to increase roughly in an exposure-dependent manner.

Table 3 shows the incidence of each adverse event by quartile of exposure to upadacitinib. Results suggested an exposure-dependent increase in the incidence of some events such as acne.

Table 2. Results of efficacy endpoints at Week 16, by quartile of exposure (C_{avg}) (Non responder imputation [NRI])

Quartile		Q1	Q2	Q3	Q4	-
Upadacitinib alone[a)]	Range of C_{avg} (ng/mL)	4.1-12.1	12.1-17.9	17.9-27.1	27.1-69.2	0 (placebo)
	Number of subjects	76	75	75	75	322
	Rate of achieving vIGA-AD (0, 1)	22.4 (17)	45.3 (34)	48.0 (36)	62.7 (47)	7.5 (24)
	Rate of achieving EASI-75	40.8 (31)	70.7 (53)	72.0 (54)	80.0 (60)	14.9 (48)
	Rate of achieving EASI-90	23.7 (18)	48.0 (36)	54.7 (41)	64.0 (48)	7.1 (23)
Upadacitinib + TCS[b)]	Range of C_{avg} (ng/mL)	7.6-14.8	14.8-22.1	22.1-29.9	29.9-67.9	0 (placebo)
	Number of subjects	93	94	93	89	393
	Rate of achieving vIGA-AD (0, 1)	41.9 (39)	40.4 (38)	53.8 (50)	61.8 (55)	9.9 (39)
	Rate of achieving EASI-75	69.9 (65)	68.1 (64)	67.7 (63)	78.7 (70)	24.7 (97)
	Rate of achieving EASI-90	47.3 (44)	45.7 (43)	52.7 (49)	69.7 (62)	11.7 (46)

% (number of subjects)

a) Studies M16-048 and M16-045, b) Studies M16-047 and M17-377

Table 3. Incidence of adverse events by quartile of exposure (C_{avg}) (pooled data of 4 studies,[a] up to Week 16)

Quartile	Q1	Q2	Q3	Q4	-
Range of C_{avg} (ng/mL)	4.1-13.2	13.2-20.2	20.2-28.5	28.5-69.2	0 (placebo)
Number of subjects	168	167	167	168	715
Infection	45.8 (77)	46.1 (77)	47.9 (80)	53.0 (89)	33.1 (237)
Serious infection	1.8 (3)	1.8 (3)	1.2 (2)	0	0.4 (3)
Pneumonia	0.6 (1)	0.6 (1)	0.6 (1)	0	0.1 (1)
Herpes zoster	0	0.6 (1)	1.8 (3)	1.2 (2)	0.4 (3)
Acne	7.7 (13)	13.2 (22)	9.0 (15)	16.1 (27)	4.3 (31)
Grade ≥2 anaemia	0.6 (1)	0	0.6 (1)	1.8 (3)	0.4 (3)
Haemoglobin decreased by >2 g/dL	3.6 (6)	3.0 (5)	5.4 (9)	9.5 (16)	0.6 (4)
Hemoglobin <8 g/dL	0	0	0	0.6 (1)	0
Grade ≥3 lymphopenia	0	0	0	0	0.1 (1)
Grade 4 lymphopenia	0	0	0	0	0
Grade ≥3 neutropenia	0	0	1.2 (2)	0.6 (1)	0

% (number of subjects)
a) Safety data of Studies M16-048, M16-045, M16-047, and M17-377 combined

6.R Outline of the review conducted by PMDA

The applicant's explanation about ethnic difference in pharmacokinetics of upadacitinib in patients with AD, effect of disease type on pharmacokinetics, necessity of dose adjustment in patients with severe renal impairment and in patients being treated with potent cytochrome P450 (CYP)3A4 inhibitors, and pharmacokinetics in pediatric patients with AD aged ≥12 years:

- Ethnic difference in pharmacokinetics in patients with AD and effect of disease type on pharmacokinetics:

Neither race nor region was identified as a significant covariate in the population pharmacokinetic analysis [see Section 6.2.1]. Also, no clear difference was observed in the exposure to upadacitinib between Japanese and non-Japanese patients with AD estimated from the population pharmacokinetic model (Table 1). These results suggest no clear ethnic difference in the pharmacokinetics of upadacitinib in patients with AD. The exposure to upadacitinib was similar between patients with rheumatoid arthritis (RA) and patients with AD, as estimated from the population pharmacokinetic model (see Review Report "Rinvoq Tablets 7.5 mg, etc." dated November 14, 2019), suggesting that the disease difference has no clear effect on the pharmacokinetics of upadacitinib.

- Necessity of dose adjustment in patients with severe renal impairment and in patients being treated with potent CYP3A4 inhibitors

In the foreign phase I study (Study M13-551) in subjects with renal impairment, the exposure (AUC_{inf}) in once daily administration of upadacitinib 15 mg in subjects with severe renal impairment was 1.44 times higher than that in subjects with normal renal function. Also, in the foreign phase I study (Study M13-401) in healthy subjects, the exposure (AUC_{inf}) following a single administration of upadacitinib 3 mg in combination with a potent CYP3A4 inhibitor ketoconazole was 1.75 times higher than that observed without the co-administration (see Review Report "Rinvoq Tablets 7.5 mg, etc." dated November 14, 2019). By assuming that, in patients with AD with severe renal impairment or in patients with AD being treated with a potent CYP3A4 inhibitor, the exposure increases to a similar extent as that in the above study, the exposure following administration of upadacitinib 15 mg is expected to remain within the exposure range observed in the phase III study, whereas the exposure following administration of upadacitinib 30 mg may possibly exceed this range. Although the safety upper limit of the exposure to upadacitinib is unclear, it is important to avoid exceeding the exposure

range observed in clinical studies. Accordingly, the dosage regimen of upadacitinib should be once daily administration of 15 mg in these patient groups.

- Pharmacokinetics of upadacitinib in pediatric patients with AD aged ≥12 years

The population pharmacokinetic analysis [see Section 6.2.1] did not identify either age or age group (<18 years, ≥18 years) as a significant covariate. Table 4 shows pharmacokinetic parameters of upadacitinib in patients with AD aged <18 years and patients aged ≥18 years, estimated by the population pharmacokinetic model. No clear difference was observed in the exposure to upadacitinib between the two populations.

Table 4. Pharmacokinetic parameters of upadacitinib at steady states in patients with AD aged <18 years and patients with AD aged ≥18 years, estimated from the final model

Dosage regimen	Age group	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)
15 mg Once daily	<18 years	14.7 [9.6, 22.3]	37.7 [27.3, 43.6]	3.5 [1.6, 13.7]
	≥18 years	14.6 [9.5, 29.2]	35.3 [25.5, 44.0]	3.9 [1.6, 23.9]
30 mg Once daily	<18 years	29.2 [20.1, 53.5]	73.4 [56.0, 81.9]	7.9 [3.6, 40.4]
	≥18 years	29.0 [19.6, 52.8]	70.8 [54.4, 88.7]	7.4 [3.1, 43.5]

Median [5 percentile, 95 percentile]

In the phase III study in patients with AD, patients with AD aged ≥12 and <18 years weighing <40 kg were not enrolled according to the inclusion criteria [see Sections 7.2.1 to 7.2.3], while adult patients with AD were eligible regardless of body weight. Of the adult patients with AD weighing <40 kg who participated in the phase III study, 2 patients had pharmacokinetic samples collected. In both of them, the exposure to upadacitinib was estimated to be similar to that in the entire population (Table 5). Using the population pharmacokinetic model that was renewed using the pharmacokinetic data obtained from the ongoing foreign phase I studies (Studies M16-049 and M15-340) in pediatric patients with AD or patients with juvenile idiopathic arthritis, the exposure to upadacitinib following the administration of upadacitinib 15 or 30 mg was predicted in pediatric patients with AD weighing ≥30 kg and in adult and pediatric patients with AD weighing ≥40 kg. Figure 1 shows the distribution of the predicted exposure to upadacitinib ($AUC_{0\text{-}24h}$). At both doses, the exposure was predicated to be similar in both populations.

These results suggest that the pharmacokinetics of upadacitinib is not significantly affected either by age or body weight in patients with AD aged ≥12 years weighing ≥30 kg.

Table 5. Estimated exposure to upadacitinib in adult patients with AD weighing <40 kg enrolled in phase III studies

Subject	Body weight	Study	Dose	C_{avg} (ng/mL)
#1	33 kg	M16-047	15 mg	18.2
#2	37 kg	M18-891	15 mg	17.4
Median C_{avg} [90% CI] following the administration of upadacitinib 15 mg once daily in the entire population of phase III studies				14.7 [9.55, 28.2]

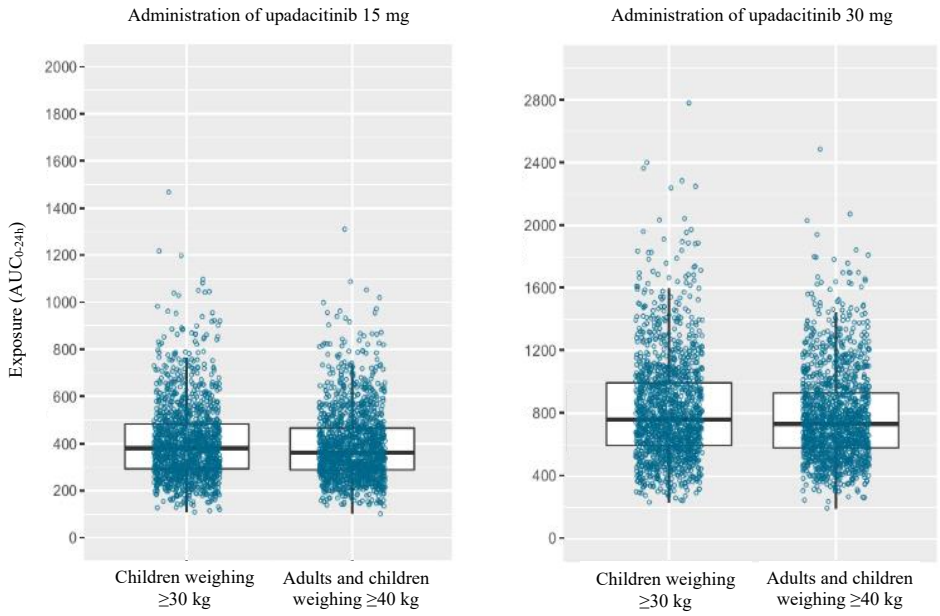

Figure 1. Distribution of predicted exposure to upadacitinib ($AUC_{0\text{-}24h}$) according to the population pharmacokinetic model that was renewed using the pharmacokinetic data of pediatric patients

PMDA accepted the applicant's explanation about (1) the ethnic difference in pharmacokinetics in patients with AD, (2) effect of disease difference on the pharmacokinetics of upadacitinib, and (3) necessity of dose adjustment in patients with severe renal impairment and patients being treated with CYP3A4 inhibitors. Also, the applicant's explanation about the effect of age and body weight on the pharmacokinetics of upadacitinib is understandable. However, the dosage regimen of upadacitinib in pediatric patients with AD aged ≥12 years (including body weight requirement) will be reviewed, also taking account of efficacy and safety information [see Section 7.R.6].

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

The applicant submitted the main efficacy and safety data, in the form of results from 4 clinical studies listed in Table 6.

Table 6. Main efficacy and safety data

Data category	Region	Study identifier	Phase	Subjects	No. of subjects	Dosage regimen (p.o. in all studies)	Main endpoints
Evaluation	Global	M16-048	II	Patients with AD for whom topical therapy was not recommended for a reason of an inadequate response to TCS or TCI or for a safety reason	(a) 42 (b) 42 (c) 42 (d) 41	(a) Upadacitinib 7.5 mg once daily[a)] (b) Upadacitinib 15 mg once daily[b)] (c) Upadacitinib 30 mg once daily[c)] (d) Placebo once daily[c)]	Efficacy Safety
Evaluation	Global	M16-045	III	Patients with AD for whom topical therapy was not recommended for a reason of an inadequate response to TCS or TCI, for a prior systemic treatment, or for a safety reason	(a) 281 (b) 285 (c) 281	(a) Upadacitinib 15 mg once daily (b) Upadacitinib 30 mg once daily (c) Placebo once daily[d)]	Efficacy Safety
Evaluation	Global	M16-047	III	Patients with AD who have an inadequate response to TCS or TCI, or a prior systemic treatment	(a) 300 (b) 297 (c) 304	(a) Upadacitinib 15 mg once daily (b) Upadacitinib 30 mg once daily (c) Placebo once daily[d)]	Efficacy Safety
Evaluation	Japan	M17-377	III	Patients with AD who have an inadequate response to TCS or TCI, or a prior systemic treatment	(a) 91 (b) 91 (c) 90	(a) Upadacitinib 15 mg once daily (b) Upadacitinib 30 mg once daily (c) Placebo once daily[d)]	Efficacy Safety

a) to c) Upadacitinib 7.5 mg (a), 15 mg (b), 30 mg (c) or placebo once daily from Week 16 on
d) Upadacitinib 15 mg or 30 mg once daily from Week 16 on

7.1 Phase II study

7.1.1 Global study (single dose study, CTD 5.3.5.1-6, Study M16-048 [October 2016 to January 2019])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of upadacitinib in patients with AD for whom topical therapy was not recommended for a reason of an inadequate response to TCS or TCI or, for a safety reason (target sample size 160 subjects [40 per group]) in 8 countries or regions including Japan, US, and Canada. Table 7 shows the main inclusion criteria of the study.

Table 7. Main inclusion criteria

1. Diagnosis of AD confirmed according to the Hanifin and Rajka criteria and onset of symptoms at least 1 year prior to baseline.
2. Documented history of an inadequate response to TCS or TCI, or for whom topical treatments are otherwise medically inadvisable because of safety risks, etc. within 1 year of the baseline visit
3. EASI score ≥16
4. IGA score ≥3
5. Lesion covering ≥10% of the body surface area
6. ≥18 and ≤75 years of age

The study consisted of 2 periods (Period 1, up to Week 16; Period 2, from Week 16-88). In Period 1, upadacitinib 7.5 mg, 15 mg, 30 mg, or placebo was administered. In Period 2, upadacitinib (the same dose as in Period 1) or placebo was administered to subjects who had received upadacitinib in Period 1, and upadacitinib 30 mg or placebo was administered to subjects who had received placebo in Period 1. Each administration was given orally once daily. A topical moisturizing agent was applied concomitantly twice daily throughout the study period from 7 days before baseline. If EASI-50 was not achieved during Period 2, upadacitinib 30 mg was administered once daily from Week 20 as a rescue treatment under blinded conditions. If the subject failed to achieve EASI-50 again, he/she was allowed to receive a rescue treatment[4)] with TCS from Week 24. If worsening of symptoms[5)] was observed during the period from Week 4 to 12 or if EASI-50 was not achieved after Week 4 of the rescue treatment with TCS, the study drug was to be discontinued.

All of the 167 randomized[6)] subjects (42 in the 7.5 mg group, 42 in the 15 mg group, 42 in the 30 mg group, 41 in the placebo group) were included in the intent to treat (ITT) population, and the ITT population was handled as the efficacy analysis population. Of those in the ITT population, 166 subjects (42 in the 7.5 mg group, 42 in the 15 mg group, 42 in the 30 mg group, 40 in the placebo group), excluding 1 subject (placebo group) who did not receive the study drug, were included in the safety analysis population up to Week 16.

In Period 1, treatment discontinuation occurred in 26.2% (11 of 42) of subjects in the 7.5 mg group, 11.9% (5 of 42) of subjects in the 15 mg group, 7.1% (3 of 42) of subjects in the 30 mg group, and 43.9% (18 of 41) of subjects in the placebo group. The main reasons for the discontinuation were consent withdrawal (14.3% [6 of 42] in the 7.5 mg group, 7.1% [3 of 42] in the 15 mg group, 29.3% [12 of 41] in the placebo group) and adverse events (9.5% [4 of 42] in the 7.5 mg group, 2.4% [1 of 42] in the 15 mg group, 4.8% [2 of 42] in the 30 mg group, 4.9% [2 of 41] in the placebo group).

4) Triamcinolone acetonide 0.1% cream (up to twice daily) or mometasone furoate 0.1% cream (once daily only) could be used.
5) ≥25% worsening from baseline in EASI score at 2 continuous scheduled office visits.
6) Stratified by region (US/Puerto Rico/Canada, EU/Australia, or Japan).

At Week 16, 126 subjects (31 in the 7.5 mg group, 37 in the 15 mg group, 38 in the 30 mg group, 20 in the placebo group) were re-randomized (the 7.5 mg→7.5 mg group in 16, the 7.5 mg→placebo group in 15, the 15 mg→15 mg group in 18, the 15 mg→placebo group in 19, the 30 mg→30 mg group in 19, the 30 mg→placebo group in 19, the placebo→30 mg group in 10, the placebo→placebo group in 10). The study drug was administered to all subjects at least once. Subjects receiving at least 1 dose of upadacitinib during the study period (42 subjects in the 7.5 mg group,[7)] 42 subjects in the 15 mg group,[7)] 114 subjects in the 30 mg group[7)]) were included in the safety analysis population of the entire period. In Period 2, treatment discontinuation occurred in 31.3% (5 of 16) of subjects in the 7.5 mg→7.5 mg group, 40.0% (6 of 15) of subjects in the 7.5 mg→placebo group, 33.3% (6 of 18) of subjects in the 15 mg→15 mg group, 31.6% (6 of 19) of subjects in the 15 mg→placebo group, 26.3% (5 of 19) of subjects in the 30 mg→30 mg group, 42.1% (8 of 19) of subjects in the 30 mg→placebo group, 50.0% (5 of 10) of subjects in the placebo→30 mg group, and 20.0% (2 of 10) of subjects in the placebo→placebo group. The main reason for the discontinuation was consent withdrawal (18.8% [3 of 16] in the 7.5 mg→7.5 mg group, 26.7% [4 of 15] in the 7.5 mg→placebo group, 11.1% [2 of 18] in the 15 mg→15 mg group, 10.5% [2 of 19] in the 15 mg→placebo group, 10.5% [2 of 19] in the 30 mg→30 mg group, 10.5% [2 of 19] in the 30 mg→placebo group, 10.0% [1 of 10] in the placebo→30 mg group).

In the ITT population, the Japanese subpopulation consisted of 10 subjects (2 in the 7.5 mg group, 3 in the 15 mg group, 3 in the 30 mg group, 2 in the placebo group), and treatment discontinuation in Period 1 occurred in 1 subject in the 30 mg group (consent withdrawal) and in 2 subjects in the placebo group (inadequate response). At Week 16, 7 subjects (2 in the 7.5 mg group, 3 in the 15 mg group, 2 in the 30 mg group) were re-randomized (the 7.5 mg→7.5 mg group in 1, 7.5 mg→placebo group in 1, the 15 mg→15 mg group in 1, the 15 mg→placebo group in 2, the 30 mg→30 mg group in 1, the 30 mg→placebo group in 1), and all of them received at least 1 dose of the study drug. In period 2, treatment discontinuation occurred in 1 subject in the 7.5 mg→placebo group (consent withdrawal) and in 1 subject in the 15 mg→placebo group (inadequate response).

Table 8 shows the results of percent change in the EASI score from baseline to Week 16, the primary efficacy endpoint. Table 8 also includes results in the Japanese subpopulation.

7) Subjects in the 7.5 mg and 15 mg groups include subjects who switched to placebo. Subjects in the 30 mg group include subjects who switched to or from placebo and subjects who received a rescue treatment.

Table 8. Percent change in the EASI score from baseline to Week 16 (ITT population, last observation carried forward [LOCF])

Population	Endpoint	7.5 mg	15 mg	30 mg	Placebo
Entire population	Baseline	31.4 ± 15.8 (42)	31.4 ± 12.3 (42)	28.2 ± 11.6 (42)	32.6 ± 14.5 (41)
	Week 16	18.8 ± 17.5 (42)	11.7 ± 12.9 (42)	5.8 ± 7.6 (42)	23.9 ± 17.4 (39)
	Percent change from baseline (%)	-43.4 ± 40.9 (42)	-65.6 ± 30.3 (42)	-79.5 ± 24.2 (42)	-27.0 ± 40.5 (39)
	Percent change from baseline (%)[a)] [95% CI]	-39.4 [-51.7, -27.1]	-61.7 [-73.8, -49.6]	-74.4 [-86.5, -62.3]	-23.0 [-35.7, -10.3]
	Difference from placebo[a)] [95% CI]	-16.4 [-31.4, -1.4]	-38.7 [-53.7, -23.6]	-51.4 [-66.5, -36.3]	
	Adjusted *P* value (one-sided)[b)]	<0.0001			
Japanese subpopulation	Baseline	16.2, 27.2 (2)	45.7 ± 17.1 (3)	21.0 ± 2.9 (3)	44.4, 49.7 (2)
	Week 16	21.0, 30.6 (2)	19.5 ± 1.8 (3)	5.4 ± 8.4 (3)	10.0, 23.6 (2)
	Percent change from baseline (%)	12.5, 29.6 (2)	-53.0 ± 17.4 (3)	-76.3 ± 36.3 (3)	-77.5, -52.5 (2)
	Percent change from baseline (%)[a)] [95% CI]	12.2 [-43.9, 68.4]	-44.2 [-93.2, 4.8]	-85.6 [-100.0, -35.3]	-55.2 [-100.0, 2.7]
	Difference from placebo[a)] [95% CI]	67.5 [-25.3, 160.3]	11.0 [-49.7, 71.7]	-30.4 [-120.5, 59.7]	

Mean ± standard deviation (number of subjects), Individual value for n ≤2
Two subjects in the placebo group (entire population) were not included in the analysis at Week 16 because all EASI scores after baseline were missing.
a) Analysis of covariance model with treatment group as the fixed factor and baseline value and stratification factor as covariates.
b) Contrast test adjusted for multiplicity of 6 dose response relation models with MCP-Mod method at a one-sided significance level of 5%

Within 16 weeks, adverse events occurred in 73.8% (31 of 42) of subjects in the 7.5 mg group, 76.2% (32 of 42) of subjects in the 15 mg group, 78.6% (33 of 42) of subjects in the 30 mg group, and 62.5% (25 of 40) of subjects in the placebo group. Table 9 shows the main events observed.

No death occurred.

Serious adverse events were observed in 4.8% (2 of 42) of subjects in the 7.5 mg group (pericoronitis, skin infection/dermatitis atopic in 1 subject each), 2.4% (1 of 42) of subjects in the 15 mg group (appendicitis), and 2.5% (1 of 40) of subjects in the placebo group (atrial fibrillation). A causal relationship to the study drug could not be ruled out for skin infection/dermatitis atopic and atrial fibrillation.

Adverse events leading to discontinuation occurred in 9.5% (4 of 42) of subjects in the 7.5 mg group, 4.8% (2 of 42) of subjects in the 15 mg group, 9.5% (4 of 42) of subjects in the 30 mg group, and 7.5% (3 of 40) of subjects in the placebo group.

Adverse drug reactions were observed in 40.5% (17 of 42) of subjects in the 7.5 mg group, 35.7% (15 of 42) of subjects in the 15 mg group, 57.1% (24 of 42) of subjects in the 30 mg group, and 27.5% (11 of 40) of subjects in the placebo group.

Table 9. Adverse events with an incidence of ≥3.0% in any group (up to Week 16, safety analysis population)

Event term	7.5 mg (n = 42)	15 mg (n = 42)	30 mg (n = 42)	Placebo (n = 40)
Upper respiratory tract infection	7 (16.7)	5 (11.9)	5 (11.9)	4 (10.0)
Dermatitis atopic	6 (14.3)	2 (4.8)	4 (9.5)	2 (5.0)
Acne	4 (9.5)	2 (4.8)	6 (14.3)	1 (2.5)
Headache	3 (7.1)	3 (7.1)	4 (9.5)	1 (2.5)
Nausea	3 (7.1)	1 (2.4)	3 (7.1)	1 (2.5)
Influenza	3 (7.1)	0	0	0
Oropharyngeal pain	3 (7.1)	0	0	0
Nasopharyngitis	2 (4.8)	4 (9.5)	3 (7.1)	1 (2.5)
Urinary tract infection	2 (4.8)	2 (4.8)	1 (2.4)	0
Diarrhoea	2 (4.8)	2 (4.8)	0	2 (5.0)
Folliculitis	2 (4.8)	2 (4.8)	0	0
Skin infection	2 (4.8)	0	0	1 (2.5)
Conjunctivitis	2 (4.8)	0	0	0
Neutropenia	1 (2.4)	2 (4.8)	2 (4.8)	0
Fatigue	1 (2.4)	2 (4.8)	2 (4.8)	0
Rash pustular	1 (2.4)	2 (4.8)	0	0
Impetigo	1 (2.4)	0	2 (4.8)	0
Blood creatine phosphokinase increased	0	3 (7.1)	4 (9.5)	2 (5.0)
Abdominal pain	0	2 (4.8)	1 (2.4)	1 (2.5)
Herpes simplex	0	2 (4.8)	1 (2.4)	0
Night sweats	0	2 (4.8)	0	0
Dizziness	0	1 (2.4)	2 (4.8)	0
Skin laceration	0	1 (2.4)	2 (4.8)	0
Dermatitis contact	0	1 (2.4)	1 (2.4)	2 (5.0)
Hypertriglyceridaemia	0	0	2 (4.8)	0
Haematuria	0	0	0	2 (5.0)
Proteinuria	0	0	0	2 (5.0)
Ligament sprain	0	0	0	2 (5.0)

Number of subjects (%)

In the Japanese subpopulation, the incidence of adverse events up to Week 16 was 100% (2 of 2) of subjects in the 7.5 mg group (pericoronitis and folliculitis/dermatitis atopic in 1 subject each), 33.3% (1 of 3) of subjects in the 15 mg group (folliculitis/headache/herpes simplex/otitis externa/punctate keratitis), and 33.3% (1 of 3) of subjects in the 30 mg group (amenorrhoea/pyelonephritis).

No death occurred.

A serious adverse event was observed in 50.0% (1 of 2) of subjects in the 7.5 mg group (pericoronitis). Its causal relationship to the study drug was ruled out.

There were no adverse events leading to discontinuation.

Adverse drug reactions were observed in 50.0% (1 of 2) of subjects in the 7.5 mg group, 33.3% (1 of 3) of subjects in the 15 mg group, and 33.3% (1 of 3) of subjects in the 30 g group.

During the entire period, adverse events were observed in 78.6% (33 of 42) of subjects receiving 7.5 mg, 78.6% (33 of 42) of subjects receiving 15 mg, and 77.2% (88 of 114) of subjects receiving 30 mg. Table 10 shows the main events observed.

Death occurred in 2 subjects receiving 30 mg (oesophageal fistula/sepsis/pericarditis and cardio-respiratory arrest in 1 subject each). A causal relationship to the study drug could not be ruled out for either of them.

Serious adverse events were observed in 4.8% (2 of 42) of subjects receiving 7.5 mg (pericoronitis and skin infection/dermatitis atopic in 1 subject each), in 2.4% (1 of 42) of subjects receiving 15 mg (appendicitis), and in 6.1% (7 of 114) of subjects receiving 30 mg (oesophageal fistula/sepsis/pericarditis, cardio-respiratory arrest, osteoarthritis, rotator cuff syndrome, squamous cell carcinoma of skin, ureterolithiasis, and pulmonary embolism in 1 subject each). A causal relationship to the study drug could not be ruled out for skin infection/dermatitis atopic, oesophageal fistula/sepsis/pericarditis, and cardio-respiratory arrest.

Adverse events leading to discontinuation were observed in 9.5% (4 of 42) of subjects receiving 7.5 mg, 4.8% (2/ of 42) of subjects receiving 15 mg, and 8.8% (10 of 114) of subjects receiving 30 mg.

Adverse drug reactions were observed in 42.9% (18 of 42) of subjects receiving 7.5 mg, 42.9% (18 of 42) of subjects receiving 15 mg, and 48.2% (55 of 114) of subjects receiving 30 mg.

Table 10. Adverse events with an incidence of ≥3.0% at any dose (entire period, safety analysis population)

Event term	Subjects receiving 7.5 mg (n = 42)	Subjects receiving 15 mg (n = 42)	Subjects receiving 30 mg (n = 114)
Upper respiratory tract infection	7 (16.7)	7 (16.7)	26 (22.8)
Dermatitis atopic	7 (16.7)	5 (11.9)	22 (19.3)
Acne	4 (9.5)	2 (4.8)	13 (11.4)
Nasopharyngitis	3 (7.1)	5 (11.9)	11 (9.6)
Headache	3 (7.1)	3 (7.1)	7 (6.1)
Nausea	3 (7.1)	1 (2.4)	6 (5.3)
Influenza	3 (7.1)	0	3 (2.6)
Skin infection	3 (7.1)	0	1 (0.9)
Oropharyngeal pain	3 (7.1)	0	0
Urinary tract infection	2 (4.8)	2 (4.8)	6 (5.3)
Folliculitis	2 (4.8)	2 (4.8)	5 (4.4)
Diarrhoea	2 (4.8)	2 (4.8)	2 (1.8)
Conjunctivitis	2 (4.8)	0	0
Neutropenia	1 (2.4)	2 (4.8)	3 (2.6)
Fatigue	1 (2.4)	2 (4.8)	3 (2.6)
Rash pustular	1 (2.4)	2 (4.8)	0
Gastroenteritis	1 (2.4)	1 (2.4)	4 (3.5)
Impetigo	1 (2.4)	0	8 (7.0)
Back pain	1 (2.4)	0	4 (3.5)
Blood creatine phosphokinase increased	0	3 (7.1)	7 (6.1)
Herpes simplex	0	2 (4.8)	4 (3.5)
Abdominal pain	0	2 (4.8)	2 (1.8)
Night sweats	0	2 (4.8)	0
Herpes zoster	0	0	10 (8.8)

Number of subjects (%)

In the entire period in the Japanese subpopulations, adverse events were observed in 100% (2 of 2) of subjects receiving 7.5 mg (pericoronitis and folliculitis/dermatitis atopic in 1 subject each), 66.7% (2 of 3) of subjects receiving 15 mg (folliculitis/headache/herpes simplex/otitis externa/punctate keratitis/dermatitis atopic and blood uric acid increased in 1 subject each), and 57.1% (4 of 7) of

subjects receiving 30 mg (amenorrhoea/pyelonephritis, haemoptysis/gastritis/upper respiratory tract infection, molluscum contagiosum/nasopharyngitis/dermatitis atopic, and bullous impetigo/herpes simplex/folliculitis/nasopharyngitis/skin infection/meibomianitis/conjunctivitis allergic/ureterolithiasis /dermatitis atopic/insomnia in 1 subject each).

No death occurred.

Serious adverse events were observed in 50.0% (1 of 2) of subjects receiving 7.5 mg (pericoronitis) and in 14.3% (1 of 7) of subjects receiving 30 mg (ureterolithiasis). A causal relationship to the study drug was ruled out for both of them.

There were no adverse events leading to discontinuation.

Adverse drug reactions were observed in 50.0% (1 of 2) of subjects receiving 7.5 mg, 33.3% (1 of 3) of subjects receiving 15 mg, and 57.1% (4 of 7) of subjects receiving 30 mg.

7.2 Phase III studies

7.2.1 Global study (monotherapy study, CTD 5.3.5.1-1 to 5.3.5.1-2, Study M16-045 [ongoing since August 2018 (data cut-off [redacted] 20[redacted], up to Week 52)])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to investigate the superiority of upadacitinib to placebo and safety in patients with AD for whom topical therapy was not recommended for a reason of an inadequate response to TCS or TCI, prior systemic treatment for AD, or for safety reasons (target sample size 810 subjects [270 per group][8)]) in 24 countries or regions including Japan, US, and Canada. Table 11 shows the main inclusion criteria for this study.

Table 11. Main inclusion criteria

1. Diagnosis of AD confirmed according to the Hanifin and Rajka criteria and onset of symptoms at least 3 years prior to baseline.
2. Documented history (within 6 months of the baseline visit) of an inadequate response to TCS or TCI, or documented prior systemic treatment for AD within 6 months prior to the baseline visit, or for whom topical treatments are otherwise medically inadvisable because of safety risks, etc.
3. EASI score ≥16
4. vIGA-AD score ≥3
5. Lesion covering ≥10% of the body surface area
6. Mean pruritus NRS score ≥4 during 7 days immediately before randomization
7. Subjects aged ≥12 and <18 years should weigh ≥40 kg.
8. ≥12 and ≤75 years of age

The study consisted of 2 periods (double-blind period up to Week 16, extended administration period from Week 16 to 260). In the double-blind period, upadacitinib 15 mg, 30 mg, or placebo was administered orally once daily. In the extended administration period, subjects in the upadacitinib groups in the double-blind period received upadacitinib at the same dose as in the double-blind period, and subjects in the placebo group in the double-blind period orally received upadacitinib 15 or 30 mg once daily. In combination, a topical moisturizing agent was applied twice daily from ≥7 days before

8) For rate of achieving vIGA-AD (0, 1) and rate of achieving EASI-75 at Week 16, the primary endpoints, the expected values were assumed to be 15% and 10%, respectively, in the placebo group and the expected treatment differences were assumed 32% and 21%, respectively, in each upadacitinib groups. In order to ensure statistical significance in 2 primary endpoints at the two-sided significance level of 5% with the statistical power of ≥90% under the above assumptions, the number of subjects required was calculated to be 270 subjects per group (810 in 3 groups).

baseline up to Week 16. If improvement of symptoms was insufficient[9)] after Week 4, rescue therapy[10)] was permitted. After Week 16, an additional topical therapy for AD was permitted at the discretion of the physician. This topical therapy was not regarded as rescue therapy; only additional systemic therapy for AD was handled as rescue therapy.

All of the 847 randomized[11)] subjects (281 in the 15 mg group, 285 in the 30 mg group, 281 in the placebo group) were included in ITT_M population, and the ITT_M population was handled as the efficacy analysis population. All subjects in the ITT_M population received the study drug at least once and were included in the safety analysis population up to Week 16. Within 16 weeks of administration, treatment discontinuation occurred in 2.8% (8 of 281) of subjects in the 15 mg group, 3.9% (11 of 285) of subjects in the 30 mg group, and 11.7% (33 of 281) of subjects in the placebo group. The main reasons for the discontinuation were consent withdrawal (1.1% [3 of 281] in the 15 mg group, 1.8% [5 of 285] in the 30 mg group, 7.1% [20 of 281] in the placebo group), and adverse events (0.4% [1 of 281] in the 15 mg group, 1.8% [5 of 285] in the 30 mg group, 3.2% [9 of 281] in the placebo group).

At Week 16, 244 subjects in the placebo group were re-randomized to the upadacitinib 15 mg group (121 subjects) or 30 mg group (123 subjects). A total of 809 subjects receiving at least 1 dose of upadacitinib during the study period (401 receiving 15 mg,[12)] 408 receiving 30 mg[12)]), except 1 subject who did not receive upadacitinib (placebo→15 mg group), were included in the safety analysis population for the entire period. Treatment discontinuation occurred from Week 16 to 52 in 13.7% (55 of 402) of subjects receiving 15 mg and in 10.0% (41 of 408) of subjects receiving 30 mg. The main reasons for discontinuation were consent withdrawal (6.7% [27 of 402] in subjects receiving 15 mg, 5.1% [21 of 408] in subjects receiving 30 mg) and adverse events (2.5% [10 of 402] in subjects receiving 15 mg, 3.4% [14 of 408] in subjects receiving 30 mg).

In the ITT_M population, the Japanese subpopulation consisted of 45 subjects (15 in the 15 mg group, 16 in the 30 mg group, 14 in the placebo group). Treatment discontinuation occurred within 16 weeks of administration in 2 subjects in the 30 mg group (consent withdrawal in 2 subjects) and in 5 subjects in the placebo group (consent withdrawal in 4 subjects, and consent withdrawal/adverse events in 1 subject). At Week 16, 8 subjects in the placebo group were re-randomized to the upadacitinib 15 mg group (5 subjects) or 30 mg group (3 subjects) and all of them received at least 1 dose of upadacitinib. During the period from Week 16 to 52, treatment discontinuation occurred in 3 subjects receiving 15 mg (consent withdrawal in 2 subjects, consent withdrawal/adverse events in 1 subject) and in 1 subject receiving 30 mg (consent withdrawal).

The rate of achieving vIGA-AD (0, 1) and the rate of achieving EASI-75 at Week 16 were measured as co-primary endpoints. As shown in Table 12, a statistically significant difference was observed in

---

9) When rescue therapy was deemed necessary by the physician and the following criteria were met: EASI-50 not achieved at 2 consecutive office visits (Week 4-24) or EASI-50 not achieved at an office visit (from Week 24 on)

10) The rescue therapy was to be started with topical treatment and, if no adequate response was observed after topical treatment for ≥7 days, then systemic therapy was permitted.

11) Baseline severity (vIGA-AD score of 3 or 4), region (US/Puerto Rico/Canada, Japan, China, other), and age (<18 years, ≥18 years) were used as stratification factors.

12) Including subjects who switched from placebo.

the paired comparison of both endpoints between the placebo group and the 15 mg group and between the placebo group and the 30 mg group, confirming the superiority of upadacitinib 15 mg and 30 mg to placebo. Table 12 also shows results in the Japanese subpopulation.

Table 12. Rate of achieving vIGA-AD (0, 1) and rate of achieving EASI-75 at Week 16 (ITT_M population, NRI-C[a])

Population	Endpoint	15 mg	30 mg	Placebo
Entire population	Rate of achieving vIGA-AD (0, 1)	48.1 (135/281)	62.0 (177/285)	8.4 (24/281)
	Difference from placebo [95% CI][b)] 2-sided *P* value[b) c)]	39.8 [33.2, 46.4] <0.001	53.6 [47.2, 60.0] <0.001	
	Rate of achieving EASI-75	69.6 (196/281)	79.7 (227/285)	16.3 (46/281)
	Difference from placebo [95% CI][b)] 2-sided *P* value[b) c)]	53.3 [46.4, 60.2] <0.001	63.4 [57.1, 69.8] <0.001	
Japanese subpopulation	Rate of achieving vIGA-AD (0, 1)	33.3 (5/15)	50.0 (8/16)	0 (0/14)
	Difference from placebo [95% CI][b)]	34.6 [16.0 53.1]	49.9 [25.6, 74.2]	
	Rate of achieving EASI-75	73.3 (11/15)	56.3 (9/16)	7.1 (1/14)
	Difference from placebo [95% CI][b)]	66.5 [40.8, 92.2]	49.0 [22.2, 75.8]	

% (number of subjects)

a) Non-responder imputation with the following exceptions. After the start of rescue therapy, subjects were regarded as non-responders.
   - If a subject was judged as a responder both before and after the scheduled visit, he/she was regarded as a responder on the day of the visit.
   - Coronavirus disease 2019 (COVID-19)-related missing values were imputed by a multiple imputation method.

b) Cochran-Mantel-Haenszel test with baseline vIGA-AD score (3 or 4) and age (<18 years, ≥18 years) as stratification factors.

c) Two-sided significance level of 5%. Multiplicity of hypothesis testing was adjusted by the following method: If comparison of both endpoints between the placebo group and the 30 mg group showed a statistically significant difference, both endpoints of the placebo group and the 15 mg group were compared.

Up to Week 16, adverse events were observed in 62.6% (176 of 281) of subjects in the 15 mg group, 73.3% (209 of 285) of subjects in the 30 mg group, and 59.1% (166 of 281) of subjects in the placebo group. Table 13 shows the main events.

No death occurred.

Serious adverse events were observed in 2.1% (6 of 281) of subjects in the 15 mg group, 2.8% (8 of 285) of subjects in the 30 mg group, and 2.8% (8 of 281) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out in 2 subjects in the 15 mg group (chest pain and impetigo in 1 subject each), 1 subject in the 30 mg group (pharyngeal abscess) and 2 subjects in the placebo group (rhinitis allergic and dermatitis exfoliative generalized in 1 subject each).

Adverse events leading to discontinuation were observed in 1.4% (4 of 281) of subjects in the 15 mg group, 3.9% (11 of 285) of subjects in the 30 mg group, and 4.3% (12 of 281) of subjects in the placebo group.

Adverse drug reactions were observed in 30.6% (86 of 281) of subjects in the 15 mg group, 43.2% (123 of 285) of subjects in the 30 mg group, and 19.6% (55 of 281) of subjects in the placebo group.

Table 13. Adverse events with an incidence of ≥3.0% in any group (up to Week 16, safety analysis population)

Event term	15 mg (n = 281)	30 mg (n = 285)	Placebo (n = 281)	Event term	15 mg (n = 281)	30 mg (n = 285)	Placebo (n = 281)
Upper respiratory tract infection	25 (8.9)	38 (13.3)	20 (7.1)	Dermatitis atopic	9 (3.2)	4 (1.4)	26 (9.3)
Nasopharyngitis	22 (7.8)	33 (11.6)	16 (5.7)	Diarrhoea	8 (2.8)	10 (3.5)	7 (2.5)
Acne	19 (6.8)	49 (17.2)	6 (2.1)	Oral herpes	5 (1.8)	14 (4.9)	3 (1.1)
Blood creatine phosphokinase increased	16 (5.7)	16 (5.6)	7 (2.5)	Weight increased	5 (1.8)	9 (3.2)	0
Headache	14 (5.0)	19 (6.7)	12 (4.3)	Neutropenia	3 (1.1)	13 (4.6)	1 (0.4)
Nausea	10 (3.6)	10 (3.5)	2 (0.7)	Back pain	2 (0.7)	7 (2.5)	9 (3.2)

Number of subjects (%)

In the Japanese subpopulation, the incidence of adverse events up to Week 16 was 66.7% (10 of 15) of subjects in the 15 mg group, 75.0% (12 of 16) of subjects in the 30 mg group, and 64.3 % (9 of 14) of subjects in the placebo group. Table 14 shows the main events observed.

No death occurred.

Serious adverse events were observed in 6.3% (1 of 16) of subjects in the 30 mg group (dermatitis contact) and 7.1% (1 of 14) of subjects in the placebo group (dermatitis atopic). A causal relationship to the study drug was ruled out for both of them.

Adverse events leading to discontinuation were observed in 6.3% (1 of 16) of subjects in the 30 mg group and 28.6% (4 of 14) of subjects in the placebo group.

Adverse drug reactions were observed in 20.0% (3 of 15) of subjects in the 15 mg group, 37.5% (6 of 16) of subjects in the 30 mg group, and 21.4% (3 of 14) of subjects in the placebo group.

Table 14. Adverse events observed in ≥2 subjects in any group (up to Week 16, safety analysis population, Japanese subpopulation)

Event term	15 mg (n =15)	30 mg (n = 16)	Placebo (n = 14)
Nasopharyngitis	3 (20.0)	7 (43.8)	1 (7.1)
Influenza	2 (13.3)	1 (6.3)	0
Dermatitis atopic	2 (13.3)	0	6 (42.9)
Acne	1 (6.7)	4 (25.0)	1 (7.1)
Abdominal pain upper	0	2 (12.5)	0

Number of subjects (%)

The incidence of adverse events throughout the study period was 75.8% (304 of 401) of subjects receiving 15 mg and 84.3% (344 of 408) of subjects receiving 30 mg. Table 15 shows the main events observed.

Death occurred in 0.2% (1 of 408) of subjects receiving 30 mg (myocardial infarction), but its causal relationship to the study drug was ruled out.

Serious adverse events were observed in 6.5% (26 of 401) of subjects receiving 15 mg and in 8.3% (34 of 408) of subjects receiving 30 mg. A causal relationship to the study drug could not be ruled out in 12 subjects receiving 15 mg (chest pain, appendicitis, corona virus infection, impetigo, intervertebral discitis, pneumonia, pulmonary tuberculosis, blood creatine phosphokinase increased, breast

cancer/colon cancer, ischaemic stroke, suicidal ideation, deep vein thrombosis in 1 subject each) and in 11 subjects receiving 30 mg (pneumonia and pyelonephritis in 2 subjects each, and corona virus infection, eczema herpeticum, eczema herpeticum/herpes simplex, herpes zoster cutaneous disseminated, pharyngeal abscess, staphylococcal sepsis, and myalgia in 1 subject each).

Adverse events leading to discontinuation were observed in 4.5% (18 of 401) of subjects receiving 15 mg and in 7.1% (29 of 408) of subjects receiving 30 mg.

Adverse drug reactions were observed in 39.2% (157 of 401) of subjects receiving 15 mg and in 55.6% (227 of 408) of subjects receiving 30 mg.

Table 15. Adverse events with an incidence of ≥3.0% at either dose (entire period, safety analysis population)

Event term	Subjects receiving 15 mg (n = 401)	Subjects receiving 30 mg (n = 408)	Event term	Subjects receiving 15 mg (n = 401)	Subjects receiving 30 mg (n = 408)
Upper respiratory tract infection	53 (13.2)	55 (13.5)	Nausea	13 (3.2)	14 (3.4)
Nasopharyngitis	50 (12.5)	49 (12.0)	Impetigo	13 (3.2)	7 (1.7)
Acne	41 (10.2)	99 (24.3)	Herpes simplex	12 (3.0)	20 (4.9)
Dermatitis atopic	41 (10.2)	25 (6.1)	Urticaria	12 (3.0)	9 (2.2)
Headache	23 (5.7)	24 (5.9)	Folliculitis	11 (2.7)	19 (4.7)
Blood creatine phosphokinase increased	22 (5.5)	44 (10.8)	Viral upper respiratory tract infection	10 (2.5)	15 (3.7)
Cough	20 (5.0)	11 (2.7)	Weight increased	9 (2.2)	16 (3.9)
Pyrexia	17 (4.2)	8 (2.0)	Alanine aminotransferase increased	9 (2.2)	13 (3.2)
Herpes zoster	16 (4.0)	24 (5.9)	Back pain	8 (2.0)	16 (3.9)
Urinary tract infection	15 (3.7)	21 (5.1)	Neutropenia	8 (2.0)	14 (3.4)
Corona virus infection	14 (3.5)	13 (3.2)	Gastroenteritis	5 (1.2)	14 (3.4)
Oral herpes	13 (3.2)	25 (6.1)	Dermatitis acneiform	3 (0.7)	15 (3.7)
Diarrhoea	13 (3.2)	15 (3.7)	Dermatitis contact	3 (0.7)	13 (3.2)

Number of subjects (%)

In the Japanese subpopulation, the incidence of adverse events during the entire study period was 95.0% (19 of 20) of subjects receiving 15 mg and 94.7% (18 of 19) of subjects receiving 30 mg. Table 16 shows the main events observed.

No death occurred.

Serious adverse events were observed in 10.0% (2 of 20) of subjects receiving 15 mg (breast cancer/colon cancer and retinal detachment in 1 subject each) and in 5.3% (1 of 19) of subjects receiving 30 mg (dermatitis contact). A causal relationship to the study drug could not be ruled out for breast cancer/colon cancer.

Adverse events leading to discontinuation were observed in 15.0% (3 of 20) of subjects receiving 15 mg and in 15.8% (3 of 19) of subjects receiving 30 mg.

Adverse drug reactions were observed in 50.0% (10 of 20) of subjects receiving 15 mg and in 68.4% (13 of 19) of subjects receiving 30 mg.

Table 16. Adverse events observed in ≥ 2 subject at either dose (entire period, safety analysis population, Japanese subpopulation)

Event term	Subjects receiving 15 mg (n = 20)	Subjects receiving 30 mg (n = 19)	Event term	Subjects receiving 15 mg (n = 20)	Subjects receiving 30 mg (n = 19)
Dermatitis atopic	11 (55.0)	6 (31.6)	Skin papilloma	1 (5.0)	2 (10.5)
Nasopharyngitis	6 (30.0)	7 (36.8)	Dermatitis contact	1 (5.0)	2 (10.5)
Herpes zoster	3 (15.0)	2 (10.5)	Blood creatine phosphokinase increased	0	3 (15.8)
Acne	2 (10.0)	5 (26.3)	Abdominal pain	0	2 (10.5)
Kaposi's varicelliform eruption	2 (10.0)	4 (21.1)	Abdominal pain upper	0	2 (10.5)
Herpes simplex	2 (10.0)	3 (15.8)	Cystitis	0	2 (10.5)
Influenza	2 (10.0)	1 (5.3)	Skin infection	0	2 (10.5)
Arthropod bite	2 (10.0)	0	Tonsillitis	0	2 (10.5)
Pruritus	2 (10.0)	0	Back pain	0	2 (10.5)
Folliculitis	1 (5.0)	4 (21.1)	Dermatitis acneiform	0	2 (10.5)

Number of subjects (%)

7.2.2 Global study (TCS combination study, CTD 5.3.5.1-3 to 5.3.5.1-4, Study M16-047 [ongoing since August 2018 (data cut-off [redacted], up to Week 52)])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to investigate the superiority to placebo and safety of upadacitinib in combination with TCS in patients with AD who have an inadequate response to TCS or TCI or, a prior systemic treatment for AD (target sample size 810 subjects [270 per group][13]) in 22 countries or regions including Japan, US, and Canada.

Table 17. Main inclusion criteria

1. Diagnosis of AD confirmed according to the Hanifin and Rajka criteria and onset of symptoms at least 3 years prior to baseline.
2. Documented history (within 6 months of the baseline visit) of an inadequate response to TCS or TCI or documented prior systemic treatment for AD within 6 months prior to the baseline visit.
3. EASI score ≥16
4. vIGA-AD score ≥3
5. Lesion covering ≥10% of the body surface area
6. Mean pruritus NRS score ≥4 during 7 days immediately before randomization
7. Subjects aged ≥12 and <18 years should weigh ≥40 kg.
8. ≥12 and ≤75 years of age

The study consisted of 2 periods (double-blind period up to Week 16, extended administration period from Week 16 to 260). In the double-blind period, upadacitinib 15 mg, 30 mg, or placebo was administered orally once daily. In the extended administration period, subjects of the upadacitinib groups in the double-blind period received upadacitinib at the same dose as in the double-blind period, and subjects of the placebo group in the double-blind period received orally upadacitinib 15 or 30 mg once daily. In combination, a topical moisturizing agent was applied twice daily from ≥7 days before baseline up to Week 52. TCS therapy was started at baseline and terminated when the disease improved.[14] If symptoms did not improve sufficiently[9] after Week 4, rescue treatment[15] was

[13] For rate of achieving vIGA-AD (0, 1) and rate of achieving EASI-75 at week 16, the primary endpoints, the expected values were assumed to be 24% and 13%, respectively, in the placebo group and the expected treatment differences were assumed 38% and 20%, respectively, in each upadacitinib groups. In order to ensure statistical significance in 2 primary endpoints at the two-sided significance level of 5% with the statistical power of ≥90% under the above assumptions, the number of subjects required was calculated to be 270 subjects per group (810 in 3 groups).

[14] Medium potency TCS (strong class according to Japanese classification) was applied once daily to highly active dermatitis and, when rash had completely or mostly resolved or 3 weeks had elapsed, the treatment was switched to low potency TCS (medium class according to Japanese classification) which was applied once daily for 7 days after which TCS was discontinued. For thin-skinned sites (facial surface, neck, intertriginous zones, and inguinal region) or sites where medium potency TCS is not considered safe (e.g., atrophic skin), low potency TCS or TCI was used instead of medium potency TCS, and the treatment was tapered off and discontinued.

[15] The treatment was started with high potency or very high potency TCS (very strong to strongest class according to Japanese classification) or other topical drugs for AD and, if no adequate response was observed after topical therapy for ≥7 days, systemic treatment was permitted.

permitted. From Week 52, additional topical treatment for AD was permitted at the discretion of the physician. This topical therapy was not regarded as rescue therapy; only additional systemic therapy for AD was handled as rescue therapy.

All of the 901 randomized[11)] subjects (300 in the 15 mg group, 297 in the 30 mg group, 304 in the placebo group) were included in ITT_M population, and the ITT_M population was included in the efficacy analysis population. A total of 900 subjects (300 in the 15 mg group, 297 in the 30 mg group, 303 in the placebo group), excluding 1 subject (in the placebo group) who did not receive the study drug, were included in the safety analysis population up to Week 16. Within 16 weeks, treatment discontinuation occurred in 3.3% (10 of 300) of subjects in the 15 mg group, 2.7% (8 of 297) of subjects in the 30 mg group, and 5.9% (18 of 304) of subjects in the placebo group. The main reasons for the discontinuation were consent withdrawal (1.7% [5 of 300] in the 15 mg group, 0.7% [2 of 297] in the 30 mg group, 2.3% [7 of 304] in the placebo group) and lost to follow-up (0.7% [2 of 300] in the 15 mg group, 0.7% [2 of 297] in the 30 mg group, and 2.0% [6 of 304] in the placebo group).

At Week 16, 283 subjects in the placebo group were re-randomized to the upadacitinib 15 mg group (144 subjects) or 30 mg group (139 subjects). A total of 879 subjects (443 subjects receiving 15 mg,[12)] 436 subjects receiving 30 mg[12)]) receiving at least 1 dose of upadacitinib during the study period, excluding 1 subject who did not receive upadacitinib (placebo→15 mg group), were included in the safety analysis population for the entire study period. During the period from Week 16 to 52, treatment discontinuation occurred in 16.0% (71 of 444) of subjects receiving 15 mg and in 7.8% (34 of 436) of subjects receiving 30 mg. The main reasons for the discontinuation were consent withdrawal (6.8% [30 of 444] of subjects receiving 15 mg, 3.2% [14 of 436] of subjects receiving 30 mg) and adverse events (2.9% [13 of 444] of subjects receiving 15 mg, 1.8% [8 of 436] of subjects receiving 30 mg).

In the ITT_M population, the Japanese subpopulation consisted of 51 subjects (16 in the 15 mg group, 17 in the 30 mg group, 18 in the placebo group). No treatment discontinuation occurred up to Week 16. At Week 16, 18 subjects in the placebo group were re-randomized the upadacitinib 15 mg group (9 subjects) or 30 mg group (9 subjects), and all of them except 1 subject (placebo→15 mg group) received at least 1 dose of upadacitinib. During the period from Week 16 to 52, treatment discontinuation occurred in 3 subjects receiving 15 mg (consent withdrawal in 2 subjects, adverse events/consent withdrawal in 1 subject).

Rate of achieving vIGA-AD (0, 1) and rate of achieving EASI-75 at Week 16 were assessed as the co-primary endpoints. As shown in Table 18, a statistically significant difference was observed in the paired comparison of both endpoints between the placebo group and the 15 mg group and between the placebo group and the 30 mg group, confirming the superiority of upadacitinib 15 mg and 30 mg over placebo. Table 18 also includes results in the Japanese subpopulation.

Table 18. Rates of achieving vIGA-AD (0, 1) and EASI-75 at Week 16 (ITT_M population, NRI-C [a])

Population	Endpoint	15 mg	30 mg	Placebo
Entire population	Rate of achieving vIGA-AD (0, 1)	39.6 (119/300)	58.6 (174/297)	10.9 (33/304)
	Difference from placebo [95% CI][b] 2-sided *P* value[b) c)]	28.5 [22.1, 34.9] <0.001	47.6 [41.1, 54.0] <0.001	
	Rate of achieving EASI-75	64.6 (194/300)	77.1 (229/297)	26.4 (80/304)
	Difference from placebo [95% CI][b] 2-sided *P* value[b) c)]	38.1 [30.8, 45.4] <0.001	50.6 [43.8, 57.4] <0.001	
Japanese subpopulation	Rate of achieving vIGA-AD (0, 1)	43.8 (7/16)	52.9 (9/17)	11.1 (2/18)
	Difference from placebo [95% CI][b]	33.8 [8.5, 59.0]	43.3 [17.9, 68.7]	
	Rate of achieving EASI-75	68.8 (11/16)	76.5 (13/17)	27.8 (5/18)
	Difference from placebo [95% CI][b]	41.8 [15.5, 68.0]	51.0 [27.6, 74.3]	

% (number of subjects)

a) Non-responder imputation with the following exceptions. After the start of rescue therapy, subjects were regarded as non-responders.
- If a subject was judged as a responder both before and after the scheduled visit, he/she was regarded as a responder on the day of the visit.
- COVID-19-related missing values were imputed by a multiple imputation method.

b) Cochran-Mantel-Haenszel test with baseline vIGA-AD score (3 or 4) and age (<18 years, ≥18 years) as stratification factors.

c) Two-sided significance level of 5%. Multiplicity of hypothesis testing was adjusted by the following method: If comparison of both endpoints between the placebo group and the 30 mg group showed a statistically significant difference, both endpoints of the placebo group and the 15 mg group were compared.

Up to Week 16, adverse events were observed in 66.7% (200 of 300) of subjects in the 15 mg group, 72.4% (215 of 297) of subjects in the 30 mg group, and 62.7% (190 of 303) of subjects in the placebo group. Table 19 shows the main events.

No death occurred.

Serious adverse events were observed in 2.3% (7 of 300) of subjects in the 15 mg group, 1.3% (4 of 297) of subjects in the 30 mg group, and 3.0% (9 of 303) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out in 4 subjects in the 15 mg group (retinal detachment, appendicitis, overdose, and pleural effusion in 1 subject each) and in 1 subject in the placebo group (staphylococcal sepsis).

Adverse events leading to discontinuation occurred in 1.3% (4 of 300) of subjects in the 15 mg group, 1.3% (4 of 297) of subjects in the 30 mg group, and 2.3% (7 of 303) of subjects in the placebo group.

Adverse drug reactions were observed in 37.3% (112 of 300) of subjects in the 15 mg group, 43.4% (129 of 297) of subjects in the 30 mg group, and 21.8% (66 of 303) of subjects in the placebo group.

Table 19. Adverse events with an incidence of ≥3.0% in any group (up to Week 16, safety analysis population)

Event term	15 mg (n = 300)	30 mg (n = 297)	Placebo (n = 303)	Event term	15 mg (n = 300)	30 mg (n = 297)	Placebo (n = 303)
Nasopharyngitis	37 (12.3)	40 (13.5)	34 (11.2)	Influenza	11 (3.7)	7 (2.4)	2 (0.7)
Acne	30 (10.0)	41 (13.8)	6 (2.0)	Abdominal pain upper	11 (3.7)	3 (1.0)	1 (0.3)
Upper respiratory tract infection	21 (7.0)	23 (7.7)	22 (7.3)	Dermatitis atopic	11 (3.7)	2 (0.7)	20 (6.6)
Headache	15 (5.0)	14 (4.7)	15 (5.0)	Oral herpes	10 (3.3)	23 (7.7)	5 (1.7)
Blood creatine phosphokinase increased	13 (4.3)	18 (6.1)	7 (2.3)	Folliculitis	8 (2.7)	11 (3.7)	3 (1.0)
Cough	13 (4.3)	11 (3.7)	4 (1.3)	Oropharyngeal pain	6 (2.0)	9 (3.0)	3 (1.0)
Diarrhoea	11 (3.7)	12 (4.0)	7 (2.3)	Urinary tract infection	5 (1.7)	11 (3.7)	6 (2.0)

Number of subjects (%)

In the Japanese subpopulation, the incidence of adverse events up to Week 16 was 62.5% (10 of 16) of subjects in the 15 mg group, 47.1% (8 of 17) of subjects in the 30 mg group, and 55.6% (10 of 18) of subjects in the placebo group. Table 20 shows the main events observed.

No death occurred.

A serious adverse event was observed in 5.6% (1 of 18) of subjects in the placebo group (rhegmatogenous retinal detachment), but its causal relationship to the study drug was ruled out.

An adverse event leading to discontinuation was observed in 5.6% (1 of 18) of subjects in the placebo group.

Adverse drug reactions were observed in 18.8% (3 of 16) of subjects in the 15 mg group, 29.4% (5 of 17) of subjects in the 30 mg group, and 5.6% (1 of 18) of subjects in the placebo group.

Table 20. Adverse events observed in ≥2 subjects in any group (up to Week 16, safety analysis population, Japanese subpopulation)

Event term	15 mg (n = 16)	30 mg (n = 17)	Placebo (n = 18)
Nasopharyngitis	6 (37.5)	2 (11.8)	0
Influenza	4 (25.0)	2 (11.8)	1 (5.6)
Acne	0	3 (17.6)	2 (11.1)
Pyrexia	0	2 (11.8)	0
Upper respiratory tract infection	0	0	2 (11.1)
Erysipelas	0	0	2 (11.1)

Number of subjects (%)

The incidence of adverse events throughout the study period was 80.4% (356 of 443) of subjects receiving 15 mg and 86.0% (375 of 436) of subjects receiving 30 mg. Table 21 shows the main events observed.

No death occurred.

Serious adverse events were observed in 5.6% (25 of 443) of subjects receiving 15 mg and in 6.2% (27 of 436) of subjects receiving 30 mg. A causal relationship to the study drug could not be ruled out in 10 subjects receiving 15 mg (retinal detachment, duodenal ulcer haemorrhage, appendicitis, bartonellosis, device related infection, herpes zoster cutaneous disseminated, large intestine infection, pneumonia, suicide attempt, and pleural effusion in 1 subject each) and in 7 subjects receiving 30 mg (herpes zoster in 2 subjects, rhegmatogenous retinal detachment, eczema infected, herpes simplex, herpes zoster disseminated, and haemoglobin decreased in 1 subject each).

Adverse events leading to discontinuation were observed in 4.1% (18 of 443) of subjects receiving 15 mg and in 3.7% (16 of 436) of subjects receiving 30 mg.

Adverse drug reactions were observed in 46.7% (207 of 443) of subjects receiving 15 mg and in 54.8% (239 of 436) of subjects receiving 30 mg.

Table 21. Adverse events observed in ≥3.0% of subjects at either dose (entire period, safety analysis population)

Event term	Subjects receiving 15 mg (n = 443)	Subjects receiving 30 mg (n = 436)	Event term	Subjects receiving 15 mg (n = 443)	Subjects receiving 30 mg (n = 436)
Nasopharyngitis	76 (17.2)	73 (16.7)	Herpes zoster	18 (4.1)	28 (6.4)
Acne	62 (14.0)	81 (18.6)	Abdominal pain upper	17 (3.8)	5 (1.1)
Dermatitis atopic	47 (10.6)	29 (6.7)	Diarrhoea	15 (3.4)	19 (4.4)
Upper respiratory tract infection	45 (10.2)	45 (10.3)	Nausea	15 (3.4)	17 (3.9)
Blood creatine phosphokinase increased	37 (8.4)	49 (11.2)	Influenza	15 (3.4)	11 (2.5)
Headache	29 (6.5)	28 (6.4)	Influenza like illness	12 (2.7)	16 (3.7)
Cough	23 (5.2)	26 (6.0)	Gastroenteritis	12 (2.7)	13 (3.0)
Herpes simplex	23 (5.2)	24 (5.5)	Urinary tract infection	11 (2.5)	21 (4.8)
Oral herpes	20 (4.5)	36 (8.3)	Weight increased	9 (2.0)	14 (3.2)
Folliculitis	19 (4.3)	21 (4.8)	Bronchitis	8 (1.8)	13 (3.0)
Pyrexia	19 (4.3)	18 (4.1)			

Number of subjects (%)

In the Japanese subpopulation, the incidence of adverse events throughout the entire study period was 87.5% (21 of 24) of subjects receiving 15 mg and 84.6% (22 of 26) of subjects receiving 30 mg. Table 22 shows the main events observed.

No death occurred.

Serious adverse events were observed in 8.3% (2 of 24) of subjects receiving 15 mg (herpes zoster cutaneous disseminated and ligament injury/peripheral nerve paresis/tarsal tunnel syndrome in 1 subject each) and 3.8% (1 of 26) of subjects receiving 30 mg (herpes zoster). A causal relationship to the study drug could not be ruled out for herpes zoster cutaneous disseminated and herpes zoster.

There was no adverse event leading to discontinuation.

Adverse drug reactions were observed in 50.0% (12 of 24) of subjects receiving 15 mg and in 42.3% (11 of 26) of subjects receiving 30 mg.

Table 22. Adverse events observed in ≥2 subjects at either dose (entire period, safety analysis population, Japanese subpopulation)

Event term	Subjects receiving 15 mg (n = 24)	Subjects receiving 30 mg (n = 26)	Event term	Subjects receiving 15 mg (n = 24)	Subjects receiving 30 mg (n = 26)
Nasopharyngitis	13 (54.2)	7 (26.9)	Cough	2 (8.3)	0
Acne	8 (33.3)	8 (30.8)	Impetigo	2 (8.3)	0
Dermatitis atopic	5 (20.8)	1 (3.8)	Miliaria	2 (8.3)	0
Influenza	4 (16.7)	4 (15.4)	Skin papilloma	2 (8.3)	0
Folliculitis	4 (16.7)	2 (7.7)	Upper respiratory tract infection	2 (8.3)	0
Herpes zoster	3 (12.5)	5 (19.2)	Tinea pedis	1 (4.2)	3 (11.5)
Dental caries	3 (12.5)	1 (3.8)	Epistaxis	0	2 (7.7)
Back pain	2 (8.3)	1 (3.8)	Hordeolum	0	2 (7.7)
Herpes simplex	2 (8.3)	1 (3.8)	Insomnia	0	2 (7.7)
Urticaria	2 (8.3)	1 (3.8)	Pyrexia	0	2 (7.7)

Number of subjects (%)

7.2.3 Japanese long-term treatment study (TCS combination study, CTD 5.3.5.1-5, Study M17-377 [ongoing since October 2018 (data cut-off [redacted] 20[redacted], up to Week 52)])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to investigate the safety and efficacy of upadacitinib in combination with TCS in Japanese patients with AD who have an inadequate response to TCS or TCI or, a prior systemic treatment for AD (target sample size 264 subjects [88 per group]). Table 23 shows the main inclusion criteria.

Table 23. Main inclusion criteria

1. Diagnosis of AD confirmed according to the Hanifin and Rajka criteria and onset of symptoms at least 3 years prior to baseline.
2. Documented history (within 6 months of the baseline visit) of an inadequate response to TCS or TCI or documented prior systemic treatment for AD within 6 months prior to the baseline visit.
3. EASI score ≥16
4. vIGA-AD score ≥3
5. Lesion covering ≥10% of the body surface area
6. Mean pruritus NRS score ≥4 during 7 days immediately before randomization
7. Subjects aged ≥12 and <18 years should weigh ≥40 kg.
8. ≥12 and ≤75 years of age

The study consisted of 2 periods (double-blind period up to Week 16, extended administration period from Week 16 to 160). During the double-blind period, subjects received orally upadacitinib 15, 30 mg, or placebo once daily. During the extended administration period, subjects who had received upadacitinib during the double-blind period received upadacitinib at the same dose as that during the double-blind period, and subjects who had received placebo during the double-blind period received orally upadacitinib 15 or 30 mg once daily. In combination, a topical moisturizing agent was applied twice daily from ≥7 days before baseline up to Week 16. TCS therapy was started at baseline and terminated when the disease improved.[14)] If symptoms did not improve sufficiently[9)] after Week 4, rescue treatment[15)] was permitted. From Week 16, additional topical treatment for AD was permitted at the discretion of the physician. This topical therapy was not regarded as rescue therapy; only additional systemic therapy for AD was handled as rescue therapy.

All of the 272 randomized[16)] subjects (91 in the 15 mg group, 91 in the 30 mg group, 90 in the placebo group) were included in the ITT population, and the ITT population was handled as the efficacy analysis population. All subjects in the ITT population received at least 1 dose of the study drug and were included in the safety analysis population up to Week 16. Within 16 weeks, treatment discontinuation occurred in 1.1% (1 of 91) of subjects in the 15 mg group, 2.2% (2 of 91) of subjects in the 30 mg group, and 3.3% (3 of 90) of subjects in the placebo group. The main reason for the discontinuation was consent withdrawal (2.2% [2 of 91] in the 30 mg group, 2.2% [2 of 90] in the placebo group).

At Week 16, 87 subjects in the placebo group were re-randomized the upadacitinib 15 mg group (42 subjects) or 30 mg group (45 subjects), and all of them received at least 1 dose of upadacitinib. A total of 296 subjects receiving at least 1 dose of upadacitinib during the study period (133 subjects receiving 15 mg,[12)] 136 subjects receiving 30 mg[12)]) were included in the safety analysis population for the entire period. During the period from Week 16 to 52, treatment discontinuation occurred in 3.8% (5 of 131) of subjects receiving 15 mg and in 6.8% (9 of 133) of subjects receiving 30 mg. The main

[16)] Baseline severity (vIGA-AD score of 3 or 4) and age (<18 years, ≥18 and ≤40 years, or >40 years) were used as stratification factors.

reason for the discontinuation was consent withdrawal (3.1% [4 of 131] of subjects receiving 15 mg, 3.8% [5 of 133] of subjects receiving 30 mg).

Up to Week 16, adverse events were observed in 56.0% (51 of 91) of subjects in the 15 mg group, 63.7% (58 of 91) of subjects in the 30 mg group, and 42.2% (38 of 90) of subjects in the placebo group. Table 24 shows the main events.

No death occurred.

Serious adverse events were observed in 1.1% (1 of 91) of subjects in the 15 mg group (cerebellar haemorrhage), 1.1% (1 of 91) of subjects in the 30 mg group (herpes simplex), and 1.1% (1 of 90) of subjects in the placebo group (cholelithiasis). A causal relationship to the study drug could not be ruled out for cerebellar haemorrhage and herpes simplex.

Adverse events leading to discontinuation were observed in 2.2% (2 of 91) of subjects in the 15 mg group, 1.1% (1 of 91) of subjects in the 30 mg group, and 1.1% (1 of 90) of subjects in the placebo group.

Adverse drug reactions were observed in 13.2% (12 of 91) of subjects in the 15 mg group, 26.4% (24 of 91) of subjects in the 30 mg group, and 12.2% (11 of 90) of subjects in the placebo group.

Table 24. Adverse events observed with an incidence of ≥3.0% in any group (up to Week 16, safety analysis population)

Event term	15 mg (n = 91)	30 mg (n = 91)	Placebo (n = 90)	Event term	15 mg (n = 91)	30 mg (n = 91)	Placebo (n = 90)
Acne	12 (13.2)	18 (19.8)	5 (5.6)	Dermatitis atopic	3 (3.3)	0	3 (3.3)
Nasopharyngitis	12 (13.2)	14 (15.4)	14 (15.6)	Arthralgia	0	5 (5.5)	0
Pyrexia	4 (4.4)	3 (3.3)	1 (1.1)	Herpes zoster	0	4 (4.4)	0
Folliculitis	3 (3.3)	2 (2.2)	2 (2.2)	Neutropenia	0	3 (3.3)	0
Kaposi's varicelliform eruption	3 (3.3)	1 (1.1)	0	Abdominal discomfort	0	3 (3.3)	0
Upper respiratory tract infection	3 (3.3)	1 (1.1)	0	Number of patients (%)			

The incidence of adverse events throughout the study period was 75.2% (100 of 133) of subjects receiving 15 mg and 80.9% (110 of 136) of subjects receiving 30 mg. Table 25 shows the main events observed.

No death occurred.

Serious adverse events were observed in 4.5% (6 of 133) of subjects receiving 15 mg (cataract diabetic, appendicitis, cellulitis, herpes zoster, *Pneumocystis jirovecii* pneumonia, and cerebellar haemorrhage in 1 subject each) and in 2.9% (4 of 136) of subjects receiving 30 mg (herpes zoster in 2 subjects and herpes simplex and appendicitis/pneumothorax in 1 subject each). A causal relationship to the study drug could not be ruled out in 4 subjects receiving 15 mg (appendicitis, herpes zoster, *Pneumocystis jirovecii* pneumonia, and cerebellar haemorrhage in 1 subject each) and in 4 subjects receiving 30 mg (herpes zoster in 2 subjects, herpes simplex and appendicitis/pneumothorax in 1 subject each).

Adverse events leading to discontinuation were observed in 3.0% (4 of 133) of subjects receiving 15 mg and in 2.2% (3 of 136) of subjects receiving 30 mg.

Adverse drug reactions were observed in 33.8% (45 of 133) of subjects receiving 15 mg and in 39.0% (53 of 136) of subjects receiving 30 mg.

Table 25. Adverse events observed in ≥3.0% of subjects at either dose (entire period, safety analysis population)

Event term	Subjects receiving 15 mg (n = 133)	Subjects receiving 30 mg (n = 136)	Event term	Subjects receiving 15 mg (n = 133)	Subjects receiving 30 mg (n = 136)
Nasopharyngitis	32 (24.1)	42 (30.9)	Oropharyngeal pain	4 (3.0)	3 (2.2)
Acne	23 (17.3)	44 (32.4)	Pharyngitis	4 (3.0)	3 (2.2)
Herpes simplex	9 (6.8)	4 (2.9)	Cough	4 (3.0)	2 (1.5)
Folliculitis	9 (6.8)	4 (2.9)	Upper respiratory tract infection	4 (3.0)	2 (1.5)
Herpes zoster	7 (5.3)	18 (13.2)	Blood creatine phosphokinase increased	3 (2.3)	6 (4.4)
Dermatitis atopic	7 (5.3)	6 (4.4)	Oral herpes	3 (2.3)	6 (4.4)
Pyrexia	7 (5.3)	7 (5.1)	Alanine aminotransferase increased	3 (2.3)	5 (3.7)
Kaposi's varicelliform eruption	7 (5.3)	3 (2.2)	Asthma	2 (1.5)	7 (5.1)
Influenza	6 (4.5)	11 (8.1)	Tinea pedis	2 (1.5)	5 (3.7)
Furuncle	6 (4.5)	2 (1.5)	Arthralgia	1 (0.8)	10 (7.4)
Skin papilloma	6 (4.5)	1 (0.7)	Diarrhoea	1 (0.8)	5 (3.7)

Number of subjects (%)

Table 26 shows the rates of achieving vIGA-AD (0, 1) and EASI-75 at Week 16.

Table 26. Rates of achieving vIGA-AD (0, 1) and EASI-75 at Week 16 (ITT population, NRI[a])

Endpoint	15 mg	30 mg	Placebo
Rate of achieving vIGA-AD (0, 1)	40.7 (37/91)	47.3 (43/91)	6.7 (6/90)
Difference from placebo [95% CI][b]	33.6 [22.6, 44.6]	40.3 [28.9, 51.8]	
Rate of achieving EASI-75	64.8 (59/91)	74.7 (68/91)	17.8 (16/90)
Difference from placebo [95% CI][b]	46.8 [34.4, 59.2]	56.4 [44.8, 68.1]	

% (number of subjects)

a) Non-responder imputation with the following exceptions. After the start of rescue therapy, subjects were regarded as non-responders.
- If a subject was judged as a responder both before and after the scheduled visit, he/she was regarded as a responder on the day of the visit.

b) Cochran-Mantel-Haenszel test with baseline vIGA-AD score (3 or 4) and age (<18 years, ≥18 years) as stratification factors.

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

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

In Japan, diagnosis of AD is done according to the Japanese clinical practice guidelines which are different from Hanifin and Rajka criteria commonly used in foreign countries in the handling of personal or family history of atopic disorders (reference criterion in Japan, major criterion in foreign countries). However, since atopic disposition is explicitly cited as a definition of AD in the Japanese guidelines as well, there is no inherent difference in the diagnostic criteria of AD (*Acta Derm-Venereol Suppl*. 1980;92:44-7, *J Am Acad Dermatol.* 2014;70:338-351, Japanese clinical practice guidelines for AD 2018). Also, the treatment algorithm for AD is similar between Japan and foreign countries, as exemplified by the following: (1) The basis of drug therapy for AD is use of topical anti-inflammatory agents combined with continuous use of a topical moisturizing agent, (2) TCS is the first-line anti-inflammatory drug, and (3) systemic therapy should be considered when the disease does not adequately respond to the above topical treatments (*J Am Acad Dermatol*. 2014;70:338-351, Japanese

clinical practice guidelines for AD 2018). Furthermore, clinical studies in healthy subjects and patients with RA did not reveal any clinically significant ethnic difference in the pharmacokinetics of upadacitinib (see Review Report "Rinvoq Tablets 7.5 mg, etc." dated November 14, 2019). Accordingly, it was considered appropriate to evaluate the efficacy and safety of upadacitinib in Japanese patients with AD based on the clinical data package constructed from global studies including Japan.

To fulfill the above requirements for AD treatment algorithm, the following phase III studies were conducted: (1) Study M16-045 to investigate the efficacy and safety of upadacitinib monotherapy and (2) Studies M16-047 and M17-377 to investigate the efficacy and safety of upadacitinib in combination with TCS. Topical moisturizing agents were used during the main evaluation period in all of these studies. Other study plans in phase III studies were described below.

- **Target patients**

To satisfy the above requirements for AD treatment algorithm, the phase III studies (Studies M16-045, M16-047, and M17-377) were conducted in patients requiring systemic treatment who have an inadequate response to TCS or TCI or, a prior systemic treatment for AD, and have a certain level of disease activity (EASI score ≥16, vIGA-AD score ≥3, lesion covering ≥10% of the body surface area, and pruritus numeric rating scale (NRS) score ≥4). Study M16-045 also included patients for whom topical treatment is not recommended for safety reasons, etc.

Since the current clinical practice guidelines for AD do not distinguish the diagnosis, evaluation, and the treatment algorithm for children aged ≥12 years from those for adults (*Allergy*. 2006;61:969-87, Japanese clinical practice guidelines for AD 2018), children aged ≥12 years were included in the phase III studies. However, at the time of study planning, there was no use experience of upadacitinib in subjects aged <18 years, with the effect of body weight on the safety of upadacitinib in this population unknown. Therefore, body weight of ≥40 kg for the subject aged ≥12 and <18 years was added in the inclusion criteria.[17)]

- **Dosage regimen**

In the global phase II study (Study M16-048) investigating the dose-response relationship of upadacitinib (7.5, 15, or 30 mg) in subjects with AD for whom topical treatment was not recommended because of an inadequate response to TCS or TCI or for safety reasons, etc., the percent change in EASI score at Week 16 from baseline, the primary efficacy endpoint, showed a significant dose-response relationship within the dose range tested [see Section 7.1.1]. While superior results in multiple efficacy endpoints were observed in the 30 mg group compared to the 15 mg group,[18)] no

17) In a preliminary population pharmacokinetic analysis based on the results of clinical studies in healthy subjects, patients with RA, patients with Crohn's disease, and patients with AD, no correlation was observed between body weight and apparent upadacitinib clearance within the body weight range from 39 to 152 kg. These results suggested that the extent of exposure in children aged ≥12 years weighing ≥40 kg was similar to that in adults. However, since there was no use experience in subjects weighing <40 kg, subjects aged ≥12 and <18 years had to weigh ≥40 kg.

18) Results at Week 16 were as follows: [Rate of achieving IGA (0, 1) (Non responder imputation [NRI]): 14.3% (6 of 42) in the 7.5 mg group, 31.0% (13 of 42) in the 15 mg group, 50.0% (21 of 42) in the 30 mg group, 2.4% (1 of 41) in the placebo group], [Rate of achieving EASI-75 (NRI): 28.6% (12 of 42) in the 7.5 mg group, 52.4% (22 of 42) in the 15 mg group, 69.0% (29 of 42) in the 30 mg group, 9.8% (4 of 41) in the placebo group], [Rate of achieving EASI-90 (NRI): 14.3% (6 of 42) in the 7.5 mg group, 26.2% (11 of 42) in the 15 mg group, 50.0% (21 of 42) in the 30 mg group, 2.4% (1 of 41) in the placebo group].

sufficient efficacy was expected in the 7.5 mg group. Accordingly, once daily oral administration of upadacitinib 15 or 30 mg was used as the dosage regimen in the phase III studies.

- **Efficacy endpoints and evaluation time point**

Since the objectives of AD treatment is improvement of signs and symptoms of AD, the phase III studies used co-primary endpoints (rate of achieving vIGA-AD (0, 1) and rate of achieving EASI-75), which are a physician-assessed overall score of skin disorder and an objective score of the severity and area of skin lesion, respectively.

The co-primary endpoints were evaluated at Week 16, by taking account of the observation that in Study M16-048, the values of many efficacy endpoints reached the steady state within 16 weeks of administration, and by referring to the timing of efficacy evaluation in clinical studies on drugs in the same class.

PMDA accepted the above explanation of the applicant and concluded that it is acceptable to evaluate the efficacy and safety of upadacitinib in patients with AD based on the submitted clinical data package, focusing on the results of the phase III studies in which Japanese patients participated (Studies M16-045, M16-047, and M17-377).

7.R.2 Efficacy

The applicant's explanation about the efficacy of upadacitinib:

In the following 2 studies, rates of achieving vIGA-AD (0, 1) and EASI-75 at Week 16, the co-primary efficacy endpoints, were compared between the placebo group and the 15 mg group and between the placebo group and the 30 mg group: (a) Study M16-045 investigating the efficacy and safety of upadacitinib monotherapy in patients who have an inadequate response to TCS or TCI, or a prior systemic treatment for AD, or for whom topical treatment was not recommended for safety reasons, etc. [see Section 7.2.1]; (b) Study M16-047 investigating the efficacy and safety of upadacitinib in combination with TCS in patients who have an inadequate response to TCS or TCI, or a prior systemic treatment for AD [see Section 7.2.2]. A statistically significant difference was observed in all evaluation time points tested, confirming the superiority of upadacitinib 15 mg and 30 mg to placebo (Tables 12 and 18).

Table 27 shows the results of main efficacy endpoints in Studies M16-045 and M16-047. In both studies and for all endpoints, a greater tendency of improvement was observed in upadacitinib groups compared to the placebo group, and the efficacy lasted throughout the study period. Also, in both studies and for all endpoints, results in the 30 mg group tended to be superior to those observed in the 15 mg group.

In the Japanese subpopulations of Studies M16-045 and M16-047, the co-primary endpoints showed similar tendencies to those in the entire population (Tables 12 and 18). Table 28 shows the results of other main efficacy endpoints, which tended to be generally similar to those observed in the entire population. Table 28 also shows the results of main efficacy endpoints in the Japanese long-term treatment study in patients with AD similar to those in Study M16-047 [Study M17-377, see Section

7.2.3]. All endpoints in the upadacitinib group showed improving tendency and lasting efficacy exceeding those in the placebo group.

The applicant considers that the above results demonstrate the efficacy of upadacitinib in Japanese patients with AD.

Table 27. Results of main efficacy endpoints (ITT_M population, NRI-C[a])

Efficacy endpoint	Timing of evaluation	Study M16-045 (monotherapy)				Study M16-047 (combination with TCS)			
		15 mg	30 mg	Placebo →15 mg	Placebo →30 mg	15 mg	30 mg	Placebo →15 mg	Placebo →30 mg
Rate of achieving vIGA-AD (0, 1)	Week 2	16.4 (46/281)	21.1 (60/285)	1.1 (3/281)		10.7 (32/300)	21.9 (65/297)	4.3 (13/304)	
	Week 4	33.5 (94/281)	47.4 (135/285)	3.2 (9/281)		30.0 (90/300)	46.5 (138/297)	7.2 (22/304)	
	Week 8	47.3 (133/281)	56.1 (160/285)	7.8 (22/281)		36.0 (108/300)	54.9 (163/297)	9.2 (28/304)	
	Week 16 (*)	48.1 (135/281)	62.0 (177/285)	8.4 (24/281)		39.6 (119/300)	58.6 (174/297)	10.9 (33/304)	
	Week 32	46.3 (130/281)	56.7 (162/285)	63.0 (41/65)	86.4 (58/67)	36.0 (108/300)	54.4 (162/297)	56.4 (65/115)	67.3 (62/92)
	Week 52	49.7 (140/281)	53.4 (152/285)	67.5 (44/65)	80.4 (54/67)	33.5 (101/300)	45.2 (134/297)	56.9 (65/115)	65.5 (60/92)
Rate of achieving EASI-75	Week 2	38.1 (107/281)	47.4 (135/285)	3.6 (10/281)		31.0 (93/300)	44.1 (131/297)	6.9 (21/304)	
	Week 4	62.3 (175/281)	75.1 (214/285)	8.9 (25/281)		58.7 (176/300)	72.4 (215/297)	14.8 (45/304)	
	Week 8	69.8 (196/281)	80.0 (228/285)	13.2 (37/281)		65.3 (196/300)	79.5 (236/297)	19.4 (59/304)	
	Week 16 (*)	69.6 (196/281)	79.7 (227/285)	16.3 (46/281)		64.6 (194/300)	77.1 (229/297)	26.4 (80/304)	
	Week 32	68.0 (191/281)	71.9 (205/285)	74.6 (48/65)	94.0 (63/67)	57.2 (172/300)	72.5 (215/297)	79.0 (91/115)	94.1 (87/92)
	Week 52	66.1 (186/281)	71.0 (202/285)	81.1 (53/65)	88.9 (60/67)	50.8 (152/300)	69.0 (205/297)	79.1 (91/115)	84.7 (78/92)
Rate of achieving EASI-90	Week 2	17.8 (50/281)	20.7 (59/285)	0.4 (1/281)		8.7 (26/300)	18.9 (56/297)	2.6 (8/304)	
	Week 4	35.6 (100/281)	47.4 (135/285)	2.8 (8/281)		28.3 (85/300)	43.8 (130/297)	4.9 (15/304)	
	Week 8	50.2 (141/281)	59.6 (170/285)	5.3 (15/281)		35.7 (107/300)	61.3 (182/297)	6.6 (20/304)	
	Week 16	53.1 (149/281)	65.8 (187/285)	8.1 (23/281)		42.8 (128/300)	63.1 (187/297)	13.2 (40/304)	
	Week 32	55.5 (156/281)	59.8 (170/285)	63.9 (42/65)	83.1 (56/67)	41.4 (124/300)	60.4 (180/297)	60.4 (69/115)	79.2 (73/92)
	Week 52	51.4 (144/281)	59.8 (170/285)	67.0 (44/65)	81.8 (55/67)	37.4 (112/300)	53.9 (160/297)	61.1 (70/115)	72.4 (67/92)
Rate of achieving EASI-100	Week 2	0.4 (1/281)	2.1 (6/285)	0 (0/281)		0.7 (2/300)	4.4 (13/297)	0 (0/304)	
	Week 4	4.3 (12/281)	9.5 (27/285)	0.7 (2/281)		5.7 (17/300)	12.5 (37/297)	1.0 (3/304)	
	Week 8	10.3 (29/281)	24.2 (69/285)	1.8 (5/281)		10.7 (32/300)	17.2 (51/297)	0.7 (2/304)	
	Week 16	16.7 (47/281)	27.0 (77/285)	1.8 (5/281)		12.0 (36/300)	22.6 (67/297)	1.3 (4/304)	
	Week 32	23.2 (65/281)	28.8 (82/285)	30.8 (20/65)	52.3 (35/67)	14.7 (44/300)	24.6 (73/297)	25.2 (29/115)	39.2 (36/92)
	Week 52	22.8 (64/281)	29.2 (83/285)	30.8 (20/65)	50.9 (34/67)	13.3 (40/300)	23.6 (70/297)	27.0 (31/115)	26.2 (24/92)
Rate of achieving improvement in pruritus NRS score by ≥4 points	Week 2	32.5 (89/274)	48.2 (135/280)	2.2 (6/272)		31.6 (91/288)	45.0 (131/291)	9.5 (28/294)	
	Week 4	51.5 (141/274)	66.8 (187/280)	4.4 (12/272)		52.4 (151/288)	65.6 (191/291)	15.0 (44/294)	
	Week 8	60.6 (166/274)	71.8 (201/280)	9.9 (27/272)		52.8 (152/288)	71.8 (209/291)	15.6 (46/294)	
	Week 16	52.2 (143/274)	60.0 (168/280)	11.8 (32/272)		51.7 (149/288)	63.9 (186/291)	15.0 (44/294)	
	Week 32	56.5 (155/274)	63.7 (178/280)	67.3 (42/62)	75.8 (49/64)	45.8 (132/288)	65.1 (189/291)	65.5 (73/111)	76.9 (69/90)
	Week 52	54.2 (149/274)	56.8 (159/280)	61.7 (38/62)	65.9 (42/64)	45.3 (130/288)	57.5 (167/291)	61.3 (68/111)	70.7 (64/90)

% (number of subjects); * Primary endpoint

a) Non-responder imputation with the following exceptions. After the start of rescue therapy, subjects were regarded as non-responders. Subjects who received rescue therapy on or before Week 16 in the placebo group were not included in the analysis after Week 16.
- If a subject was judged as a responder both before and after the scheduled visit, he/she was regarded as a responder on the day of the visit.
- COVID-19-related missing values were imputed by a multiple imputation method.

Table 28. Results of main efficacy endpoints (ITT_M population, Japanese subpopulation, NRI-C[a])

Efficacy endpoint	Timing of evaluation	Study M16-045 (monotherapy)				Study M16-047 (combination with TCS)				Study M17-377 (combination with TCS)			
		15 mg	30 mg	Placebo → 15 mg	Placebo → 30 mg	15 mg	30 mg	Placebo → 15 mg	Placebo → 30 mg	15 mg	30 mg	Placebo → 15 mg	Placebo → 30 mg
Rate of achieving vIGA-AD (0, 1)	Week 2	20.0 (3/15)	12.5 (2/16)	0 (0/14)		0 (0/16)	23.5 (4/17)	11.1 (2/18)		8.8 (8/91)	11.0 (10/91)	1.1 (1/90)	
	Week 4	40.0 (6/15)	31.3 (5/16)	0 (0/14)		31.3 (5/16)	47.1 (8/17)	5.6 (1/18)		23.1 (21/91)	20.9 (19/91)	1.1 (1/90)	
	Week 8	26.7 (4/15)	43.8 (7/16)	0 (0/14)		50.0 (8/16)	41.2 (7/17)	5.6 (1/18)		30.8 (28/91)	28.6 (26/91)	5.6 (5/90)	
	Week 16 (*)	33.3 (5/15)	50.0 (8/16)	0 (0/14)		43.8 (7/16)	52.9 (9/17)	11.1 (2/18)		40.7 (37/91)	47.3 (43/91)	6.7 (6/90)	
	Week 32	33.3 (5/15)	56.3 (9/16)	0 (0/0)	0 (0/0)	31.3 (5/16)	41.2 (7/17)	60.0 (3/5)	83.3 (5/6)	41.6 (37/89)	52.3 (46/88)	28.6 (8/28)	53.3 (16/30)
	Week 52	46.7 (7/15)	37.5 (6/16)	0 (0/0)	0 (0/0)	18.8 (3/16)	41.2 (7/17)	60.0 (3/5)	66.7 (4/6)	32.6 (29/89)	50.0 (44/88)	32.1 (9/28)	50.0 (15/30)
Rate of achieving EASI-75	Week 2	46.7 (7/15)	25.0 (4/16)	0 (0/14)		12.5 (2/16)	41.2 (7/17)	11.1 (2/18)		15.4 (14/91)	23.1 (21/91)	4.4 (4/90)	
	Week 4	66.7 (10/15)	62.5 (10/16)	7.1 (1/14)		43.8 (7/16)	64.7 (11/17)	11.1 (2/18)		42.9 (39/91)	54.9 (50/91)	10.0 (9/90)	
	Week 8	73.3 (11/15)	56.3 (9/16)	7.1 (1/14)		62.5 (10/16)	70.6 (12/17)	22.2 (4/18)		57.1 (52/91)	70.3 (64/91)	13.3 (12/90)	
	Week 16 (*)	73.3 (11/15)	56.3 (9/16)	7.1 (1/14)		68.8 (11/16)	76.5 (13/17)	27.8 (5/18)		64.8 (59/91)	74.7 (68/91)	17.8 (16/90)	
	Week 32	66.7 (10/15)	50.0 (8/16)	0 (0/0)	0 (0/0)	68.8 (11/16)	82.4 (14/17)	60.0 (3/5)	83.3 (5/6)	69.7 (62/89)	77.3 (68/88)	82.1 (23/28)	73.3 (22/30)
	Week 52	66.7 (10/15)	50.0 (8/16)	0 (0/0)	0 (0/0)	50.0 (8/16)	82.4 (14/17)	60.0 (3/5)	83.3 (5/6)	71.9 (64/89)	77.3 (68/88)	67.9 (19/28)	70.0 (21/30)
Rate of achieving EASI-90	Week 2	20.0 (3/15)	0 (0/16)	0 (0/14)		0 (0/16)	5.9 (1/17)	11.1 (2/18)		4.4 (4/91)	8.8 (8/91)	2.2 (2/90)	
	Week 4	33.3 (5/15)	37.5 (6/16)	0 (0/14)		25.0 (4/16)	35.3 (6/17)	0 (0/18)		16.5 (15/91)	22.0 (20/91)	3.3 (3/90)	
	Week 8	40.0 (6/15)	43.8 (7/16)	0 (0/14)		31.3 (5/16)	52.9 (9/17)	5.6 (1/18)		28.6 (26/91)	31.9 (29/91)	4.4 (4/90)	
	Week 16	46.7 (7/15)	43.8 (7/16)	0 (0/14)		31.3 (5/16)	58.8 (10/17)	16.7 (3/18)		41.8 (38/91)	48.4 (44/91)	5.6 (5/90)	
	Week 32	53.3 (8/15)	37.5 (6/16)	0 (0/0)	0 (0/0)	31.3 (5/16)	58.8 (10/17)	40.0 (2/5)	83.3 (5/6)	40.4 (36/89)	56.8 (50/88)	46.4 (13/28)	50.0 (15/30)
	Week 52	46.7 (7/15)	50.0 (8/16)	0 (0/0)	0 (0/0)	25.0 (4/16)	64.7 (11/17)	60.0 (3/5)	83.3 (5/6)	41.6 (37/89)	59.1 (52/88)	42.9 (12/28)	50.0 (15/30)
Rate of achieving EASI-100	Week 2	6.7 (1/15)	0 (0/16)	0 (0/14)		0 (0/16)	0 (0/17)	0 (0/18)		0 (0/91)	1.1 (1/91)	0 (0/90)	
	Week 4	0 (0/15)	0 (0/16)	0 (0/14)		6.3 (1/16)	5.9 (1/17)	0 (0/18)		1.1 (1/91)	2.2 (2/91)	0 (0/90)	
	Week 8	0 (0/15)	12.5 (2/16)	0 (0/14)		0 (0/16)	5.9 (1/17)	0 (0/18)		0 (0/91)	3.3 (3/91)	0 (0/90)	
	Week 16	0 (0/15)	12.5 (2/16)	0 (0/14)		0 (0/16)	5.9 (1/17)	0 (0/18)		0 (0/91)	4.4 (4/91)	1.1 (1/90)	
	Week 32	0 (0/15)	12.5 (2/16)	0 (0/0)	0 (0/0)	0 (0/16)	5.9 (1/17)	0 (0/5)	50.0 (3/6)	3.4 (3/89)	9.1 (8/88)	10.7 (3/28)	13.3 (4/30)
	Week 52	6.7 (1/15)	6.3 (1/16)	0 (0/0)	0 (0/0)	0 (0/16)	11.8 (2/17)	0 (0/5)	16.7 (1/6)	2.2 (2/89)	6.8 (6/88)	7.1 (2/28)	13.3 (4/30)
Rate of achieving improvement in pruritus NRS score by ≥4 points	Week 2	26.7 (4/15)	18.8 (3/16)	0 (0/14)		25.0 (4/16)	41.2 (7/17)	0 (0/18)		20.0 (18/90)	24.2 (22/91)	6.7 (6/90)	
	Week 4	20.0 (3/15)	50.0 (8/16)	0 (0/14)		37.5 (6/16)	70.6 (12/17)	11.1 (2/18)		34.4 (31/90)	42.9 (39/91)	7.8 (7/90)	
	Week 8	33.3 (5/15)	62.5 (10/16)	0 (0/14)		43.8 (7/16)	82.4 (14/17)	11.1 (2/18)		43.3 (39/90)	48.4 (44/91)	8.9 (8/90)	
	Week 16	33.3 (5/15)	50.0 (8/16)	0 (0/14)		56.3 (9/16)	82.4 (14/17)	16.7 (3/18)		41.1 (37/90)	47.3 (43/91)	12.2 (11/90)	
	Week 32	40.0 (6/15)	50.0 (8/16)	0 (0/0)	0 (0/0)	31.3 (5/16)	82.4 (14/17)	40.0 (2/5)	33.3 (2/6)	44.3 (39/88)	62.5 (55/88)	50.0 (14/28)	70.0 (21/30)
	Week 52	40.0 (6/15)	43.8 (7/16)	0 (0/0)	0 (0/0)	31.3 (5/16)	58.8 (10/17)	40.0 (2/5)	33.3 (2/6)	39.8 (35/88)	51.1 (45/88)	46.4 (13/28)	63.3 (19/30)

% (number of subjects); * Primary endpoint

a) Non-responder imputation with the following exceptions. After the start of rescue therapy, subjects were regarded as non-responders. Subjects who received rescue therapy on or before Week 16 in the placebo group were not included in the analysis after Week 16.
- If a subject was judged as a responder both before and after the scheduled visit, he/she was regarded as a responder on the day of the visit.
- COVID-19-related missing values were imputed by a multiple imputation method.

PMDA's view:

Superiority of upadacitinib 15 mg and 30 mg to placebo in patients with AD requiring systemic treatment was demonstrated in Study M16-045 investigating the efficacy and safety of upadacitinib monotherapy and in Study M16-047 investigating the efficacy and safety of upadacitinib in combination with TCS. Other efficacy endpoints also showed superior results in the upadacitinib group than in the placebo group. In addition, upadacitinib showed lasting efficacy, demonstrating the effectiveness for AD. Although there were a limited number of subjects in the Japanese subpopulation of these studies, upadacitinib is expected to be effective in Japanese patients with AD, given the following observations: (1) Efficacy did not significantly differ between the Japanese subpopulation and the entire population and (2) results of the Japanese long-term treatment study (Study M17-377) were not inconsistent with those of Study M16-047.

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

7.R.3 Safety

The applicant's explanation about the safety of upadacitinib in patients with AD, based on the following data, etc.:

(1) Pooled data of 5 placebo-controlled studies: Pooled safety data of 5 Japanese and foreign placebo-controlled studies in patients with AD (Studies M16-048, M16-045, M16-047, M17-377, and M18-891[19])

(2) Pooled data of 4 long-term studies: Pooled long-term safety data of 4 Japanese and foreign phase III studies in patients with AD (Studies M16-045, M16-047, M17-377, and M18-891)

(3) Pooled data of Japanese and foreign clinical studies[20] in patients with psoriatic arthritis (PsA) and patients with RA

7.R.3.1 Outline of safety

Table 29 shows the outline of safety of upadacitinib in Japanese and foreign clinical studies in patients with AD, PsA, and RA, and Table 30 shows the incidence of adverse events possibly related to upadacitinib. In clinical studies in patients with AD, overall findings were tendencies of higher incidence of adverse events and adverse drug reactions at 30 mg than at 15 mg. Thus, dose-dependent increases were observed in the events possibly related to upadacitinib, such as herpes zoster, anaemia, haemoglobin decreased, neutropenia, blood creatinine phosphokinase increased, and acne. These results were not significantly different from the safety profile at any dose in patients with PsA and RA, the approved indications, except acne (to be described later) and skin infection [see Section 7.R.3.2]. Malignant tumor was observed more frequently in subjects receiving 30 mg than in subjects receiving 15 mg. However, 58.8% (10 of 17) of subjects with malignancy observed in the pooled data of 4 long-term studies was nonmelanoma skin cancer (NMSC) observed at a certain frequency in patients with skin disorder. The standardized incidence ratio [95% confidence interval (CI)] of malignant tumor other than NMSC, adjusted for age and sex, was 0.56 [0.07, 2.04] in subjects receiving 15 mg, 1.22 [0.40, 2.84] in subjects receiving 30 mg, and 0.92 [0.37, 1.89] in all subjects receiving

[19] Foreign phase III study conducted with a similar design to that of Study M16-045

[20] Clinical studies in patients with PsA: Studies M15-572 and M15-554; Clinical studies in patients with RA: Studies M13-537, M13-538, M13-550, M13-542, M13-545, M13-549, M14-465, M14-663, and M15-555 (pooled data of 9 studies)

upadacitinib, indicating that the risk was within the range expected in the general population. As for acne, which occurs by an unknown mechanism, the incidence was markedly higher in patients with AD than in patients with PsA or RA. However, it is considered unnecessary to take additional safety measures, for the following reasons: (1) Most of the events were mild to moderate and could be effectively treated by clinical practice, and (2) the current package insert identifies acne as an adverse drug reaction of upadacitinib and requires close monitoring and adequate treatment after the onset of the event.

Table 31 shows the outline of safety of upadacitinib in Japanese patients with AD. Except herpes zoster, the safety profile did not significantly differ between the Japanese subpopulation and the entire population. The incidence of herpes zoster tended to be higher in the Japanese subpopulation than in the entire population. A similar tendency was observed in clinical studies in patients with PsA or RA, the approved indications[21)] (Review Report "Rinvoq Tablets 7.5 mg, etc." dated April 9, 2021 and Review Report "Rinvoq Tablets 7.5 mg, etc." dated November 14, 2019), indicating that herpes zoster is not a novel safety concern unique to Japanese patients with AD.

Table 29. Outline of safety of upadacitinib (safety analysis population)

Disease	AD						PsA[a)]		RA[a)]		
Pooled data	Pooled data of 5 placebo-controlled studies (up to Week 16)			Pooled data of 4 long-term studies			Studies M15-572 and M15-554		Pooled data of 9 studies		
Treatment group	15 mg	30 mg	Placebo	15 mg[b)]	30 mg[b)]	All subjects receiving upadacitinib[c)]	15 mg[b)]	Placebo	7.5 mg	15 mg	Placebo
Number of subjects	990	997	992	1,372	1,380	2,752	907	635	226	2,883	1,621
Total exposure	298.6	300.6	282.2	1,407.0	1,446.5	2,853.5	1,247.2	268.7	228.5	3,421.6	389.6
Adverse events	625 (63.1) 381.0	688 (69.0) 461.9	566 (57.1) 331.9	1,001 (73.0) 191.1	1,086 (78.7) 254.2	2,087 (75.8) 219.5	728 (82.3) 177.2	391 (61.6) 248.3	166 (73.5) 316.8	2,260 (78.4) 170.4	784 (48.4) 288.8
Serious adverse events	20 (2.0) 6.8	20 (2.0) 6.7	27 (2.7) 9.7	70 (5.1) 5.1	79 (5.7) 5.6	149 (5.4) 5.4	86 (9.5) 7.2	17 (2.7) 6.4	24 (10.6) 11.2	334 (11.6) 10.3	31 (1.9) 8.0
Death	0	0	0	0	1 (<0.1) <0.1	1 (<0.1) <0.1	2 (0.2) 0.2	2 (0.3) 0.7	0	18 (0.6) 0.5	3 (0.2) 0.8
Adverse events leading to discontinuation	23 (2.3) 7.7	27 (2.7) 9.0	35 (3.5) 12.4	58 (4.2) 4.1	63 (4.6) 4.4	121 (4.4) 4.3	63 (6.9) 5.1	24 (3.8) 9.0	14 (6.2) 6.2	211 (7.3) 6.2	35 (2.2) 9.0
Adverse drug reactions	310 (31.3) 131.9	391 (39.2) 179.1	196 (19.8) 79.9	538 (39.2) 55.6	664 (48.1) 77.3	1,202 (43.7) 65.8	400 (44.1) 47.2	173 (27.2) 78.4	112 (49.6) 110.5	1,244 (43.1) 52.8	347 (21.4) 102.2

Upper row, number of subjects (%); Lower row, incidence per 100 person-years adjusted for the exposure period[d)]; Total exposure period, person-years

a) Only data obtained from approved dosage regimen are included.
b) Includes subjects who switched from placebo.
c) All subjects receiving upadacitinib regardless of dosage regimen
d) Sum of the period until the onset of the first event (treatment period in subjects without event)

[21)] Incidence of herpes zoster in all subjects receiving upadacitinib in Studies M15-572 and M13-554 in patients with PsA (% [number of subjects]): 6.2% (114 of 1828) in the entire population, 22.4% (11 of 49) in the Japanese subpopulation; Incidence of herpes zoster in all subjects receiving upadacitinib in the pooled data of 9 studies in patients with RA: 6.2% (287 of 4638) in the entire population, 18.1% (67 of 371) in the Japanese population.

Table 30. Incidence of adverse events possibly related to upadacitinib (safety analysis population)

Disease	AD						PsA[a]		RA[a]		
Pooled data	Pooled data of 5 placebo-controlled studies (up to Week 16)			Pooled data of 4 long-term studies			Studies M15-572 and M15-554		Pooled data of 9 studies		
Treatment group	15 mg	30 mg	Placebo	15 mg[b]	30 mg[b]	All subjects receiving upadacitinib[c]	15 mg[b]	Placebo	7.5 mg	15 mg	Placebo
Number of subjects	990	997	992	1,372	1,380	2,752	907	635	226	2,883	1,621
Total exposure (person-years)	298.6	300.6	282.2	1,407.0	1,446.5	2,853.5	1,247.2	268.7	228.5	3,421.6	389.6
Infections	377 (38.1) 164.3	423 (42.4) 190.3	296 (29.8) 128.4	718 (52.3) 88.2	773 (56.0) 101.5	1,491 (54.2) 94.6	528 (58.2) 75.6	213 (33.5) 98.0	114 (50.4) 113.7	1,470 (51.0) 68.2	356 (22.0) 103.6
Serious infection	7 (0.7) 2.4	5 (0.5) 1.7	5 (0.5) 1.8	30 (2.2) 2.2	37 (2.7) 2.6	67 (2.4) 2.4	27 (3.0) 2.2	5 (0.8) 1.9	10 (4.4) 4.4	98 (3.4) 2.9	8 (0.5) 2.1
Pneumonia	4 (0.4) 1.3	6 (0.6) 2.0	5 (0.5) 1.8	27 (2.0) 1.9	32 (2.3) 2.2	59 (2.1) 2.1	37 (4.1) 3.0	4 (0.6) 1.5	5 (2.2) 2.2	152 (5.3) 4.5	9 (0.6) 2.3
Pneumocystis jirovecii pneumonia	0	0	0	1 (<0.1) <0.1	0	1 (<0.1) <0.1	0	0	0	0	2 (0.1) 0.5
Active/latent tuberculosis	0	0	0	9 (0.7) 0.6	10 (0.7) 0.7	19 (0.7) 0.7	9 (1.0) 0.7	0	0	67 (2.3) 2.0	0
Opportunistic infection	9 (0.9) 3.0	8 (0.8) 2.7	4(0.4) 1.4	28 (2.0) 2.0	29 (2.1) 2.0	57 (2.1) 2.0	11 (1.2) 0.9	0	2 (0.9) 0.9	26 (0.9) 0.8	4 (0.2) 1.0
Herpes zoster	14 (1.4) 4.7	18 (1.8) 6.0	5 (0.5) 1.8	56 (4.1) 4.1	88 (6.4) 6.3	144 (5.2) 5.2	42 (4.6) 3.4	5 (0.8) 1.9	17 (7.5) 7.8	124 (4.3) 3.7	6 (0.4) 1.5
Reactivation of hepatitis B	0	0	0	0	0	0	1 (0.1) <0.1	0	0	1 (<0.1) <0.1	0
Malignant tumor	3 (0.3) 1.0	6 (0.6) 2.0	0	6 (0.4) 0.4	11 (0.8) 0.8	17 (0.6) 0.6	17 (1.9) 1.4	1 (0.2) 0.4	1 (0.4) 0.4	37 (1.3) 1.1	4 (0.2) 1.0
NMSC	3 (0.3) 1.0	2 (0.2) 0.7	0	4 (0.3) 0.3	6 (0.4) 0.4	10 (0.4) 0.4	9 (1.0) 0.7	1 (0.2) 0.4	0	10 (0.3) 0.3	2 (0.1) 0.5
Malignant tumor other than NMSC	0	4 (0.4) 1.3	0	2 (0.1) 0.1	5 (0.4) 0.3	7 (0.3) 0.2	9 (1.0) 0.7	0	1 (0.4) 0.4	28 (1.0) 0.8	2 (0.1) 0.5
Gastrointestinal perforation	0	0	0	1 (<0.1) <0.1	0	1 (<0.1) <0.1	1 (0.1) <0.1	0	0	6 (0.2) 0.2	0
Interstitial pneumonia	0	0	0	0	0	0	1 (0.1) <0.1	0	0	2 (<0.1) <0.1	0
Dyslipidaemia	13 (1.3) 4.4	16 (1.6) 5.4	6 (0.6) 2.1	32 (2.3) 2.3	40 (2.9) 2.8	72 (2.6) 2.6	46 (5.1) 3.8	12 (1.9) 4.5	22 (9.7) 10.8	242 (8.4) 7.6	19 (1.2) 4.9
MACE	1 (0.1) 0.3	0	0	3 (0.2) 0.2	1 (<0.1) <0.1	4 (0.1) 0.1	4 (0.4) 0.3	1 (0.2) 0.4	1 (0.4) 0.4	16 (0.6) 0.5	4 (0.2) 1.0
Venous thromboembolism	0	0	1 (0.1) 0.4	2 (0.1) 0.1	0	2 (<0.1) <0.1	4 (0.4) 0.3	1 (0.2) 0.4	1 (0.4) 0.4	17 (0.6) 0.5	1 (<0.1) 0.3
Anaemia	3 (0.3) 1.0	14 (1.4) 4.7	4 (0.4) 1.4	15 (1.1) 1.1	41 (3.0) 2.9	56 (2.0) 2.0	23 (2.5) 1.9	6 (0.9) 2.2	4 (1.8) 1.8	123 (4.3) 3.7	28 (1.7) 7.2
Haemoglobin decreased	1 (0.1) 0.3	3 (0.3) 1.0	1 (0.1) 0.4	5 (0.4) 0.4	14 (1.0) 1.0	19 (0.7) 0.7	2 (0.2) 0.2	2 (0.3) 0.7	0	21 (0.7) 0.6	3 (0.2) 0.8
Neutrophil count decreased	11 (1.1) 3.7	30 (3.0) 10.2	3 (0.3) 1.1	24 (1.7) 1.7	41 (3.0) 2.9	65 (2.4) 2.3	19 (2.1) 1.5	2 (0.3) 0.7	5 (2.2) 2.2	84 (2.9) 2.5	5 (0.3) 1.3
Platelet count decreased	0	1 (0.1) 0.3	1 (0.1) 0.4	0	2 (0.1) 0.1	2 (<0.1) <0.1	2 (0.2) 0.2	2 (0.3) 0.7	1 (0.4) 0.4	13 (0.5) 0.4	1 (<0.1) 0.3
Lymphocyte count decreased	2 (0.2) 0.7	3 (0.3) 1.0	3 (0.3) 1.1	4 (0.3) 0.3	10 (0.7) 0.7	14 (0.5) 0.5	16 (1.8) 1.3	5 (0.8) 1.9	7 (3.1) 3.1	59 (2.0) 1.7	18 (1.1) 4.7
Rhabdomyolysis, myopathy	1 (0.1) 0.3	0	1 (0.1) 0.4	1 (<0.1) <0.1	0	1 (<0.1) <0.1	0	0	0	1 (<0.1) <0.1	0
Blood creatine phosphokinase increased	42 (4.2) 14.4	52 (5.2) 17.9	21 (2.1) 7.5	80 (5.8) 6.0	124 (9.0) 9.2	204 (7.4) 7.6	84 (9.3) 7.3	10 (1.6) 3.7	9 (4.0) 4.1	160 (5.5) 4.9	10 (0.6) 2.6
Liver disorder	16 (1.6) 5.4	16 (1.6) 5.4	12 (1.2) 4.3	51 (3.7) 3.7	68 (4.9) 4.9	119 (4.3) 4.3	99 (10.9) 8.6	19 (3.0) 7.2	15 (6.6) 7.0	249 (8.6) 7.7	50 (3.1) 13.0
Renal dysfunction	1 (0.1) 0.3	0	0	1 (<0.1) <0.1	2 (0.1) 0.1	3 (0.1) 0.1	3 (0.3) 0.2	2 (0.3) 0.7	1 (0.4) 0.4	13 (0.5) 0.4	2 (0.1) 0.5
Depression (except suicide and self-injury)	9 (0.9) 3.0	9 (0.9) 3.0	7 (0.2) 2.5	21 (1.5) 1.5	20 (1.4) 1.4	41 (1.5) 1.5	16 (1.8) 1.3	5 (0.8) 1.9	0	37 (1.3) 1.1	7 (0.4) 1.8
Suicide or self-injury	3 (0.3) 1.0	2 (0.2) 0.7	2 (0.2) 0.7	4 (0.3) 0.3	2 (0.1) 0.1	6 (0.2) 0.2	16 (1.8) 1.3	5 (0.8) 1.9	0	39 (1.4) 1.1	7 (0.4) 1.8
Acne	98 (9.9) 35.0	155 (15.5) 57.2	25 (2.5) 9.0	179 (13.0) 14.3	290 (21.0) 24.3	469 (17.0) 19.2	10 (1.1) 0.8	2 (0.3) 0.7	3 (1.3) 1.3	22 (0.8) 0.6	2 (0.1) 0.5

Upper row, number of subjects (%); Lower row, incidence per 100 person-years adjusted for the exposure period[d]

a) Only data obtained from approved dosage regimen are included.
b) Includes subjects who switched from placebo.
c) All subjects receiving upadacitinib regardless of dosage regimen
d) Sum of the period until the onset of the first event (treatment period in subjects without event)

Table 31. Outline of safety of upadacitinib in Japanese patients with AD (safety analysis population, Japanese subpopulation)

Pooled data	Pooled data of 5 placebo-controlled studies (up to Week 16)			Pooled data of 4 long-term studies		
Treatment group	15 mg	30 mg	Placebo	15 mg[a)]	30 mg[a)]	All subjects receiving upadacitinib[b)]
Number of subjects	125	127	124	177	181	358
Total exposure (person-years)	37.9	38.0	35.9	225.5	228.3	453.8
Summary of adverse events						
Adverse events	72 (57.6) 289.2	79 (62.2) 379.6	57 (46.0) 218.8	140 (79.1) 166.5	150 (82.9) 235.0	290 (81.0) 196.1
Serious adverse events	1 (0.8) 2.6	2 (1.6) 5.3	3 (2.4) 8.4	10 (5.6) 4.6	6 (3.3) 2.7	16 (4.5) 3.6
Death	0	0	0	0	0	0
Adverse events leading to discontinuation	2 (1.6) 5.3	2 (1.6) 5.3	6 (4.8) 16.7	7 (4.0) 3.1	6 (3.3) 2.6	13 (3.6) 2.9
Adverse drug reactions	19 (15.2) 56.0	36 (28.3) 116.4	15 (12.1) 45.1	67 (37.9) 39.3	77 (42.5) 49.8	144 (40.2) 44.3
Adverse events possibly related to upadacitinib						
Infections	49 (39.2) 165.9	49 (38.6) 169.9	37 (29.8) 122.5	108 (61.0) 87.0	118 (65.2) 105.1	226 (63.1) 95.6
Serious infection	0	1 (0.8) 2.7	0	5 (2.8) 2.2	5 (2.8) 2.2	10 (2.8) 2.2
Pneumonia	0	0	0	2 (1.1) 0.9	1 (0.6) 0.4	3 (0.8) 0.7
Pneumocystis jirovecii pneumonia	0	0	0	1 (0.6) 0.4	0	1 (0.3) 0.2
Active/latent tuberculosis	0	0	0	0	0	0
Opportunistic infection	4 (3.2) 10.6	1 (0.8) 2.7	1 (0.8) 2.8	11 (6.2) 5.0	8 (4.4) 3.6	19 (5.3) 4.3
Herpes zoster	1 (0.8) 2.6	4 (3.1) 10.7	0	15 (8.5) 7.0	25 (13.8) 11.8	40 (11.2) 9.4
Reactivation of hepatitis B	0	0	0	0	0	0
Malignant tumor	0	0	0	1 (0.6) 0.4	0	1 (0.3) 0.2
NMSC	0	0	0	0	0	0
Malignant tumor other than NMSC	0	0	0	1 (0.6) 0.4	0	1 (0.3) 0.2
Gastrointestinal perforation	0	0	0	0	0	0
Interstitial pneumonia	0	0	0	0	0	0
Dyslipidaemia	0	0	1 (0.8) 2.8	3 (1.7) 1.3	0	3 (0.8) 0.7
MACE	1 (0.8) 2.6	0	0	1 (0.6) 0.4	0	1 (0.3) 0.2
Venous thromboembolism	0	0	0	0	0	0
Anaemia	0	1 (0.8) 2.7	1 (0.8) 2.8	4 (2.3) 1.8	6 (3.3) 2.7	10 (2.8) 2.2
Haemoglobin decreased	0	0	0	1 (0.6) 0.4	3 (1.7) 1.3	4 (1.1) 0.9
Neutrophil count decreased	1 (0.8) 2.7	4 (3.1) 10.8	0	2 (1.1) 0.9	6 (3.3) 2.7	8 (2.2) 1.8
Platelet count decreased	0	0	1 (0.8) 2.8	0	0	0
Lymphocyte count decreased	0	0	0	0	1 (0.6) 0.4	1 (0.3) 0.2
Rhabdomyolysis, myopathy	0	0	0	0	0	0
Blood creatine phosphokinase increased	1 (0.8) 2.6	2 (1.6) 5.3	1 (0.8) 2.8	3 (1.7) 1.3	10 (5.5) 4.5	13 (3.6) 2.9
Liver disorder	1 (0.8) 2.7	2 (1.6) 5.3	0	8 (4.5) 3.7	12 (6.6) 5.5	20 (5.6) 4.6
Renal dysfunction	0	0	0	0	0	0
Depression (except suicide and self-injury)	1 (0.8) 2.6	0	0	2 (1.1) 0.9	0	2 (0.6) 0.4
Suicide or self-injury	0	0	0	0	0	0
Acne	13 (10.4) 36.9	25 (19.7) 75.6	8 (6.5) 22.9	33 (18.6) 17.1	57 (31.5) 32.8	90 (25.1) 24.6

Upper row, number of subjects (%); Lower row, incidence per 100 person-years adjusted for the exposure period[c)]

a) Includes subjects who switched from placebo.
b) All subjects receiving upadacitinib regardless of dosage regimen
c) Sum of the period until the onset of the first event (treatment period in subjects without event)

According to the post-marketing safety information of upadacitinib, there are no new safety concerns among 64,427 adverse events in 28,244 patients (271 events in 170 Japanese patients) reported after the market launch in Japan and foreign countries (August 16, 2019 through February 17, 2021). There are no situations requiring any change in the safety specifications stipulated in the risk management plan, such as infections (e.g., pneumonia and herpes zoster) and interstitial pneumonia.

Based on the above, it is considered possible to control the safety risk in patients with AD receiving upadacitinib by the same safety measures as those currently taken for the approved indications, except for skin infection to be described later.

7.R.3.2 Skin infection

Table 32 shows the incidence of skin infection in Japanese and foreign clinical studies in patients with AD, PsA, or RA. No clear difference was observed among treatment groups in the incidences of skin bacterial infection and fungal skin infection in patients with AD, whereas the incidence of viral skin infection was higher in the upadacitinib groups than in the placebo group, and the incidence was dose-dependent. In the pooled data of 4 long-term studies, serious viral skin infection was observed in 0.5% (7 of 1,372) of subjects receiving 15 mg and in 0.7% (10 of 1,380) of subjects receiving 30 mg. A causal relationship to the study drug could not be ruled out in 6 subjects receiving 15 mg (eczema herpeticum in 3 subjects, herpes zoster, herpes zoster cutaneous disseminated, and herpes zoster disseminated in 1 subject each) and in 10 subjects receiving 30 mg (herpes zoster in 4 subjects, herpes simplex in 3 subjects, eczema herpeticum in 2 subjects, herpes zoster cutaneous disseminated, and herpes zoster disseminated in 1 subject each). Skin bacterial infection and viral skin infection were observed more frequently in patients with AD than in patients with PsA or RA, the diseases for which upadacitinib have already been approved. This may be due to the increased risk of skin bacterial infection in patients with AD (*Br J Dermatol*. 2020;182:1331-42) and to increased occurrence of herpes simplex virus infection and eczema herpeticum in patients with AD. Table 33 shows the incidence of skin infection in Japanese patients with AD, which was not significantly different from the incidence in the entire population.

Taking account of the above clinical study results and of the finding that skin barrier function and skin immune activity are reduced in patients with AD, the applicant plans to provide advice in the package insert, etc., that while treating with upadacitinib, patients with AD should be carefully monitored for the occurrence of skin infection.

Table 32. Incidence of skin infection (safety analysis population)

Disease	AD						PsA[a]		RA[a]		
Pooled data	Pooled data of 5 placebo-controlled studies (up to Week 16)			Pooled data of 4 long-term studies			Studies M15-572 and M13-554		Pooled data of 9 studies		
Treatment group	15 mg	30 mg	Placebo	15 mg[b]	30 mg[b]	All subjects receiving upadacitinib[c]	15 mg[b]	Placebo	7.5 mg	15 mg	Placebo
Number of subjects	990	997	992	1,372	1,380	2,752	907	635	226	2,883	1,621
Total exposure (person-years)	298.6	300.6	282.2	1,407.0	1,446.5	2,853.5	1,247.2	268.7	228.5	3,421.6	389.6
Skin bacterial infection	68 (6.9) 23.8	72 (7.2) 25.0	73 (7.4) 27.2	163 (11.9) 12.6	182 (13.2) 14.0	345 (12.5) 13.3	49 (5.4) 4.1	9 (1.4) 3.4	10 (4.4) 4.7	100 (3.5) 3.0	16 (1.0) 4.1
Fungal skin infection	12 (1.2) 4.0	10 (1.0) 3.3	6 (0.6) 2.1	41 (3.0) 3.0	60 (4.3) 4.3	101 (3.7) 3.6	28 (3.1) 2.3	4 (0.6) 1.5	5 (2.2) 2.2	58 (2.0) 1.7	7 (0.4) 1.8
Viral skin infection	64 (6.5) 22.2	108 (10.8) 38.3	25 (2.5) 9.0	171 (12.5) 13.3	250 (18.1) 19.9	421 (15.3) 16.6	66 (7.3) 5.5	12 (1.9) 4.5	27 (11.9) 13.4	199 (6.9) 6.0	16 (1.0) 4.1
Herpes simplex virus infection[d]	40 (4.0) 13.7	80 (8.0) 27.9	17 (1.7) 6.1	91 (6.6) 6.8	146 (10.6) 11.1	237 (8.6) 8.9	28 (3.1) 2.3	8 (1.3) 3.0	11 (4.9) 5.2	80 (2.8) 2.4	10 (0.6) 2.6
Eczema herpeticum[e]	9 (0.9) 3.0	8 (0.8) 2.7	4 (0.4) 1.4	27 (2.0) 1.9	28 (2.0) 2.0	55 (2.0) 2.0	0	0	0	0	0

Upper row, number of subjects (%); Lower row, incidence per 100 person-years adjusted for the exposure period[f]

a) Only data obtained from approved dosage regimen are included.
b) Includes subjects who switched from placebo.
c) All subjects receiving upadacitinib regardless of dosage regimen
d) Genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, herpes virus infection, nasal herpes, ophthalmic herpes simplex, oral herpes, proctitis herpes
e) Kaposi's varicelliform eruption, eczema herpeticum
f) Sum of the period until the onset of the first event (treatment period in subjects without event)

Table 33. Incidence of skin infection in Japanese patients with AD (safety analysis population, Japanese subpopulation)

Pooled data	Pooled data of 5 placebo-controlled studies (up to Week 16)			Pooled data of 4 long-term studies		
Treatment group	15 mg	30 mg	Placebo	15 mg[a]	30 mg[a]	All subjects receiving upadacitinib[b]
Number of subjects	125	127	124	177	181	358
Total exposure (person-years)	37.9	38.0	35.9	225.5	228.3	453.8
Skin bacterial infection	10 (8.0) 27.7	8 (6.3) 21.9	13 (10.5) 38.2	33 (18.6) 16.5	28 (15.5) 13.8	61 (17.0) 15.2
Fungal skin infection	0	1 (0.8) 2.7	3 (2.4) 8.5	7 (4.0) 3.2	11 (6.1) 5.0	18 (5.0) 4.1
Viral skin infection	9 (7.2) 24.7	14 (11.0) 39.7	4 (3.2) 11.3	37 (20.9) 18.5	45 (24.9) 24.1	82 (22.9) 21.2
Herpes simplex virus infection[c]	5 (4.0) 13.6	8 (6.3) 22.0	4 (3.2) 11.2	17 (9.6) 7.9	16 (8.8) 7.6	33 (9.2) 7.8
Eczema herpeticum[d]	4 (3.2) 10.6	1 (0.8) 2.7	1 (0.8) 2.8	10 (5.6) 4.5	8 (4.4) 3.6	18 (5.0) 4.1

Upper row, number of subjects (%); Lower row, incidence per 100 person-years adjusted for the exposure period[e]

a) Includes subjects who switched from placebo.
b) All subjects receiving upadacitinib regardless of dosage regimen
c) Genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, herpes virus infection, nasal herpes, ophthalmic herpes simplex, oral herpes, proctitis herpes
d) Kaposi's varicelliform eruption, eczema herpeticum
e) Sum of the period until the onset of the first event (treatment period in subjects without event)

PMDA's view based on the reviews in Sections 7.R.3.1 and 7.R.3.2:

Patients with AD are prone to bacterial, fungal, and viral infection due to decreased skin barrier function and decreased skin immune activity (Clinical Practice Guidelines for AD 2018). However, clinical studies of upadacitinib in patients with AD showed not only that the incidence of viral skin infection was higher than the incidence in patients with approved indications, but also that viral skin infection occurred more frequently in the upadacitinib group than in the placebo group, showing a

tendency of dose-dependent increase, and that serious skin infection for which a causal relationship to upadacitinib could not be ruled out was observed in a certain number of subjects. Accordingly, the applicant should add precautions for infection in the current package insert of upadacitinib with immunosuppressive activity, alert physicians to the occurrence of skin infection, and closely monitor the occurrences continuously.

As for the safety risk other than skin infection, there is no new safety concern unique to patients with AD compared with the safety profile in the approved indications, as judged from the submitted clinical study data and the post-marketing safety information in Japan and other countries, although there are limits to direct comparison because of the difference in patient characteristics, concomitant drugs, etc., from study to study. The applicant should take similar safety measures for patients with AD as those taken for diseases with approved indications, such as providing precautions that physicians should monitor carefully for known adverse drug reactions and that upadacitinib should be used by physicians in medical institutions capable of emergency response.

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

7.R.4 Clinical positioning

The applicant's explanation about the expected clinical positioning of upadacitinib in the treatment of AD:

For the drug therapy of AD, a step-wise treatment based on severity is recommended. Thus, the basis of drug therapy is disease control with topical anti-inflammatory drugs such as TCS and TCI with the continuous use of topical moisturizing agents. When the disease becomes inadequately responsive to the above topical treatments, systemic treatment such as oral cyclosporine is performed. Because of the safety concerns in the long-term use of oral cyclosporine, a short-period or intermittent administration is recommended (Clinical Practice Guidelines for AD 2018). In recent years, dupilumab (genetical recombination) and baricitinib have been approved with indication for AD, providing new options of systemic therapies.

With the above treatment algorithm in mind, a clinical study was conducted in patients with AD who had a certain level of disease activity in spite of extensive topical treatment, requiring systemic treatment [see Section 7.R.1]. Upadacitinib was shown to be effective and safe in this patient population [see Sections 7.R.2 and 7.R.3], suggesting that upadacitinib is positioned as a treatment option for patients who have an inadequate response to due treatment with topical anti-inflammatory drugs, as is the case with approved systemic drugs for AD.

As for co-administration with topical therapy, since topical moisturizing agents are essential for the recovery and maintenance of the skin barrier function, and clinical study protocols of upadacitinib required the use of topical moisturizing agents every day, topical moisturizing agents should be used continuously in combination with upadacitinib, and this will be described in the package insert. For topical anti-inflammatory drugs, the efficacy of upadacitinib was demonstrated either with or without TCS in combination, as shown in the monotherapy study (Study M16-045) and in TCS combination

studies (Studies M16-047 and M17-377). Accordingly, it is desirable to consider co-administration with anti-inflammatory drugs, depending on the condition of the lesion.

PMDA's view:
Given the currently available efficacy and safety profile of upadacitinib and the treatment algorithm for AD, upadacitinib is expected to be similarly positioned as approved systemic drugs such as JAK inhibitors, as explained by the applicant.

Clinical studies demonstrated the efficacy of upadacitinib with or without topical anti-inflammatory drugs, without any serious safety concern. In Japan, however, the standard therapy for AD is combination of topical moisturizing agents and topical anti-inflammatory drugs. Based on the above, as a rule, upadacitinib should be used in combination with a topical anti-inflammatory drug, with the continuous use of topical moisturizing agents. Since upadacitinib has an immunosuppressive activity, co-administration with the following drug should be avoided: Biological drugs for AD, other oral JAK inhibitors, and immunosuppressants such as cyclosporine. Thus, similar precautions should be provided as those for approved JAK inhibitors for AD.

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

7.R.5 Indications

Based on the submitted data, and the review in Sections 7.R.2, 7.R.3, and 7.R.4, PMDA considers that upadacitinib should be indicated for "atopic dermatitis that have an inadequate response to conventional treatments" as proposed and that the following precautions should be provided in the package insert, as is the case with approved JAK inhibitors and biological products used for AD:

- Upadacitinib should be used in patients with wide-spread, severe inflammatory rash who have an inadequate response even after a certain period of appropriate treatment with topical anti-inflammatory drugs, such as TCS and TCI.
- As a general rule, upadacitinib should be administered in combination with topical anti-inflammatory drugs according to the conditions of the site affected by AD
- A topical moisturizing agent should be used continuously during the treatment with upadacitinib.

Information on the inclusion criteria in clinical studies should be provided as reference information for selecting patients eligible for treatment with upadacitinib. Also, caution should be provided that only physicians well versed in the diagnosis and treatment of AD should use upadacitinib, in order to facilitate appropriate diagnosis and selection of patients treatable with upadacitinib and proper use of upadacitinib.

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

7.R.6 Dosage and administration

The applicant's explanation about the dosage regimen of upadacitinib for AD:

Dosage regimen in adults

Based on the clinical study results and the descriptions in the guidelines in Japan and foreign countries shown in (a) to (c) below, "once daily 15 or 30 mg administration" was proposed as the appropriate dosage regimen of upadacitinib. However, when the appropriateness of the dosage regimen was re-evaluated during the review process, it was determined that while some of adverse events tended to increase in a dose-dependent manner, clinically significant efficacy was observed even at 15 mg as well. Also, an additional effect of 30 mg to that of 15 mg could be expected, as shown in (d) below. Because of these findings, it was considered that the usual dose should be 15 mg once daily and that the dose may be increased to 30 mg, depending on the patient's condition. In the patient subpopulation aged ≥65 years, the incidences of serious adverse events, adverse events leading to discontinuation, serious infection, anaemia, etc., tended to be higher in patients receiving 30 mg than in patients receiving 15 mg.[22)] Accordingly, it will be advised that elderly patients aged ≥65 years should be treated with upadacitinib 15 mg.

(a) Studies M16-045 and M16-047 confirmed the superiority of upadacitinib to placebo, both at 15 mg and 30 mg, and showed a superior improving effect of 15 mg and 30 mg to placebo in other efficacy endpoints as well (Tables 12, 18, 27, 28). A paired comparison of 2 doses showed that efficacy tended to be higher in 30 mg group than in 15 mg group in multiple efficacy endpoints (Tables 27 and 28). A similar tendency was observed in Study M17-377 as well (Table 28).

(b) For safety, tolerability of upadacitinib was acceptable both at 15 and 30 mg [see Section 7.R.3], while the incidences of adverse events, adverse drug reactions, and some events including herpes zoster tended to be higher at 30 mg than at 15 mg (Tables 29 and 30). A similar tendency was observed in the Japanese subpopulation as well (Table 31).

(c) According to the Japanese and foreign clinical practice guidelines, it is considered important in the treatment of AD to select a treatment method based on the condition of individual patients, by taking account of not only the severity of the disease but also the patient characteristics (e.g., age, treatment history, concurrent illness) and the patient's request for treatment (Clinical Practice Guidelines for AD 2018, *J Am Acad Dermatol*. 2014;71:327-49).

(d) Table 34 shows the changes over time in the rate of achieving EASI-75 among subjects who failed to achieve EASI-50 during in Period 2 of Study M16-048 and received the rescue treatment with upadacitinib 30 mg under blinded conditions. All populations showed a tendency of improvement in the rate of achieving EASI-75 after the start of the rescue treatment, although caution is required in the interpretation of the results.

---

22) The number of subjects with events of each event per 100 person-years adjusted for the exposure period, classified by age group (<65 years, ≥65 years) in the pooled data of 4 long-term studies [(a) subjects aged <65 years receiving 15 mg (1,323 subjects; total exposure period, 1366.2 person-years), (b) subjects aged <65 years receiving 30 mg (1,311 subjects; total exposure period, 1377.0 person-years), (c) subjects aged ≥65 years of receiving 15 mg (49 subjects; total exposure period, 40.8 person-years), (d) subjects aged ≥65 years receiving 30 mg (69 subjects; total exposure period, 69.4 person-years)] was as follows: Serious adverse events, (a) 6.7, (b) 6.6, (c) 9.8, (d) 37.4; adverse events leading to discontinuation, (a) 4.4, (b) 4.7, (c) 12.3, (d) 20.2; serious infection, (a) 2.5, (b) 2.8, (c) 0, (d) 10.1; and anaemia, (a) 1.2, (b) 2.5, (c) 4.9, (d) 21.6.

Table 34. Rate of achieving EASI-75 in subjects receiving the rescue treatment (upadacitinib 30 mg) (Study M16-048, observed cases [OC])

Treatment group Period 1 → Period 2	At the start of Period 2	At the start of rescue treatment	8 weeks after the start of rescue treatment	Treatment group Period 1 → Period 2	At the start of Period 2	At the start of rescue treatment	8 weeks after the start of rescue treatment
P → P	0 (0/8)	0 (0/8)	50 (4/8)	P → 30 mg	0 (0/1)	0 (0/1)	100 (1/1)
7.5 mg → P	23 (3/13)	0 (0/13)	58 (7/12)	7.5 mg → 7.5 mg	9 (1/11)	0 (0/11)	30 (3/10)
15 mg → P	65 (11/17)	0 (0/17)	94 (15/16)	15 mg → 15 mg	50 (6/12)	0 (0/12)	56 (5/9)
30 mg → P	77 (10/13)	0 (0/13)	69 (9/13)	30 mg → 30 mg	67 (2/3)	0 (0/3)	33 (1/3)

% (number of patients); P, placebo

Dosage regimen in children aged ≥12 years

Given the following findings, the currently available data suggest that the efficacy and safety profiles of upadacitinib in pediatric patients with AD aged ≥12 years are similar to those in adult patients with AD and that there are no new safety concerns unique to pediatric patients with AD.

- The population pharmacokinetic analysis using the data of clinical studies in patients with AD and healthy subjects did not identify age and body weight as covariates [see Section 6.2.1]. The exposure to upadacitinib estimated by the above population pharmacokinetic model did not show any clear difference between patients with AD aged <18 years and patients aged ≥18 years.
- Table 35 shows the results of the subpopulation analysis on efficacy by age group in Studies M16-045, M16-047, and M17-377. All subpopulations showed a similar efficacy as that observed in the entire population.
- Table 36 shows the outline of safety of upadacitinib in the subpopulation aged <18 years in Japanese and foreign clinical studies in patients with AD. No clear difference was observed in the population aged <18 years although there are limitations to the comparison with the entire population due to the limited number of subjects (Tables 29 and 31).
- Mice with mutations in the JAK-STAT signaling system show abnormality in bone growth (*JAK-STAT*. 2013;2:e23930), and upadacitinib and other JAK inhibitors cause abnormalities in fetal skeleton formation (see Review Report "Rinvoq Tablets 7.5 mg, etc." dated November 14, 2019). These results suggest the possibility that inhibition of JAK-STAT signaling may affect the bone development and growth. However, clinical studies on upadacitinib did not show any effect on the growth of patients with AD aged ≥12 and <18 years.
  - The change in height from baseline in subjects aged ≥12 and <18 years (mean ± standard deviation [number of subjects]) was 0.613 ± 1.53 cm (120 subjects) in the 15 mg group, 0.634 ± 2.31 cm (117 subjects) in the 30 mg group, and 0.428 ± 2.22 cm (111 subjects) in the placebo group at Week 16 in the pooled data of 5 placebo-controlled studies; and 1.72 ± 2.66 cm (111 subjects) in subjects receiving 15 mg and 1.65 ± 3.13 cm (111 subjects) in subjects receiving 30 mg in the pooled data of 4 long-term studies.
  - In Study M17-377, height data were collected from subjects aged ≥12 and <18 years during and before the study (≥10 years at the longest) and, using the growth curve and the height velocity curve, the effect on growth was evaluated individually by confirming the detailed supplementary data such as body weight, prior treatment, concomitant drugs, etc. Results showed no findings suggestive of the effect of upadacitinib on growth in any of 29 subjects studied.

However, the dose for pediatric patients aged ≥12 years will be limited to 15 mg for the time being, for the following reasons: (a) A dose-dependent occurrence of some adverse events was observed in

clinical studies, and (2) while safety data on 15 mg have been collected including those in other diseases, safety information on 30 mg is insufficient for concluding the benefit-risk balance of each dose in pediatric patients, the new intended population. When additional safety data have been collected from the additional studies[23] of Studies M16-045, M16-047, etc., the benefit-risk balance of upadacitinib 30 mg in pediatric patients aged ≥12 years of will be evaluated.

In clinical studies in pediatric patients aged ≥12 years, an intended patient group for treatment with upadacitinib, body weight had been ≥40 kg, and the same criterion had been included in the proposed dosage and administration, but the criterion was relaxed to ≥30 kg for the following reasons:

- The exposure to upadacitinib in pediatric patients weighing ≥30 kg was estimated by the population pharmacokinetic model renewed using pharmacokinetic data obtained from pediatric patients with AD and patients with juvenile idiopathic arthritis. Results showed that the exposure was similar between adult patients weighing ≥40 kg and pediatric patients [see Section 6.R].
- In the phase III study in patients with AD, upadacitinib 15 mg was administered to 2 adult patients weighing <40 kg, and pharmacokinetic samples were collected. The exposure in both patients was estimated to be similar to that in the entire population [see Section 6.R]. They showed improvement in EASI score and vIGA-AD score, with no serious safety concerns.[24]

According to the body weight growth curve in Japanese people reported in recent years, body weight is ≥30 kg in >98% of Japanese aged ≥12 and <18 years (*Clin Pediatr Endocrinol.* 2016;25:71-6), which suggests that most of pediatric patients with AD aged ≥12 years become eligible for the treatment with upadacitinib by the above relaxation in the body weight criterion. As for pediatric patients with AD aged <12 years, the appropriate dose in each body weight subgroup is being estimated in the foreign phase I study (Study M16-049). Japan will participate in a global phase III study in pediatric patients with AD aged <12 years, which will be conducted based on the results of the above study.

Table 35. Results of main efficacy endpoints at Week 16, by age group (ITT_M population,[a] NRI-C[b])

Study	Age group	Rate of achieving vIGA-AD (0, 1)			Rate of achieving EASI-75		
		15 mg	30 mg	Placebo	15 mg	30 mg	Placebo
M16-045	<18 years	38.1 (16/42)	69.0 (29/42)	7.5 (3/40)	71.4 (30/42)	83.3 (35/42)	8.3 (3/40)
	≥18 years	49.9 (119/239)	60.8 (148/243)	8.6 (21/241)	69.3 (166/239)	79.1 (192/243)	17.7 (43/241)
M16-047	<18 years	30.8 (12/39)	64.9 (24/37)	7.5 (3/40)	56.4 (22/39)	75.7 (28/37)	30.0 (12/40)
	≥18 years	40.9 (107/261)	57.7 (150/260)	11.4 (30/264)	65.8 (172/261)	77.4 (201/260)	26.0 (69/264)
M17-377	<18 years	70.0 (7/10)	50.0 (5/10)	11.1 (1/9)	70.0 (7/10)	90.0 (9/10)	22.2 (2/9)
	≥18 years	37.0 (30/81)	46.9 (38/81)	6.2 (5/81)	64.2 (52/81)	72.8 (59/81)	17.3 (14/81)

% (number of subjects)

a) ITT population in Study M17-377

b) Non-responder imputation with the following exceptions (without exception [b] in Study M17-377). After the start of rescue therapy, subjects were regarded as non-responders.
   (a) If a subject was judged as a responder both before and after the scheduled visit, he/she was regarded as a responder on the day of the visit.
   (b) COVID-19-related missing values were imputed by a multiple imputation method.

[23] The additional studies use the same design as the main study of Studies M16-045 and M16-047. After the target number of subjects for the main study was enrolled, enrollment of patients with AD aged ≥12 and <18 years was continued (target sample size for the main and additional studies combined: 180 subjects [60 per group]) and completed as of [redacted] 20[redacted]. According to the applicant, 372 subjects are participating in the ongoing 2 studies combined, and the safety of upadacitinib (including the incidence of adverse events related to height and bone growth) will continue to be monitored in the studies, which will last for 5 years.

[24] In 1 subject (7[redacted]-year-old woman) in Study M18-891, treatment was discontinued because of a serious adverse event (flares of AD), but the event was unrelated to the study drug.

Table 36. Outline of safety of upadacitinib in patients with AD aged ≥12 and <18 years (safety analysis population)

Study	Pooled data of 5 placebo-controlled studies (up to Week 16)			Pooled data of 4 long-term studies		
Treatment group	15 mg	30 mg	Placebo	15 mg[a)]	30 mg[a)]	All subjects receiving upadacitinib[b)]
Entire population						
Number of subjects	124	124	124	181	180	361
Total exposure (person-years)	37.7	37.9	35.9	194.3	197.0	391.3
Adverse events	83 (66.9) 402.9	91 (73.4) 450.4	59 (47.6) 253.3	135 (74.6) 193.7	136 (75.6) 245.4	271 (75.1) 216.6
Serious adverse events	3 (2.4) 8.0	0	3 (2.4) 8.5	9 (5.0) 4.7	4 (2.2) 2.1	13 (3.6) 3.4
Death	0	0	0	0	0	0
Adverse events leading to discontinuation	3 (2.4) 8.0	0	3 (2.4) 8.4	9 (5.0) 4.6	6 (3.3) 3.1	15 (4.2) 3.9
Adverse drug reactions	37 (29.8) 122.4	41 (33.1) 136.5	15 (12.1) 45.8	67 (37.0) 49.8	76 (42.2) 63.1	143 (39.6) 56.1
Japanese subpopulation						
Number of subjects	11	12	10	16	16	32
Total exposure (person-years)	3.4	3.7	3.1	19.9	18.3	38.2
Adverse events	9 (81.8) 428.6	10 (83.3) 601.7	6 (60.0) 314.9	12 (75.0) 140.9	14 (87.5) 378.8	26 (81.3) 212.9
Serious adverse events	0	0	0	1 (6.3) 5.1	0	1 (3.1) 2.6
Death	0	0	0	0	0	0
Adverse events leading to discontinuation	0	0	0	1 (6.3) 5.1	1 (6.3) 5.5	2 (6.3) 5.3
Adverse drug reactions	2 (18.2) 65.5	2 (16.7) 60.9	1 (10.0) 35.2	6 (37.5) 37.9	4 (25.0) 27.8	10 (31.3) 33.1

Upper row, number of subjects (%); Lower row, incidence per 100 person-years adjusted for the exposure period[c)]
a) Includes subjects who switched from placebo.
b) All subjects receiving upadacitinib regardless of dosage regimen
c) Sum of the period until the onset of the first event (treatment period in subjects without event)

PMDA's view:

Taking account of the above explanation of the applicant, submitted data, and the reviews in Sections 7.R.2 and 7.R.3, it is acceptable to specify the usual dose of upadacitinib in adult patients with AD as once daily administration of 15 mg, with the option of once daily administration of 30 mg depending on the patient condition. However, given that the incidence of some adverse events tended to be higher at 30 mg than at 15 mg in clinical studies in non-elder subjects as well (Tables 29 to 31), and that an appropriate dose should be chosen with consideration given to the severity, age, treatment history, etc., of individual patients, instead of uniformly requiring 15 mg administration in the elderly aged ≥65 years, appropriate dose selection should be encouraged by providing to healthcare professionals information on dose-dependent occurrences of adverse events in clinical studies and on the incidence of adverse events by age group, in the form of the package insert and materials for healthcare professionals.

It is acceptable to specify the dosage regimen for pediatric patients with AD aged ≥12 years as 15 mg once daily administration. It is also acceptable to a certain extent to specify the body weight criterion in this patient group as ≥30 kg, given the information thus far available. However, since pediatric patients with AD weighing ≥30 kg to <40 kg were not included in clinical studies and since there are limited studies on the efficacy and safety in Japanese pediatric patients, information on upadacitinib administration in pediatric patients with AD, which will be obtained from the additional studies of

ongoing Studies M16-045 and M16-047 and from the specified use-results survey planned by the applicant [see Section 7.R.7], should be provided promptly to healthcare professionals.

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

7.R.7 Post-marketing safety measures

In order to confirm the safety and efficacy in clinical use after the market launch, including the safety and efficacy during a long-term treatment, the applicant plans to conduct, in addition to the usual pharmacovigilance activities, Studies M16-045, M16-047, and M17-377 continuously after marketing approval, and a specified use-results survey in patients with AD aged ≥12 and <18 years.

PMDA's view:

As reviewed in Section 7.R.3, there are no new safety concerns currently, except skin infection, unique to patients with AD compared with the safety profile in the approved indications. Since skin infection is considered to be manageable by appropriate precautions, upadacitinib has an acceptable safety profile in patients with AD. Given the limited number of Japanese pediatric patients with AD investigated in clinical studies, it is necessary to further investigate the safety and efficacy of upadacitinib, including those in the long-term administration, by extended phase III studies and a specified use-results survey, as planned by the applicant. The specified use-results survey, in particular, should be conducted by an appropriate method to allow collection of a certain amount of safety and efficacy data in pediatric patients with AD aged ≥12 years weighing ≥30 kg to <40 kg, the patient group not investigated in clinical studies, and information thus collected should be provided to healthcare professionals in an appropriate manner. Although upadacitinib did not show any effect on bone growth in clinical studies, many subjects had reached the adult height at the start of the study. Information on the effect of upadacitinib on bone growth in patients including those during the growth stage should be collected from post-marketing surveillance and from published literature.

Upadacitinib should be used by physicians with sufficient knowledge on upadacitinib and with sufficient knowledge and experience of treating AD and, in the event of serious infection, etc., the patients should be treated in collaboration with other medical departments or institutions. In addition, information should be provided to physicians and other healthcare professionals by using materials to facilitate the proper use of upadacitinib.

The above conclusions of PMDA and the necessity of additional safety measures will be discussed at the Expert Discussion.

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

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that upadacitinib has efficacy in the treatment of atopic dermatitis that have an inadequate response to conventional treatment, and that upadacitinib has acceptable safety in view of its benefits. Upadacitinib provides a new treatment option for patients with atopic dermatitis who have an inadequate response to conventional treatment, and thus upadacitinib is clinically meaningful. The safety in clinical use in Japanese patients with AD should be further investigated via post-marketing surveillance.

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

10. Other

Methods for efficacy evaluation and definitions of endpoints in clinical studies of upadacitinib are as shown below.

Endpoint	Definition
EASI score	For each of 4 body regions (head/neck, trunk, upper extremities, lower extremities), calculate the sum of severity (none = 0, mild = 1, moderate = 2, severe = 3) of 4 elements of rash (erythema, thickening, excoriation, lichenification), multiply region score based on the area of eczema (0% = 0, 1%-9% = 1, 10%-29% = 2, 30%-49% = 3, 50%-69% = 4, 70%-89% = 5, 90%-100% = 6), multiply the factor of each body region (head/neck = 0.1, trunk = 0.3, upper extremities = 0.2, lower extremities =0.4), and total the body region scores. Minimum score = 0, maximum score = 72.
vIGA-AD score	Physician-assessed global score of rash according to the following 5-point rating scale: 0 Clear: No inflammatory sign of AD (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present. 1 Almost clear: Barely perceptible erythema, barely perceptible induration/papulation, or minimal lichenification. No oozing or crusting. 2 Mild: Slight but definite erythema (pink), slight but definite induration/papulation, or slight but definite lichenification. No oozing or crusting. 3 Moderate: Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, or clearly perceptible lichenification. Oozing and crusting may be present. 4 Severe: Marked erythema (deep or bright red), marked induration/papulation, or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.
Pruritus NRS score	A scale for evaluating pruritus according to the 11-point rating scale of 0 (no itch) to 10 (worst imaginable itch). Subjects are asked to rate the intensity of their worst itch over the previous 24 hours.
Rate of achieving EASI-50 Rate of achieving EASI-75 Rate of achieving EASI-90 Rate of achieving EASI-100	Percentage of subjects showing ≥50%, ≥75%, ≥90%, or 100% decrease in EASI score from baseline
Rate of achieving vIGA-AD (0, 1)	Percentage of subjects who achieved vIGA-AD score of 0 (disappeared) or 1 (almost disappeared) by decreasing from baseline by ≥2.

Review Report (2)

July 16, 2021

Product Submitted for Approval

Brand Name	(a) Rinvoq Tablets 7.5 mg (b) Rinvoq Tablets 15 mg (c) Rinvoq Tablets 30 mg
Non-proprietary Name	Upadacitinib Hydrate
Applicant	AbbVie GK
Date of Application	October 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, clinical positioning, indications, and dosage and administration

At the Expert Discussion, the expert advisors generally supported the PMDA's conclusion on the efficacy, clinical positioning, indications, and dosage and administration presented in the Review Report (1), with the following comments:

- The efficacy of upadacitinib increases in a dose-dependent manner, but the incidence of adverse events also increases dose-dependently. It is therefore understandable to determine 15 mg as the usual dose for adult patients with AD and to make 30 mg available as an option depending on the patient condition. Specific information on the choice between 15 mg and 30 mg, including the data from clinical studies, should be provided to healthcare professionals.

In addition, the following comments were raised by the expert advisors:

(1) The efficacy and safety of upadacitinib have not been investigated in pediatric patients with AD aged ≥12 years weighing <40 kg. When additional data become available from the ongoing clinical study in pediatric patients with AD aged <12 years, it is appropriate to discuss whether to accept pediatric patients weighing <40 kg as eligible patients for upadacitinib therapy.

(2) Pediatric patients with AD are often underweight. It is understandable to determine that pediatric patients with AD aged ≥12 years are eligible if they weigh ≥30 kg, although available information is limited.

In view of the discussion, etc., at the Expert Discussion, PMDA instructed the applicant to disseminate the following information, which is useful for selecting the dose of upadacitinib, through a guide for healthcare professionals:

(a) The efficacy results of upadacitinib 15 and 30 mg.
(b) The fact that some adverse events occurred dose-dependently.
(c) The incidence of adverse events by age group.

The applicant agreed to take appropriate actions.

Also, PMDA concluded that, in order to accept pediatric patients with AD aged ≥12 years weighing ≥30 kg to <40 kg as eligible patients for treatment with upadacitinib, it is necessary to provide the following precautions for careful use and to collect information from this patient population and provide the information thus obtained to healthcare professionals. PMDA instructed the applicant to take the above safety measures, and the applicant agreed to take appropriate actions.

- The package insert and the guide for healthcare professionals should contain the following precautionary statement:

  No clinical study data are available on the efficacy or safety in pediatric patients with AD weighing ≥30 kg to <40 kg. When upadacitinib is administered to such patients, it should be used with care and the patients should be closely monitored.
- In the specified use-results survey in pediatric patients with AD, information on pediatric patients weighing ≥30 kg to <40 kg should be collected as soon as possible and provided to healthcare professionals. Other information useful in upadacitinib administration to pediatric patients weighing ≥30 kg to <40 kg, including the results of the ongoing clinical studies, should also be provided promptly to healthcare professionals.

1.2 Safety and risk management plan (draft)

The expert advisors supported the conclusion by PMDA on the safety of upadacitinib and post-marketing safety measures presented in the Review Report (1).

In view of the review in Section "7.R.7 Post-marketing safety measures" in the Review Report (1) and the discussion at the Expert Discussion, PMDA has concluded that the current risk management plan (draft) for upadacitinib should include the safety and efficacy specifications presented in Table 37, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Table 38. PMDA instructed the applicant to conduct post-marketing surveillances, etc., that allow investigations of these items.

Table 37. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious infection (including tuberculosis, pneumonia, *Pneumocystis jirovecii* pneumonia, sepsis, opportunistic infection) • Herpes zoster • Venous thromboembolism • Gastrointestinal perforation • Hepatic dysfunction • Interstitial pneumonia • Neutrophil count decreased, lymphocyte count decreased, haemoglobin decreased • Reactivation of hepatitis B	• Malignant tumor • Cardiovascular events • Rhabdomyolysis, myopathy • Renal dysfunction	• None
Efficacy specification		
• None		

(No change)

Table 38. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance (PsA) • Early post-marketing phase vigilance (AD) • Specified use-results survey [long-term survey] (RA) • Specified use-results survey [≥12 and <18 years of age] (AD) • Post-marketing database survey [malignant tumor] (RA) • Post-marketing database survey [cardiovascular events and venous thromboembolism] (RA) • Post-marketing database survey [serious infection] (PsA) • Post-marketing clinical study (RA)[a)] • Post-marketing clinical study (PsA)[b)]	• None	• Disseminate data gathered during early post-marketing phase vigilance (PsA) • Disseminate data gathered during early post-marketing phase vigilance (AD) • Prepare and distribute materials for healthcare professionals (a proper use guide) • Prepare and distribute patient card • Ensure to disseminate information on proper use prior to delivery of upadacitinib.

a) Clinical studies in patients with RA (Studies M13-545, M15-555, and M14-663) will be reclassified as post-marketing clinical studies after approval.

b) Clinical studies in patients with PsA (Studies M15-554 and M15-572) will be reclassified as post-marketing clinical studies after approval.

(The underlined words are added to the proposed text.)

The applicant's explanation:

As shown in Table 39, a specified use-results survey will be conducted in patients with AD aged ≥12 and <18 years, with an observation period of 104 weeks and a target sample size of 170 patients. The survey will investigate the long-term safety and efficacy of upadacitinib in clinical use based on the following safety specifications:

Serious infections (including tuberculosis, pneumonia, *Pneumocystis jirovecii* pneumonia, sepsis, and opportunistic infection), herpes zoster, venous thromboembolism, gastrointestinal perforation, hepatic dysfunction, interstitial pneumonia, neutrophil count decreased, lymphocyte count decreased, hemoglobin decreased, reactivation of hepatitis B virus, malignant tumor, cardiovascular events, rhabdomyolysis, myopathy, and renal dysfunction.

The applicant will also promptly collect data from patients weighing <40 kg, a population not investigated in clinical studies, to further evaluate the safety and efficacy of upadacitinib.

Table 39. Outline of specified use-results survey (≥12 and <18 years of age, long-term survey) (AD) (draft)

Objective	To collect and identify information on the long-term safety and efficacy of upadacitinib in patients with AD aged ≥12 and <18 years in clinical use.
Survey method	Central registry system
Population	Patients with AD aged ≥12 and <18 years
Observation period	104 weeks
Planned sample size	170 (safety analysis population)
Main survey items	• Safety specification: Serious infections (including tuberculosis, pneumonia, *Pneumocystis jirovecii* pneumonia, sepsis, and opportunistic infection), herpes zoster, venous thromboembolism, gastrointestinal perforation, hepatic dysfunction, interstitial pneumonia, neutrophil count decreased, lymphocyte count decreased, hemoglobin decreased, reactivation of hepatitis B virus, malignant tumor, cardiovascular events, rhabdomyolysis, myopathy, and renal dysfunction. • Patient characteristics (age, height, body weight, severity of AD, disease duration, past illness/complications, etc.) • Exposure to upadacitinib • Prior treatment for AD • Concomitant drugs, concomitant therapies • Laboratory tests • Adverse events • Efficacy evaluation

PMDA accepted the above response of the applicant. The information thus obtained should be provided appropriately and promptly to healthcare professionals, etc.

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

2.1 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.

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

The new drug application data (CTD 5.3.5.1-1, CTD 5.3.5.1-1-2, CTD 5.3.5.1-3, and CTD 5.3.5.1-3-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA concluded that the product may be approved after modifying the proposed indications and the dosage and administration as shown below, with the following approval condition. Although the present application is for drugs with new indications and new dosage, the re-examination period for the present application is the remainder of re-examination period for the initial approval of the product (until January 22, 2028) because it has more than 4 years left. Rinvoq

Tablets 30 mg is not classified as a biological product or a specified biological product. The drug product is classified as poisonous drugs.

Indications

(a) (b) The following diseases that have an inadequate response to conventional treatments:
Rheumatoid arthritis (including prevention of structural joint damage)
Psoriatic arthritis
Atopic dermatitis

(c) The following disease that has an inadequate response to conventional treatments:
Atopic dermatitis

(The underlined words are added to the proposed text.[25])

Dosage and Administration

(a) (b) Rheumatoid arthritis
The usual adult dosage is 15 mg of upadacitinib administered orally once daily. The dose may be changed to 7.5 mg once daily according to the patient's condition.

Psoriatic arthritis
The usual adult dosage is 15 mg of upadacitinib administered orally once daily.

Atopic dermatitis
The usual adult dosage ~~in patients aged ≥18 years~~ is 15 mg ~~or 30 mg~~ of upadacitinib administered orally once daily. The dose may be changed to 30 mg once daily according to the patient's condition.
The usual dosage in pediatric patients aged ≥12 ~~and <18~~ years weighing ≥30 ~~≥40~~ kg is 15 mg of upadacitinib administered orally once daily.

(c) Atopic dermatitis
The usual adult dosage ~~in patients aged ≥18 years~~ is 15 mg ~~or 30 mg~~ of upadacitinib administered orally once daily. The dose may be changed to 30 mg once daily according to the patient's condition.
The usual dosage in pediatric patients aged ≥12 ~~and <18~~ years weighing ≥30 ~~≥40~~ kg is 15 mg of upadacitinib administered orally once daily.

(The underlined words are added to,[25] and the strikethrough words are deleted from, the proposed text.)

Approval Condition

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

[25] The dotted-line part indicates addition pursuant to the approval of the partial change dated May 27, 2021.

Appendix

List of Abbreviations

AD	Atopic dermatitis
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to 't' (where t = the final time of detection)
AUC_{inf}	Area under the plasma concentration-time curve up to infinity
C_{avg}	Average plasma concentration over a dosing interval
CI	Confidence interval
CL/F	Apparent systemic clearance
Clinical Practice Guidelines for AD 2018	Guideline for Management of Atopic Dermatitis 2018, edited by Japanese Dermatological Association/Japanese Society for Allergology
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
COVID-19	Coronavirus disease 2019
CYP	Cytochrome P450
EASI	Eczema area and severity index
IFN	Interferon
IL	Interleukin
ITT	Intent to treat
JAK	Janus kinase
LOCF	Last observation carried forward
MACE	Major adverse cardiovascular event
NMSC	Nonmelanoma skin cancer
NRI	Non responder imputation
NRS	Numeric rating scale
OC	Observed cases
PMDA	Pharmaceuticals and Medical Devices Agency
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
Rinvoq	Rinvoq Tablets 7.5 mg, Rinvoq Tablets 15 mg, Rinvoq Tablets 30 mg
STAT	Signal transducer and activator of transcription
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroids
vIGA-AD	Validated investigator global assessment for atopic dermatitis