Amsterdam, 13 November 2025
EMADOC-1700519818-2672206
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Rinvoq

Upadacitinib

Procedure no: EMA/PAM/0000295186

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	20 October 2025	03 October 2025
☐	CHMP comments	3 November 2025	n/a
☐	Updated CHMP Rapporteur AR	6 November 2025	n/a
☒	CHMP adoption of conclusions:	13 November 2025	13 November 2025

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Table of contents

1. Introduction

On 29 August 2025, the MAH submitted a completed paediatric study for RINVOQ, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study P23-433 (A Study to Evaluate Effectiveness of Upadacitinib in Moderate to Severe AD With Prurigo Nodules in the Real World in Japan) is a stand alone study.

Updacitinib (UPA) is an oral JAK1-selective inhibitor approved for the treatment of patients with moderate-to-severe AD. RINVOQ (UPA) was approved for the treatment of RA in the US on 16 August 2019 and in the EU on 18 December 2019. Since then, RINVOQ has been approved for the treatment of adults with AS, PsA, nonradiographic axial spondyloarthritis, ulcerative colitis, Crohn's disease, and giant cell arteritis, and adults and adolescents in AD. On 26 April 2024, RINVOQ was approved by the US FDA for paediatric patients 2 years of age and older in PsA and pJIA (limited to RF-negative polyarticular and RF-positive pJIA). RINVOQ is being further evaluated for other inflammatory diseases.

UPA has shown significant efficacy for moderate-to-severe AD in multiple Phase 3 clinical trials, but no evaluation has been performed to differentiate the presence or absence of Prurigo Nodules (PNs). Therefore, the effectiveness of UPA in AD patients with PN could not be addressed and remains unknown. In addition, UPA utilization patterns and outcomes in real-world clinical practice in Japan remains unclear.

The objective of this prospective observational study was to evaluate real-world effectiveness of UPA 15- and 30-mg QD in adolescent and adult patients with prurigo-type AD in Japan.

2.2. Information on the pharmaceutical formulation used in the study<ies>

The product is formulated as a depot tablet to adult and adolescent patients with atopic dermatitis according to the Rinvoq label.

Rinvoq was prescribed to patients as per Japan label by a physician with sufficient knowledge and experience in the treatment of Atopic dermatitis.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study P23-433: A Study to Evaluate Effectiveness of Upadacitinib in Moderate to Severe AD With Prurigo Nodules in the Real World in Japan

2.3.2. Clinical study

Study P23-433 - A Study to Evaluate Effectiveness of Upadacitinib in Moderate to Severe AD With Prurigo Nodules in the Real World in Japan

Description

Study P23-433 was a non-interventional, prospective, observational cohort study of UPA in the treatment of AD with prurigo nodules in adolescent and adult patients at 22 investigative sites in Japan. Subjects who met the inclusion criteria were centrally registered and followed by effectiveness evaluation up to 48 weeks after the first dose of UPA.

The study enrolled adolescents (12-17 years of age at baseline) and adults (≥18 years of age at baseline), with a physician-confirmed diagnosis of AD, who were prescribed UPA according to the label and practice in Japan. Patients were systemic-naïve or systemic-experienced. The decision to prescribe UPA was made prior to and independently of study participation.

Methods

Study participants

At baseline, eligible patients must have been ≥ 12 years old, with a physician-confirmed diagnosis of moderate-to-severe AD, AD symptom onset > 1 year prior, a WP-NRS ≥ 4, and the presence of palpable PN. Also, the initiation of UPA treatment for AD had to be indicated and prescribed per the label in Japan for patients to be eligible. (The decision to prescribe UPA was made prior to and independently of study participation.)

Patients were excluded if they had prior treatment with UPA; contraindications to UPA; chronic pruritus resulting from another condition (e.g., neuropathic disorders) other than AD with PN; or PN caused by medication, metal allergy, infection, or insect bite; or if they were currently participating in any interventional research.

The sponsor did not provide any study medication. Instead, UPA was prescribed to patients as per the label in Japan by a physician with sufficient knowledge and experience in the treatment of AD.

Treatments

Patients received 15- or 30-mg doses initially, as determined by the treating physician.

Research Questions and Objectives

Research Question: What is the effectiveness of UPA for moderate-to-severe AD patients with prurigo nodules in the RW setting in Japan?

The primary objective of this study was to evaluate the real-world effectiveness of UPA 15- and 30-mg QD, specifically the proportion in patients with moderate-to-severe AD with PNs and a WP-NRS (Worst Pruritus Numerical Rating Scale) reduction ≥ 4.

Secondary objectives evaluated the effectiveness of UPA 15- and 30-mg QD across multiple clinician- and patient-reported measurements of disease activity up to 48 weeks after the initial UPA administration in adult and adolescent moderate to severe AD patients with prurigo nodules in Japan.

Data sources included clinician assessments as well as patient charts and questionnaires.

Outcomes/endpoints

Primary Outcome Measure:

• WP-NRS reduction ≥ 4 at Week 12

Secondary Outcome Measures:

• Clinician Assessment (ClinRO)

- EASI 75/90/100, EASI ≤ 1/7
- vIGA-AD 0/1
- IGA-CNPG activity 0/1
- IGA-CNPG stage 0/1

• Patient Reported Outcomes (PROs)

- WP-NRS 0/1, ≤ 3, reduction ≥ 4 (except week 12 – primary outcome)
- Skin Pain NRS ≤ 0/1
- POEM ≤ 2/≤ 7/reduction ≥ 4
- DLQI 0/1/≤ 5/reduction ≥ 4
- (c)DLQI 0/1/≤ 5/reduction ≥ 4
- ADCT < 7/reduction ≥ 5

No additional diagnostic or monitoring procedures were applied to patients enrolled in this study other than those procedures that were ordinarily applied during the therapeutic strategy and per the label.

Sample size

The planned sample size was 120 participants with a study enrolment period of 52 weeks and a follow-up period of up to 48 weeks. Patients were expected to complete up to 4 study visits during the follow-up period:

• Visit 1 (V1): Baseline/Enrollment

• Visit 2 (V2): Follow-up at 4 weeks (± 2 weeks)

• Visit 3 (V3): Follow-up at 12 weeks (± 4 weeks)

• Visit 4 (V4): Follow-up at 24 weeks (± 4 weeks)

• Visit 5 (V5): Follow-up at 48 weeks (± 6 weeks)

Results

Baseline Demographics

In this study, 121 patients were enrolled with informed consent. Out of 121 enrolled patients, 108 patients (89.3%) completed the study and 13 patients (10.7%) discontinued. For the analysis sets that were defined in the protocol and statistical analysis plan, 119 patients were included in the Safety Analysis Set and 2 patients were excluded due to not receiving UPA. Out of the Safety Analysis Set, 112 patients were included in the Efficacy Analysis Set, and 7 patients were excluded; of the exclusions, 6 were due to off-label use and 1 due to missing efficacy assessments. For the Efficacy Analysis Set, 112 patients were included while 9 patients were excluded (6 due to receiving treatment with a dosage regimen other than those specified in the package insert, 2 due to not receiving UPA, and 1 for whom the efficacy evaluation was not obtained.

For the demographic characteristics, slightly more than half of patients were male (57.1%). The mean age in the Safety Analysis Set was 32.9 years (12 to 75 years in range) with 35 (31.3%) patients < 18 years of age enrolled. The most common prior systemic therapies for AD (≥ 10%) were cyclosporine, dupilumab, oral corticosteroids, and UV light therapy. The majority of patients (91.6%) had concomitant medication for AD.

The mean (SD) number of prurigo lesions in total was 25.9 (39.1), and the mean physician's assessments were 26.5 for EASI and 46.3% for BSA. The mean PROs were 7.2 for WP-NRS, 5.7 for skin pain NRS, and 12.1 for DLQI. Most of the patients showed moderate or severe disease status for each physician's assessment (52.1% and 44.5% for vIGA-AD score, 45.4% and 37.8% for IGA-CNPG activity score, and 43.7% and 29.4% for IGA-CNPG stage score, respectively).

Most patients (81.5% in the Safety Analysis Set) started UPA at 15 mg with the most common reasons of "Per label (pediatric, severe renal impairment, concomitant use of strong CYP3A4 inhibitors" (26.9%), "To observe response at a low dose" (26.1%), and "For safety reason" (26.1%).

Efficacy results

In this study, the primary analysis was based on the marginal structural model with IPW. None of the patients in the Efficacy analysis set (N = 112) switched treatment from UPA to other biological products or JAK inhibitors from Week 4 to Week 8, so that the marginal structural model with IPW was not applied and non-adjusted calculation was applied.

In the efficacy analysis population, patients treated with UPA showed improvement in all clinical and patient reported outcomes assessed at 4, 12, and 48 weeks. Analysis of the primary outcome and key secondary effectiveness outcomes are described below.

Patients demonstrating improvement of intensity of itch as measured by WP-NRS ≥ 4 points were evident from 4 weeks (63.2%, 95% CI: 53.3–72.4) with 65.7% (95% CI: 55.4–74.9) reporting improvement at 12 weeks (primary outcome). This achievement rate was maintained at 48 weeks (64.3%, 95% CI: 53,1–74.4), see Table 1.

Table 1. Proportion of patients with improvement ≥4 points in WP-NRS score by visit (Non-adjusted, Efficacy Analysis Set)

	N = 112	
	n/N (%)	95% CI [a]
Improvement >4 points in WP-NRS score		
Week 4	67/106 (63.2)	53.3, 72.4
Week 12	65/99 (65.7)	55.4, 74.9
Week 24	63/95 (66.3)	55.9, 75.7
Week 48	54/84 (64.3)	53.1, 74.4

a. Clopper-Pearson 95% confidence interval

The proportion of patients with improvement ≥ 4 points in WP-NRS score at Week 12 using a non-adjusted calculation was 65.7%. Of the patients who saw an improvement of ≥ 4 points in WP-NRS score at Week 12, 75.0% started at the 30-mg dose while 63.9% started at 15 mg (See Table 2).

Table 2. Proportion of subjects who achieved an improvement in WP-NRS ≥ 4 at Week 12 by initial dose of this drug (unadjusted summary) -Efficacy Analysis Set

N = 112				
	Improved ≥ 4		Not improved ≥ 4	Missing
	n/N (%)	95% CI[a]	N (%)	n
15 mg	53/83 (63.9)	52.6, 74.1	30/83 (36.1)	11
30 mg	12/16 (75.0)	47.6, 92.7	4/16 (25.0)	1
Other	0/0 (--)	--	0/0 (--)	0

a: 95% confidence interval by the Clopper-Pearson method

For subjects with WP-NRS < 4 at baseline	0
Missing baseline	1
Number of subjects to be evaluated	111
Starting dose of this drug unknown	0

The largest proportion of patients showing improvement in WP-NRS ≥ 4 were 65 years of age and older, followed by those between the ages of 40 and 64. Patients under the age of 18 and those between 18 and 39 years of age demonstrated similar proportions of improvement in WP-NRS ≥ 4 (See Table 3).

Table 3. Proportion of subjects with improvement in WP-NRS ≥ 4 at Week 12 by age category (unadjusted summary) - Efficacy Analysis Set

N = 112				
	Improved ≥ 4		Not improved ≥ 4	Missing
	n/N (%)	95% CI[a]	n/N (%)	n
Less than 18	16/29 (55.2)	35.7, 73.6	13/29 (44.8)	6
≥ 18 and < 40	19/32 (59.4)	40.6, 76.3	13/32 (40.6)	4
≥ 40 and < 65	24/32 (75.0)	56.6, 88.5	8/32 (25.0)	2
Not less than 65	6/6 (100.0)	54.1, 100.0	0/6 (0.0)	0

a: 95% confidence interval by the Clopper-Pearson method

For subjects with WP-NRS < 4 at baseline	0
Missing baseline	1
Number of subjects to be evaluated	111
Age category unknown	0

The efficacy results were also analyzed by visits at Weeks 4, 12, 24, and 48. The secondary endpoint of proportion of patients with ≤ 1 point in each efficacy score by visit (non-adjusted calculation, Efficacy Analysis Set) is shown in Table 4 and the proportion of patients achieving EASI 75/90/100 by visit is shown in Table 5.

Patients reporting little/no itch as measured by WP-NRS ≤1 increased from 35.8% at 4 weeks to 40.4% at 12 weeks and 46.4% at 48 weeks. At 4 weeks, 47.0% patients reported little/ no PN as measured by IGA-CNPG stage ≤1. This also increased to 66.0% at 12 weeks and 83.1% at 48 weeks. Patients reporting little/ no PN activity as measured by IGA-CNPG activity ≤1 was 51.9% at 4 weeks, increasing to 71.7% at 12 weeks, and 83.0% at 48 weeks. At 4 weeks, 31.5% patients reported little/ no impact of skin disease on quality of life as measured by DLQI 0/1. This increased to 39.3% at 48 weeks. At 4 weeks, 50.0% patients reported little/ no pain activity as measured by Skin Pain NRS ≤1. This increased to 52.3% at 12 weeks and 60.3% at 48 weeks (Table 4)

Improvements in skin rash were also observed from 4 weeks through to 48 weeks. Patients showing moderate improvement in skin rash as measured by EASI 75 was 55.6%, 77.2% and 79.5% at 4, 12 and 48 weeks respectively. Patients with almost clear of skin rash defined as EASI90 increased from 24.1% at 4 weeks to 53.5% at 12 weeks and 61.4% at 48 weeks. The percentage of patients with EASI 100, or no skin rash was 0.9% at 4 weeks and increased to 5.9% at 12 weeks and 15.9% at 48 weeks (Table 5).

Table 4. Proportion of patients with ≤1 point in each efficacy score by visit (Non-adjusted, Efficacy Analysis Set)

	N = 112	
	n/N (%)	95% CI[a]
WP-NRS score 0/1		
Week 4	38/106 (35.8)	26.8, 45.7
Week 12	40/99 (40.4)	30.7, 50.7
Week 24	39/95 (41.1)	31.1, 51.6
Week 48	39/84 (46.4)	35.5, 57.6
IGA CNPG stage 0/1		
Week 4	47/100 (47.0)	36.9, 57.2
Week 12	62/94 (66.0)	55.5, 75.4
Week 24	73/88 (83.0)	73.4, 90.1
Week 48	69/83 (83.1)	73.3, 90.5
IGA-CNPG activity 0/1		
Week 4	55/106 (51.9)	42.0, 61.7
Week 12	71/99 (71.7)	61.8, 80.3
Week 24	77/94 (81.9)	72.6, 89.1
Week 48	73/88 (83.0)	73.4, 90.1
DLQI 0/1		
Week 12	23/73 (31.5)	21.1, 43.4
Week 48	24/61 (39.3)	27.1, 52.7
Skin Pain NRS 0/1		
Week 4	47/94 (50.0)	39.5, 60.5
Week 12	46/88 (52.3)	41.4, 63.0
Week 24	48/85 (56.5)	45.3, 67.2
Week 48	44/73 (60.3)	48.1, 71.5

a. Clopper-Pearson 95% confidence interval

Table 5. Proportion of patients achieving EASI 75/90/100 by visit (Non- adjusted, Efficacy Analysis Set)

	N = 112	
	n/N (%)	95% CI[a]
EASI 75		
Week 4	60/108 (55.6)	45.7, 65.1
Week 12	78/101 (77.2)	67.8, 85.0
Week 24	76/96 (79.2)	69.7, 86.8
Week 48	70/88 (79.5)	69.6, 87.4
EASI 90		
Week 4	26/108 (24.1)	16.4, 33.3
Week 12	54/101 (53.5)	43.3, 63.5
Week 24	52/96 (54.2)	43.7, 64.4
Week 48	54/88 (61.4)	50.4, 71.6
EASI 100		
Week 4	1/108 (0.9)	0.0, 5.1
Week 12	6/101 (5.9)	2.2, 12.5
Week 24	14/96 (14.6)	8.2, 23.3
Week 48	14/88 (15.9)	9.0, 25.2

a. Clopper-Pearson 95% confidence interval

Paediatric Data

In the Efficacy Analysis Set, there were 35 patients between the ages of 12 and 17. Almost all (34/35) paediatric patients started with the 15-mg dose, while 1 patient started with the 30-mg dose. Slightly more than half (16/29; 55.2%) of patients < 18 years of age showed improvement in WP-NRS ≥ 4 at Week 12, while slightly less than half (13/29; 44.8%) did not (See Table 3).

Safety results

Overall Population

In the Safety Analysis Set, 71 patients (59.7%) reported 156 adverse events in this study. The most common adverse event was acne (21.0%), followed by nasopharyngitis (10.1%), influenza (8.4%), COVID-19 (5.9%), and folliculitis and herpes zoster (both 5.0%). For AESI, 11 patients (9.2%) reported 13 events. In the Safety Analysis Set, 49 patients (41.2%) reported 59 adverse events related to UPA in this study; the most common event was acne (17.6%), followed by herpes zoster (5.0%).

Two serious adverse events (herpes zoster and pneumonia) were reported in 2 adult patients (1.7%). Both events were judged to be related to UPA treatment and resolved without any sequelae. One patient with serious herpes zoster discontinued UPA treatment due to this event. 6 patients (5.0%) reported 7 adverse events leading to discontinuation of UPA treatment, of which 1 patient had herpes zoster.

The MAH´s conclusions

The results of this observational study support the effectiveness and safety of UPA 15- and 30-mg QD for adolescent and adult patients with moderate-to-severe AD with PN in real-world practice in Japan. UPA has demonstrated efficacy as early as 4 weeks and consistent efficacy over 48 weeks. Safety results showed that UPA 15- and 30-mg doses were well tolerated. The safety profile seen in this

observational study was similar to the safety profile seen in previous clinical trials and post-marketing clinical studies in the AD population; no new safety signals were observed.

The benefit-risk profile of UPA is unchanged, and no update to the Summary of Product Characteristics has been proposed as a result of this observational study.

Limitations

In this observational study, patients were assessed according to a real-world setting and based on routine clinical practice, physician's judgment and patient's availability. This resulted in variability in the timing of assessments, completeness of data collected, and duration of treatment. For clinical data, all efforts were made to retrieve any missing data points. For missing responses on questionnaire items, the coding for most of the PRO instruments used in the current study provide imputation solutions for missing responses.

2.3.3. Discussion on clinical aspects

The results of this observational study are considered to reflect the actual clinical situation of patients with moderate-to-severe AD with PN in Japan. Patients demonstrating improvement of intensity of itch as measured by WP-NRS ≥ 4 points were evident from 4 weeks.

In the Efficacy Analysis Set, there were 35 patients between the ages of 12 and 17. Almost all (34/35) paediatric patients started with the 15-mg dose, while 1 patient started with the 30-mg dose. Slightly more than half (16/29; 55.2%) of patients < 18 years of age showed improvement in WP-NRS ≥ 4 at Week 12, while slightly less than half (13/29; 44.8%) did not. The largest proportion of patients showing improvement in WP-NRS ≥ 4 were 65 years of age and older, followed by those between the ages of 40 and 64. Patients under the age of 18 and those between 18 and 39 years of age demonstrated similar proportions of improvement in WP-NRS ≥ 4.

No new safety signals were observed, the safety results were consistent with the currently documented safety profile of the product.

The results of this observational study support the clinical efficacy and safety of Rinvoq for adolescent and adult patients with moderate-to-severe AD.

The benefit-risk of upadacitinib is unchanged and no updates to the Summary of Medicinal Product Characteristics are proposed.

3. CHMP overall conclusion and recommendation

No new findings of clinical efficacy and safety were observed in the submitted observational study.

The MAH has not suggested any update to the Summary of Product Characteristics based on the performed study, which is supported by the CHMP.

☒ **Fulfilled:**

No regulatory action required.