25 April 2025
EMADOC-1700519818-2134326
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/0000248980

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**
☐	Start of Procedure	25 February 2025	25 February 2025
☐	CHMP Rapporteur AR	31 March 2025	28 February 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

Table of contents

1. Introduction

On 30 January 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.

The MAH does not propose an update of the product information.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that M23-696 "**Atopic Dermatitis: Comparison of Safety and Assessor Blinded Efficacy of Upadacitinib to Dupilumab in Adult and Adolescent Subjects**" is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Upadacitinib is a selective and reversible Janus kinase (JAK) inhibitor. The product is formulated as a depot tablet to adult and adolescent patients with atopic dermatitis (AD) according to the Rinvoq label.

In AD, the efficacy and safety of upadacitinib was assessed in three Phase 3 randomized, double-blind, multicenter studies, and the 2 doses (upadacitinib 15 mg and 30 mg QD) studied were approved for the treatment of moderate to severe AD. However, the Phase 3 studies for AD were designed with a fixed regimen of upadacitinib 15 mg or 30 mg QD for 5 years and no dose escalation or dose reduction based on the clinical response were assessed.

In addition, the efficacy and safety of upadacitinib 30 mg QD versus dupilumab for the treatment of adult subjects with moderate to severe AD who were candidates for systemic therapy was assessed in a head-to-head, Phase 3b, active-controlled clinical trial. However, the 15 mg QD dose for upadacitinib was not assessed in that study.

Dupilumab is approved in the EU for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy, and for the treatment of severe AD in children 6 months to 11 years old who are candidates for systemic therapy.

Study M23-696 aimed to provide data on the efficacy and safety of upadacitinib initiated at 15 mg QD and dose escalated based on the clinical response, compared with dupilumab as per its label, after 16 weeks of treatment. Additionally, this study aimed to provide data on the efficacy and safety of upadacitinib initiated at 15 mg QD and dose adjusted based on clinical response in subjects with inadequate response to dupilumab. Dupilumab was administered in the form of SC injection EOW after SC dose at Baseline.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study M23-696 "Atopic Dermatitis: Comparison of Safety and Assessor Blinded Efficacy of Upadacitinib to Dupilumab in Adult and Adolescent Subjects"

Upadacitinib is approved for the treatment of moderate to severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and non-radiographic axial spondyloarthritis.

Upadacitinib is also approved for the treatment of moderate to severe AD in adults and adolescents globally, including the European Union, Japan, and the US.

Further, upadacitinib has been approved on 04 April 2025 for the treatment of giant cell arteritis in adult patients.

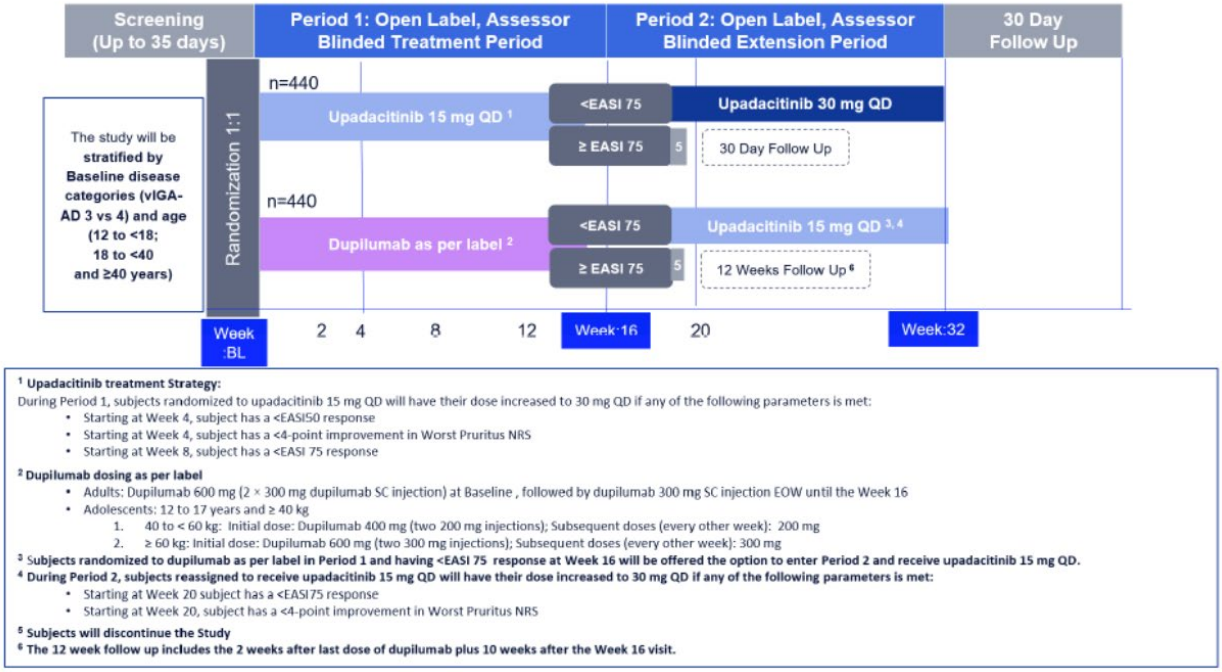
2.3.2. Clinical study - Atopic Dermatitis: Comparison of Safety and Assessor Blinded Efficacy of Upadacitinib to Dupilumab in Adult and Adolescent Subjects

Description

Study M23-696 is a global, Phase 3b/4, randomized, open-label, efficacy assessor-blinded, multicenter study that evaluated upadacitinib compared with dupilumab per its label, as monotherapy, in adolescent and adult subjects (≥ 12 and < 64 years of age weighting at least 40 kg) with moderate to severe AD who have inadequate response to systemic therapy or for whom use was medically inadvisable.

The study duration included a 35-day Screening Period; Period 1, a 16-week randomized, open-label, efficacy assessor-blinded treatment period for all subjects, and a 30-day or 12-week follow-up visit for subjects on upadacitinib or dupilumab respectively, who will not enter Period 2; Period 2, a 16-week open-label, efficacy assessor-blinded extension period for those subjects with a < EASI 75 response at Week 16 (total duration 32 weeks) (Period 2); and a 30-day follow-up visit.

Figure 1. Study design schematic



BL = Baseline; EOW = every other week; EASI 50/75 = Eczema Area and Severity Index 50/75; QD = once daily; SC = subcutaneous; vIGA-AD = Validated Investigator's Global Assessment for Atopic Dermatitis

Methods

Study participants

A total of 920 subjects, including 117 adolescents, were randomized at 214 sites. At baseline, male and female subjects enrolled in this study were ≥ 12 and < 64 years of age at Screening with chronic AD with onset of symptoms at least 3 years prior and meeting Hanifin and Rajka criteria; EASI score ≥ 16, vIGA-AD score ≥ 3, ≥10% body surface area of AD involvement at Baseline; and a Baseline weekly average of daily Worst Pruritus Numerical Rating Scale ≥ 4. Prior use of dupilumab, tralokinumab, lebrikizumab, or JAK inhibitors (oral or topical) was not allowed. Additionally, subjects were required to have a documented history of inadequate response to at least one prior systemic treatment for AD or that other systemic treatments were otherwise medically inadvisable.

Objective(s)/endpoints

The primary objective, related to Period 1 (16 weeks of duration), was to assess the efficacy and safety of upadacitinib, initiated at 15 mg QD and dose-adjusted based on clinical response, compared with dupilumab as per its label.
An additional objective, related to Period 2, was to assess the efficacy and safety of upadacitinib, initiated at 15 mg QD and dose adjusted based on clinical response, in subjects with inadequate response to dupilumab.

Efficacy:
The primary efficacy objective was based on the achievement of a composite of at least a 90% reduction in EASI from baseline (EASI 90) and a Worst Pruritus Numerical Rating Scale of 0 or 1 (WP-NRS 0/1) at Week 16 with the treatment of upadacitinib compared with dupilumab per its label in the intent-to-treat (ITT)_1 Population, which consists of all randomized subjects.
The secondary efficacy objectives were based on ranked secondary endpoints with the treatment of upadacitinib compared with dupilumab in the ITT_1 Population.

Safety:
Adverse event (AE)/treatment-emergent adverse event (TEAE), serious adverse event (SAE), adverse events of special interest (AESI), AE leading to discontinuation, vital signs, and laboratory tests were evaluated throughout the study.

Sample size

The planned sample size were 880 subjects: analyzed 920 subjects.

Randomisation and blinding (masking)

Subjects who met eligibility criteria were randomized in Period 1 in a 1:1 ratio to 1 of 2 treatment groups.

- **Upadacitinib arm:**

Daily oral doses of upadacitinib 15 mg from the Baseline visit until the Week 16 visit.

Period 1: subjects randomized to upadacitinib 15 mg had their dose increased to 30 mg if any of the following parameters were met:

- Starting at Week 4, subject had a < EASI 50 response

- Starting at Week 4, subject had a < 4-point improvement from Baseline in WP-NRS (weekly average)
- Starting at Week 8, subject had a < EASI 75 response

At Week 16: subjects receiving upadacitinib 15 or 30 mg, were reassigned based on their EASI response:

- Subjects with a < EASI 75 response were allocated or continued to receive oral doses of upadacitinib 30 mg QD in Period 2
- Subjects with a ≥ EASI 75 response completed end of study procedures

- **Dupilumab arm:**

Adults: Dupilumab 600 mg (2 x 300 mg dupilumab SC injection) administered at the Baseline visit, followed by dupilumab 300 mg SC injection EOW until the Week 16 visit.

Adolescents: Adolescents (12 to 17 years of age and weighing at least 40 kg).
Dose of dupilumab for SC administration in adolescent patients 12 to 17 years of age with AD.
Body weight of subject at Screening Visit and at each visit.

1. 40 to < 60 kg:
   - Initial dose: 400 mg (two 200 mg injections)
   - Subsequent doses (EOW): 200 mg
2. 60 kg or more
   - Initial dose: 600 mg (two 300 mg injections)
   - Subsequent doses (EOW): 300 mg

At Week 16: subjects receiving dupilumab as per its label were reassigned based on their EASI response:

- Subjects with a < EASI 75 response were offered the option to receive oral doses of upadacitinib 15 mg QD and enter Period 2
- Subjects with a ≥ EASI 75 response completed end of study procedures

Period 2: subjects reassigned to upadacitinib 15 mg QD had their dose increased to 30 mg QD if any of the following parameters were met:

- Starting at Week 20, subject had a < EASI 75 response
- Starting at Week 20, subject had a < 4-point improvement from Baseline in WP-NRS (weekly average)

Any subject treated for at least 8 weeks with upadacitinib 30 mg QD with a < EASI 50 response (reduction from Baseline) after rescue with topical corticosteroid treatment for at least 1 week was to be discontinued.

Randomization was stratified by baseline disease severity (moderate validated Investigator Global Assessment for AD [vIGA-AD 3] vs. severe [vIGA-AD 4]) and age categories (12 to < 18; 18 to < 40; ≥40 to < 64 years).

During Period 1 and Period 2 which were open-label, only the efficacy assessor was blinded to the subject's treatment assignment. Subjects and other study site personnel were aware of the subject's treatment assignment. The study team monitored and evaluated any AEs to identify findings that could put the study subjects at risk and then made clinical decisions regarding the study conduct, which could have included modification or termination of the study. No independent Drug Monitoring Committee was conducted for this study. No interim analysis was planned for this study.

Statistical Methods

Efficacy:
All efficacy analyses were conducted in the ITT Populations, with all primary and secondary endpoints analyzed using the ITT_1 Population. All tests were conducted under a 2-sided significance level of 0.05. The statistical comparisons of upadacitinib versus dupilumab for the primary efficacy endpoint and the ranked secondary endpoints were carried out in the hierarchical order under a 2-sided significance level of 0.05.
For analysis in Period 1, all primary and secondary endpoints were analyzed using Cochran-Mantel-Haenszel test. All efficacy endpoints were summarized descriptively using ITT_2 Population in Period 2.
Safety:
The Safety Population included all subjects who received at least 1 dose of study drug. A TEAE was defined as any AE that began or worsened in severity after initiation of upadacitinib or dupilumab (30 days following the last dose of upadacitinib or 84 days (12 weeks) following the last dose of dupilumab). All AEs presented were treatment-emergent, unless otherwise noted.

Results

Efficacy results

Upadacitinib demonstrated superior efficacy versus dupilumab with statistically significantly higher response rates in the primary endpoint and all ranked secondary endpoints, with p-values < 0.0001. For those subjects who received dupilumab in Period 1 but did not achieve an adequate response (EASI response < 75) at Week 16, data from Period 2 showed improved efficacy after switching to upadacitinib for 16 Weeks in Period 2. In addition, a number of subjects who received upadacitinib in Period 1 but did not achieve an adequate response at Week 16, achieved responses in various thresholds of skin and itch improvement after continuing or escalating to upadacitinib 30 mg in Period 2.

Safety results

The total population in this study is inclusive of adults and adolescents and is discussed below. Upadacitinib and dupilumab were well tolerated during this study. No deaths were reported in this study. The proportion of subjects with TEAEs, including those that the investigator assessed as having a reasonable possibility of being related to study drug, was higher in the upadacitinib group compared with the dupilumab group in Period 1.

Upadacitinib and dupilumab had a similar proportion of subjects with SAEs, AEs leading to discontinuation of study drug and severe AEs in Period 1. Nasopharyngitis was the most frequently reported event in the upadacitinib and dupilumab treatment groups. The most frequently reported AESI was creatine phosphokinase (CPK) elevation in the upadacitinib group and hepatic disorder (1.1%) in the dupilumab group. The majority of CPK elevations were mild or moderate in severity and none were serious. No treatment-emergent AESIs of malignancy, renal dysfunction, adjudicated MACE, adjudicated VTE, adjudicated GI perforations, or active TB were reported in the study.

In Period 1, SAEs were reported in 4 subjects in the upadacitinib group and 5 subjects in the dupilumab group. A SAE PT was not reported more than once per treatment group. One subject in the dupilumab group had 2 events of serious infection (PTs of pneumonia and sepsis), and no subjects in the upadacitinib group in Period 1. Five subjects in the upadacitinib group reported TEAEs of opportunistic infections excluding TB and herpes zoster, and no subjects in the dupilumab group. All events were eczema herpeticum, none of which were serious or led to discontinuation of study drug. Herpes zoster

was reported in 8 subjects in the upadacitinib group, and 2 subjects in the dupilumab group. No events were serious or severe. One event of disseminated herpes zoster led to study drug discontinuation. Hepatic disorders (including DILI) were reported in 9 subjects in the upadacitinib group and 5 subjects in the dupilumab group. Most hepatic disorder events were hepatic enzyme elevations, were mild to moderate in severity, and were considered by the investigator as having no reasonable possibility of being related to study drug. No hepatic disorder events were serious or led to study drug discontinuation in subjects in the upadacitinib group. No Hy's law cases were identified.

One subject in the upadacitinib group reported a TEAE of an adjudicated arterial thromboembolic event, PT of peripheral arterial occlusion. The peripheral arterial occlusion was serious, moderate in severity, and was considered by the investigator to be possibly related to study drug. Subject had completed treatment with study drug 3 days prior to the event. No adjudicated VTE events were reported in the upadacitinib or dupilumab group.

Other events based on safety concerns reported from dupilumab or associated with the disease state include conjunctivitis, acute allergic reactions, injection site reactions, suicidal ideation and behavior, keratitis, parasitic (Helminth) infections, and arthralgia. The majority of these events were mild or moderate in severity. No events of parasitic (Helminth) infections were reported.

One serious hypersensitivity reaction (PT of anaphylactic reaction) occurred in the upadacitinib group in Period 1. The event was severe, did not result in study drug discontinuation and was considered by the investigator as having no reasonable possibility of being related to study drug. One subject in the upadacitinib group reported a SAE of suicidal ideation in Period 1. The event resulted in the study drug being interrupted and was considered by the investigator as having no reasonable possibility of being related to study drug.

In Period 2, the proportion of subjects with any TEAE and AEs leading to discontinuation of study treatment were similar on UPA/UPA 30 mg and DUPI/UPA treatment groups. The proportion of subjects with any SAEs or severe AEs were higher on UPA/UPA 30 mg compared to DUPI/UPA group. Nasopharyngitis continued to be the most frequently reported event in both treatment (UPA/UPA 30 mg and DUPI/UPA groups). The most frequently reported AESI was CPK elevation in the UPA/UPA 30 mg group and herpes zoster, neutropenia, and hepatic disorder in the DUPI/UPA group. The majority of CPK elevations were mild or moderate in severity and none were serious.

In Period 2, SAEs were reported in 4 subjects in the UPA/UPA 30 mg group and no SAEs were reported in the DUPI/UPA group. A SAE PT was not reported more than once per treatment group. One subject in the UPA/UPA 30 mg group reported a serious infection, PT of pneumonia. The event was severe, led to study drug interruption, and was considered by the investigator as having no reasonable possibility of being related to study drug. Two subjects in the UPA/UPA 30 mg group reported 1 TEAE each of opportunistic infection excluding TB and herpes zoster, and 1 subject in the DUPI/UPA group reported 2 TEAEs of opportunistic infections excluding TB and herpes zoster. All events were eczema herpeticum, none of which were serious, severe, or led to discontinuation of study drug. All events were considered by the investigator to have a reasonable possibility of being related to study drug.

Four subjects in the UPA/UPA 30 mg group and 2 subjects in the DUPI/UPA group reported TEAEs of herpes zoster. One ophthalmic herpes zoster event was reported in the UPA/UPA 30 mg group. No events were serious, severe, or led to discontinuation of study drug. Hepatic disorder (including DILI) was reported in 2 subjects in the UPA/UPA 30 mg group and in 2 subjects in the DUPI/UPA group. All events were hepatic enzyme elevations, and the majority were mild to moderate in severity. No hepatic disorder events were serious or led to study drug discontinuation. No Hy's law cases were identified.

No TEAEs of an anaphylactic reaction, injection site reaction, suicidal ideation, keratitis, or parasitic (Helminth) infection were reported in Period 2. The majority of TEAEs of hypersensitivity reactions, conjunctivitis, and arthralgia were mild or moderate in severity. As compared to the known safety profile of upadacitinib, there were no new safety signals identified for subjects who received upadacitinib in Period 1 and continued to Period 2 or in those who initially received dupilumab in Period 1 and then switched to upadacitinib in Period 2. Per the study design there was no washout period between the switch from dupilumab in Period 1 to upadacitinib in Period 2.

Paediatric Data

In Study M23-696, a subset of 117 subjects were 12 to less than 18 years of age, comprising the adolescent group. Adolescent subjects comprised a small proportion in Period 1 (117/920) and in Period 2 (45/355) of the total population and are discussed below. The number of adolescents in this study was reasonably small particularly during Period 2; therefore, results should be interpreted with caution.

In adolescent subjects, upadacitinib demonstrated numerically higher achievement in the primary endpoint versus dupilumab, with a nominal p-value of ≤ 0.05.

Upadacitinib and dupilumab were well tolerated in adolescent subjects during this study. There were no deaths. The proportion of adolescent subjects with TEAEs was higher in the upadacitinib group compared with the dupilumab group (68.4% on upadacitinib; 54.2% on dupilumab) in Period 1. There was a lower proportion of SAEs, AEs leading to discontinuation and severe AEs on upadacitinib compared to dupilumab (1.8%, 0%, 3.5% on upadacitinib; 3.4%, 5.1%, and 5.1% on dupilumab, respectively) in Period 1. One SAE was reported in a subject in the upadacitinib group (PT of anaphylactic reaction, considered by the investigator as having no reasonable possibility of being related to study drug and dose was not changed) and 2 subjects in the dupilumab group (PT of juvenile idiopathic arthritis, considered by the investigator as having a reasonable possibility of being related to study drug, drug was withdrawn; and PT of depression, considered by the investigator as having no reasonable possibility of being related to study drug). Of note, the SAE of anaphylactic reaction noted above was also the serious hypersensitivity reaction reported in Period 1.

The most frequently reported AE in adolescent subjects in Period 1 was nasopharyngitis in the upadacitinib group and upper respiratory tract infection in the dupilumab group. No treatment-emergent AESIs of serious infections, opportunistic infections excluding TB and herpes zoster, active TB, lymphopenia, renal dysfunction, malignancy, adjudicated MACE, adjudicated VTE, adjudicated GI perforation, fractures, retinal detachment, or adjudicated arterial thromboembolic events were reported in adolescent subjects in the study.

Herpes zoster was reported in 1 adolescent subject in the upadacitinib group with study drug being interrupted. The event was nonserious, moderate in severity, considered by investigator as having a reasonable possibility of being related to study drug. Hepatic disorders (including DILI) were reported in 2 adolescent subjects in the upadacitinib group in Period 1. Both hepatic disorder events were hepatic enzyme elevations, moderate in severity, and 1 event was considered by the investigator as having no reasonable possibility of being related to study drug. Other AESIs that occurred during Period 1 in adolescents on upadacitinib was CPK elevation in 5 subjects and 1 serious hypersensitivity reaction.

In Period 2, the proportion of adolescent subjects with TEAEs was lower in the UPA/UPA 30 mg group compared with the DUPI/UPA group (40.0% on UPA/UPA 30 mg; 50.0% on DUPI/UPA). AEs leading to discontinuation of study drug were reported in 1 adolescent subject in the DUPI/UPA group, and none in the UPA/UPA 30 mg group. Severe AEs were reported in 1 adolescent subject in UPA/UPA 30 mg group, and none in the DUPI/UPA group. No SAEs were reported in adolescent subjects in Period 2. The only AESIs reported in adolescents in Period 2 were Hepatic disorder (including DILI) and CPK elevation

events which were reported in 2 adolescent subjects each in the UPA/UPA 30 mg group, and none in the DUPI/UPA group. All events were considered by the investigator as having no reasonable possibility of being related to study drug.

The MAH's conclusions

Upadacitinib demonstrated superior efficacy over dupilumab for the primary endpoint and all ranked secondary endpoints. Upadacitinib demonstrated a rapid onset of action and greater depth of response in skin and itch improvement. For those subjects who received dupilumab in Period 1 but did not achieve an adequate response at Week 16, data from Period 2 showed improved efficacy after switching to upadacitinib in Period 2. In addition, a number of subjects who received upadacitinib in Period 1 but did not achieve an adequate response at Week 16, achieved responses in various thresholds of skin and itch improvement after continuing or escalating to upadacitinib 30 mg in Period 2. Both upadacitinib and dupilumab were well-tolerated. No new safety signals were observed for upadacitinib in the total population or in adolescents as compared to the known safety profile. The benefit-risk profile of upadacitinib in this study is assessed as favourable based the efficacy outcomes and safety data for the study.

2.3.3. Discussion on clinical aspects

The MAH has submitted the results for study M23-696, in accordance with Article 46 of Regulation (EC) No1901/2006.

Study M23-696 was a global, Phase 3b/4, randomized, open-label, efficacy assessor-blinded, multicenter study that evaluated upadacitinib compared with dupilumab per its label, as monotherapy, in adolescent and adult subjects (≥ 12 and < 64 years of age weighting at least 40 kg) with moderate to severe AD who have inadequate response to systemic therapy or for whom use was medically inadvisable.

Treatment with upadacitinib was initiated at 15 mg QD and dose escalated to 30 mg based on the clinical response, compared with dupilumab as per its label, after 16 weeks of treatment. A total of 920 subjects, including 117 adolescents were randomized at 214 sites.

The results of the performed study support the clinical efficacy and safety of upadacitinib and show that dose escalation had improved outcomes in patients who did not achieve an adequate response while on treatment with 15 mg upadacitinib or dupilumab, during Period 1. The treatments were generally well-tolerated, and the safety results were consistent with the currently documented safety profile of the product, as reflected in the label. However, the number of the adolescents who continued in Period 2 is considered relatively small (47/117); thus, the interpretation of safety data in the adolescent group should be made with caution.

It is noted that upadacitinib is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy; the product information already includes paediatric Phase 3 data from a total of 542 adolescents who were exposed to 15 or 30 mg of upadacitinib, and a recommendation for dose escalation to 30 mg upon inadequate clinical response is listed in section 4.2 of the SmPC.

Overall, the benefit-risk of upadacitinib remains unchanged. No update to the Summary of Product Characteristics is proposed by the MAH, which is endorsed by the CHMP.

3. CHMP overall conclusion and recommendation

No new findings of clinical efficacy and safety were observed in the performed Post-Marketing Study M23-696. The MAH has not proposed update to the Summary of Product Characteristics based on the study M23-696, which is agreed by the CHMP.

☒ **Fulfilled:**

No regulatory action required.