25 April 2025
EMADOC-1700519818-2137829
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/0000253500

Note

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

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Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start of Procedure	25 February 2025	25 February 2025
☐	CHMP Rapporteur AR	31 March 2025	31 March 2025
☐	CHMP comments	14 April 2025	n/a
☐	Updated CHMP Rapporteur AR	16 April 2025	n/a
☒	CHMP outcome	25 April 2025	25 April 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

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1. Introduction

On 12 February 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 M16-049 is part of a clinical development program. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Upadacitinib was administered either as tablets (15 or 30 mg/tablet) or oral solution (0.5 mg/mL or 1 mg/mL).

2.3. Clinical aspects

The MAH submitted a final report for:

- Study M16-049 An Open-label Multiple-Dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Upadacitinib in Pediatric Subjects with Severe Atopic Dermatitis

2.3.1. Clinical study

Clinical study M16-049

Description

Study M16-049 was a Phase 1, multiple-dose, open-label study that consisted of two parts in 35 pediatric male and female subjects with severe AD, aged 2 years to less than 12 years.

The study was comprised of a 35-day Screening Period, a 1-week open-label treatment period in Part 1, a 108-week open-label treatment period for Part 2, and an end of study follow-up visit.

Part 1 was a multiple-dose, open-label, multiple cohort study that consists of two sequential multiple-ascending dose groups (Low Dose and High Dose levels) in the two age groups. Subjects 2 to < 12 years of age were categorized based on age group, and the dose administered for seven consecutive days was based on predefined body weight categories per dose level. The dose levels and body weight categories are presented in Table 1 for subjects 2 to < 12 years of age. After receipt of FDA advice, subjects less than 3 years of age were discontinued from the study and only subjects 3 years to < 12 years of age were enrolled in the study beginning with Protocol Version 6.0 until study conclusion.

On Study Day 7 of Part 1, serial blood samples for assay of upadacitinib were collected for up to 24 hours for QD dosing and or up to 12 hours for BID dosing.

Table 1: Upadacitinib Dosing by Body Weight Category and Dose Level for Subjects 2 to < 12 years

Body Weight Category				
Dosing Scheme Starting with Protocol Version 4.0[a]				
Dose Level	**10 to < 20 kg**	**20 to < 30 kg**	**≥ 30 kg**	
Low Dose	3 mg BID Oral Solution	4 mg BID Oral Solution	15 mg QD ER Tablet (Or 6 mg BID Oral Solution if unable to swallow tablet)	
High Dose	6 mg BID Oral Solution	8 mg BID Oral Solution	30 mg QD ER Tablet (Or 12 mg BID Oral Solution if unable to swallow tablet)	
Dosing Scheme Prior to Protocol Version 4.0				
Dose Level	**10 to < 15 kg**	**15 to < 25 kg**	**25 to < 40 kg**	**≥ 40 kg**
Low Dose	1.6 mg BID Oral Solution	2 mg BID Oral Solution	7.5 mg QD ER Tablet or 3 mg BID Oral Solution (According to ability to swallow tablet)	15 mg QD ER Tablet
High Dose	3.2 mg BID Oral Solution	4 mg BID Oral Solution	15 mg QD ER Tablet or 6 mg BID Oral Solution (According to ability to swallow tablet)	30 mg QD ER Tablet

a Dosing scheme was updated based on available data from pediatric subjects with severe AD and pcJIA.[1]

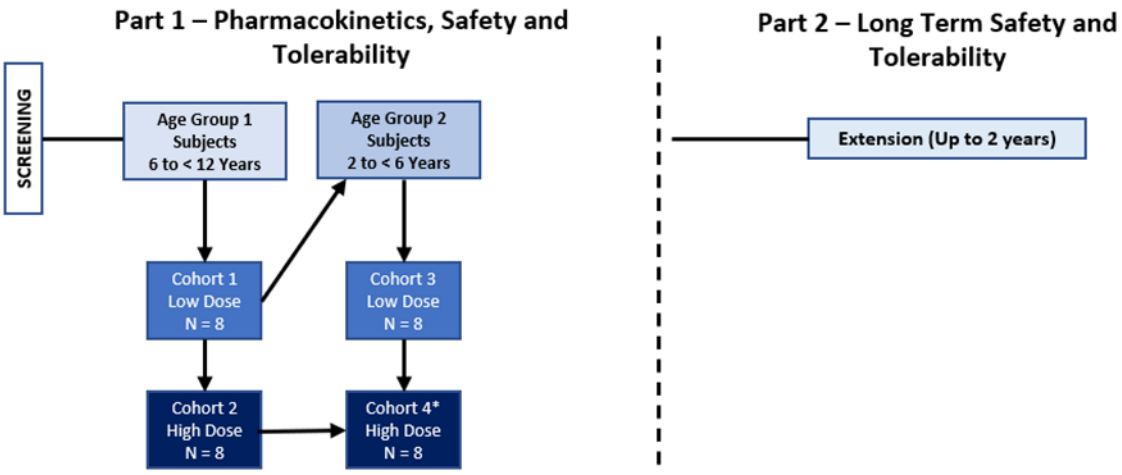
Subjects who completed Part 1 had the option to enroll in Part 2 at the investigator's discretion and when enrolled were to have received open-label upadacitinib at the Low Dose level as described in Table 1. Pharmacokinetics, safety, and tolerability data were analyzed on a periodic basis as the data became available during the course of the study.

Part 2 was a multiple-dose, open-label, long-term extension to evaluate the long-term safety and tolerability of upadacitinib.

During Part 2 of the study, subjects with an EASI score worsening of 25% or more compared with their baseline EASI score at any two consecutive scheduled study visits after Week 4 or subjects who do not achieve at least a 50% improvement in their EASI score compared to baseline at two consecutive visits on or after Week 8 were to have discontinued study drug and were to receive treatment at investigator's discretion and in accordance with local standard-of-care.

A schematic of the overall study design is shown in Figure 1.

Figure 1: Study Design Schematic



* Beginning with Protocol Version 6.0, only subjects 3 years and older were enrolled for the remainder of this study per FDA's request.

Note: All subjects were to have received upadacitinib at the low dose level in Part 2.

Results

Participant flow

Table 2: Disposition of Subjects

	Part 1				
	Cohort 1	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Total**
All Subjects	9	8	9	9	35
Completed Study (Part 1)	9	8	8	8	33
Primary Reason for Discontinuation					
Adverse Event	0	0	0	0	0
Withdrawal Consent	0	0	1	0	1
Lost to Follow-Up	0	0	0	0	0
Lack of Efficacy	0	0	0	0	0
Othera	0	0	0	1	1

	Part 2		
	Aged 6 to < 12 years	**Aged 2 to < 6 years**	**Total**
All Subjects	17	16	33
Completed Study (Part 2)	10	9	19
Primary Reason for Discontinuation			
Adverse Event	3	1	4
Withdrawal Consent	1	2	3
Lost to Follow-Up	1	0	1
Lack of Efficacy	2	2	4
Otherb	0	2	2

a. Study drug noncompliance.

b. FDA recommended discontinuation of all subjects less than 3 years. Cohort 1 = Low Dose, 6 to < 12 years.

Cohort 2 = High Dose, 6 to < 12 years. Cohort 3 = Low Dose, 2 to < 6 years. Cohort 4 = High Dose, 2 to < 6 years.

Baseline data

A total of 35 pediatric subjects were randomized at 11 study sites located in the United States and Puerto Rico. Prior to enrollment in the study, each subject was judged to be in good health based on review of his/her medical history, a physical examination, vital signs, 12-lead ECG and laboratory tests. At baseline, male and female subjects enrolled in this study were ages 2 years to less than 12 years at screening, and total body weight 10 kg or higher at the time of baseline were enrolled.

Subjects 3 years to less than 12 years were enrolled in the study from protocol version 6.0 going forward. Criteria for AD included subjects diagnosed with AD with onset of symptoms at least 6 months prior to baseline and meeting Hanifin and Rajka criteria, EASI score ≥ 21, Validated Investigator Global Assessment (vIGA)-AD score equal to 4, ≥ 15% body surface area of AD involvement. Additionally, subjects were required to have a documented history (within 12 months prior to the baseline visit) of inadequate response to topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) or for whom use of TCS and TCIs is otherwise medically inadvisable.

Efficacy results

Clinical efficacy parameters were collected as exploratory measures and to facilitate the assessment of benefit-risk to justify a continuation of Low Dose upadacitinib during Part 2. There were no formal statistical comparisons of efficacy. The overall population was summarized for efficacy.

A vIGA-AD score of 0 or 1 (with at least two grades of reduction from baseline) at Week 12 was achieved by 11/30 subjects (36.7%) in the overall population across cohorts.

EASI 75 at Week 12 was achieved by 21/30 subjects (70.0%) for the overall population across cohorts.

The mean and median percent change from baseline of the EASI score at Week 12 for the overall population across cohorts was -80.77% (N = 30, SD = 18.769) and -84.29% (Q1 = -94.56, Q3 = -69.66), respectively.

A vIGA-AD score of 0 or 1, EASI 75, and percent change from baseline in EASI were maintained through Week 108.

Safety results

Table 3: Overview of Number and Percentage of Subject with Treatment-Emergent Adverse Events in Parts 1 and 2 (Safety Population)

	Part 1				
Subjects with any Treatment-Emergent, n (%)	**Cohort 1 (N = 9)**	**Cohort 2 (N = 8)**	**Cohort 3 (N = 9)**	**Cohort 4 (N = 9)**	**Total (N = 35)**
AE	1 (11.1)	1 (12.5)	5 (55.6)	0	7 (20.0)
AE with reasonable possibility of being drug related	0	0	1 (11.1)	0	1 (2.9)
Severe AE	0	0	0	0	0
Serious AE	0	0	0	0	0
SAE with reasonable possibility of being drug related	0	0	0	0	0
AE leading to discontinuation of study drug	0	0	0	0	0
AE leading to death	0	0	0	0	0
All deaths	0	0	0	0	0

	Part 2		
Subjects with any Treatment-Emergent, n (%)	**Aged 6 to < 12 years (N = 17)**	**Aged 2 to < 6 years (N = 16)**	**Total (N = 33)**
AE	15 (88.2)	14 (87.5)	29 (87.9)
AE with reasonable possibility of being drug related	2 (11.8)	7 (43.8)	9 (27.3)
Severe AE	3 (17.6)	1 (6.3)	4 (12.1)
Serious AE	3 (17.6)	0	3 (9.1)
SAE with reasonable possibility of being drug related	1 (5.9)	0	1 (3.0)
AE leading to discontinuation of study drug	3 (17.6)	1 (6.3)	4 (12.1)
AE leading to death	0	0	0
All deaths	0	0	0

Cohort 1 = Low Dose, 6 to < 12 years.

Cohort 2 = High Dose, 6 to < 12 years.

Cohort 3 = Low Dose, 2 to < 6 years.

Cohort 4 = High Dose, 2 to < 6 years.

Table 4: Summary of Treatment-Emergent Adverse Events Reported by> 5% of All Subjects in Part 2 by Body System and MedDRA Term

	Part 2		
Medra 27.0 System Organ Class **Preferred Term**	**Aged 6 to < 12 years (N = 17)** **n (%)**	**Aged 2 to < 6 years (N = 16)** **n (%)**	**Total (N = 33)** **n (%)**
Any Adverse Event	15 (88.2)	14 (87.5)	29 (87.9)
Blood and Lymphatic System Disorders			
Neutropenia	0	2 (12.5)	2 (6.1)
Gastrointestinal Disorders			
Abdominal discomfort	2 (11.8)	1 (6.3)	3 (9.1)
Vomiting	1 (5.9)	3 (18.8)	4 (12.1)
General Disorders and Administration Site Conditions			
Pyrexia	0	2 (12.5)	2 (6.1)
Infections and Infestations			
Covid-19	4 (23.5)	0	4 (12.1)
Impetigo	0	2 (12.5)	2 (6.1)
Influenza	1 (5.9)	1 (6.3)	2 (6.1)
Molluscum contagiosum	0	2 (12.5)	2 (6.1)
Upper respiratory tract infection	2 (11.8)	2 (12.5)	4 (12.1)
Viral upper respiratory tract infection	0	2 (12.5)	2 (6.1)
Nervous System Disorders			
Headache	3 (17.6)	1 (6.3)	4 (12.1)
Respiratory, Thoracic and Mediastinal Disorders			
Asthma	0	3 (18.8)	3 (9.1)
Cough	0	5 (31.3)	5 (15.2)
Oropharygeal pain	2 (11.8)	0	2 (6.1)

Skin and Subcutaneous Tissue Disorders	2 (11.8)	2 (12.5)	4 (12.1)
Dermatitis Atopic Eczema	1 (5.9)	1 (6.3)	2 (6.1)

Note: A TEAE is defined as an adverse event with an onset date that is after the first dose of study drug, and no more than 30 days after the last dose of study drug.

Table 5: Treatment-Emergent Adverse Events Assessed by the Investigator as Having Reasonable Possibility of Being Related to Upadacitinib in Part 2 (> 5% of all Subjects in any Age Group)

	Part 2		
Medra 27.0 System Organ Class Preferred Term	**Aged 6 to <12 years (N = 17) n (%)**	**Aged 2 to < 6 years (N = 16) n (%)**	**Total (N = 33) n (%)**
Any Adverse Event	2 (11.8)	7 (43.8)	9 (27.3)
Blood and lymphatic system disorders	0	1 (6.3)	1 (3.0)
Neutropenia	0	1 (6.3)	1 (3.0)
Thrombocytopenia	0	1(6.3)	1 (3.0)
Infections and infestations	1 (5.9)	4 (25.0)	5 (15.2)
Cellulitis	0	1 (6.3)	1 (3.0)
Conjunctivitis	0	1 (6.3)	1 (3.0)
Eczema herpeticum	0	1 (6.3)	1 (3.0)
Herpes Zoster	0	1 (6.3)	1 (3.0)
Ophthalmic herpes zoster	1 (5.9)	0	1 (3.0)
Skin infection	0	1 (6.3)	1 (3.0)
Viral infection	0	1 (6.3)	1 (3.0)
Viral upper respiratory tract infection	0	1 (6.3)	1 (3.0)
Investigations	0	1 (6.3)	1 (3.0)
Blood creatine phosphokinase increased	0	1 (6.3)	1 (3.0)
Respiratory, thoracic and mediastinal disorders	1 (5.9)	2 (12.5)	3 (9.1)
Asthma	0	1 (6.3)	1 (3.0)
Cough	0	1 (6.3)	1 (3.0)
Oropharyngeal pain	1 (5.9)	0	1 (3.0)

In Part 1, 20% of subjects reported TEAEs and in Part 2, 87.9% of subjects reported TEAEs, with a similar proportion of AEs between the two age groups.

No AEs of special interest (AESI) were reported in Part 1. Six subjects reported AESIs in Part 2 with serious infections of COVID-19 and ophthalmic herpes zoster reported in the older age group (6 to < 12 years) and elevated CPK, herpes zoster, and neutropenia in the younger age group (2 to < 6 years). No SAEs were reported in Part 1. Three SAEs (COVID-19, ophthalmic herpes zoster, and major depression) during Part 2 were reported in the study.

Upadacitinib was generally safe and well tolerated for pediatric subjects with severe AD. No new safety risks were identified compared to the known safety profile for upadacitinib in adults and adolescents with AD.

Pharmacokinetic Results

In pediatric subjects with severe AD, upadacitinib maximum plasma concentrations were reached within approximately 2 to 3 hours following the administration of the extended-release tablet formulation and 0.5 to 2 hours following the administration of the immediate release oral solution. Upadacitinib functional t½, calculated from the C_{max} to C_{trough} ratio at steady state, was approximately 4 to 5 hours, for the extended-release QD and 2 to 3 hours for the oral solution BID regimens, and was consistent between the two age groups. Upadacitinib apparent oral clearance increased with increasing body weight in pediatric subjects with severe AD.

2.3.2. Discussion on clinical aspects

The primary aim of Study M16-049 was to identify a suitable dose regimen for younger paediatric patients with atopic dermatitis in the further clinical development of Rinvoq. No formal efficacy evaluation has been conducted in this study. No new safety signals were identified compared to the known safety profile for adults and adolescents. However, no definite conclusions on the safety profile for younger paediatric patients can be made at this stage due to limited data.

The final data of Study M16-049 does not warrant any further update of the SmPC.

3. CHMP overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.

Annex. Line listing of all the studies included in the development program

Area	Number of measures	Description
Quality-related studies	1	**Study 1** Development of age-appropriate oral solid dosage form (dispersible tablet or multi-particulate granules) or age-appropriate oral liquid dosage form
Non-clinical studies	2	**Study 2** Dose range-finding juvenile toxicity study Study 3 Definitive juvenile toxicity study to evaluate toxicity and impact of upadacitinib on neonatal/juvenile development
Clinical studies	6	**Study 4** Open-label, multiple-dose trial to evaluate activity, safety and tolerability (Part 1) and long-term safety and tolerability (Part 2) of upadacitinib in children from 2 to less than 12 years of age with severe atopic dermatitis (AD) **Study 5** Double-blind, randomised, placebo-controlled trial to evaluate safety and efficacy of upadacitinib in adolescents (and adults) with moderate to severe AD who are candidates for systemic therapy (M16-045) **Study 6** Double-blind, randomised, placebo-controlled trial to evaluate safety and efficacy of upadacitinib in adolescents (and adults) with moderate to severe AD who are candidates for systemic therapy in combination with topical corticosteroids (M16-047) **Study 7** Double-blind, randomised, placebo-controlled trial to evaluate safety and efficacy of upadacitinib in adolescents (and adults) with moderate to severe AD who are candidates for systemic therapy (M18-891) **Study 8** Double-blind, randomised, placebo-controlled trial to evaluate safety and efficacy of upadacitinib as add-on to standard of care in children from 2 to less than 18 years of age with severe AD **Study 9** Open-label, extension study to evaluate long-term safety and efficacy of upadacitinib monotherapy in children from 2 to less than 18 years of age with severe atopic dermatitis
Extrapolation, modelling and simulation studies	2	**Study 10** PopPK to predict initial paediatric doses to be used in further clinical studies

		PopPK to confirm or modify the paediatric posology compared to the regimen used in clinical trials **Study 11** Population exposure response analyses to identify subgroups where this relationship is altered and may need posology changes or other risk mitigation measures selection
Other studies	0	Not applicable
Other measures	0	Not applicable