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Human Medicines Division

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

RINVOQ

upadacitinib

Procedure no: EMEA/H/C/004760/P46/018

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**	**Need for discussion[2]**
☐	Start of procedure	26 Feb 2023	26 Feb 2023	☐
☐	CHMP Rapporteur Assessment Report	03 Apr 2023	29 Mar 2023	☐
☐	CHMP members comments	17 Apr 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20 Apr 2023	n/a	☐
☒	CHMP adoption of conclusions:	26 Apr 2023	26 Apr 2023	☐

Table of contents

1. Introduction

On 2023-02-26, 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 M17-377 "**Moderate to Severe Atopic Dermatitis: Evaluation of Upadacitinib in Combination with Topical Corticosteroids in Adolescent and Adult Subjects in Japan**" 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 according to the Rinvoq® label.

Treatment guidelines for atopic dermatitis (AD) do not mandate discontinuation of topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) with systemic immunomodulating therapy. To align with treatment practices in which topical agents may be provided in combination with a systemic agent, Study M17-377 aimed to test the hypothesis that upadacitinib combined with TCS would provide better efficacy versus placebo combined with TCS, and be well-tolerated in adolescent and adult subjects in Japan with moderate to severe AD.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

Study M17-377 'Moderate to Severe Atopic Dermatitis: Evaluation of Upadacitinib in Combination with Topical Corticosteroids in Adolescent and Adult Subjects in Japan'

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.

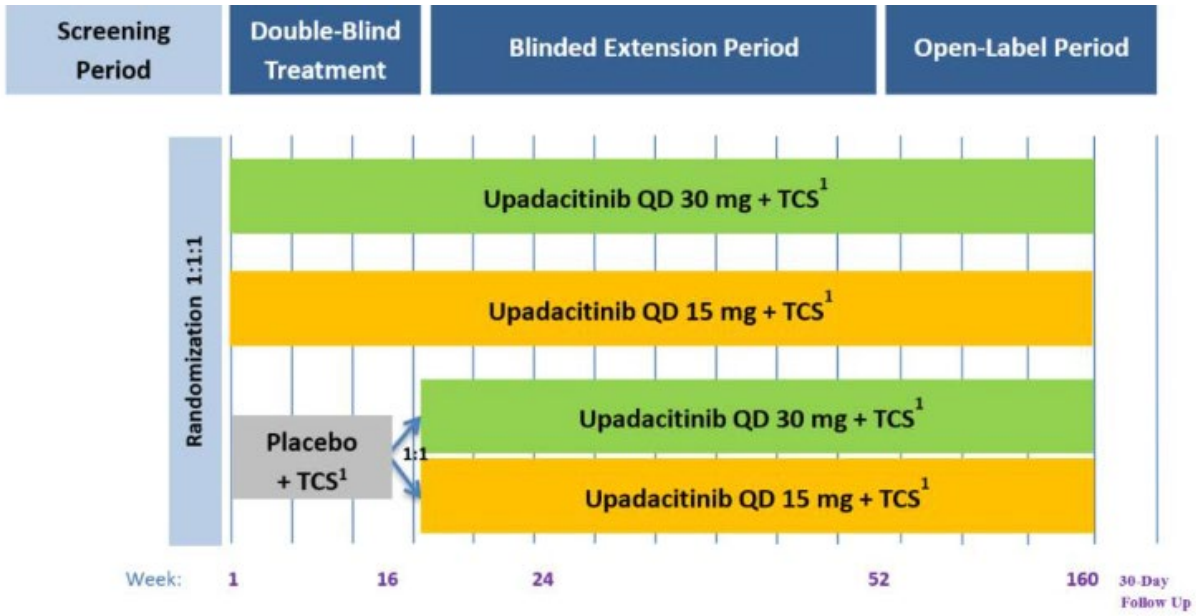
Study M17-377 - Moderate to Severe Atopic Dermatitis: Evaluation of Upadacitinib in Combination with Topical Corticosteroids in Adolescent and Adult Subjects in Japan

Description

Study M17-377 was a Phase 3, randomized, double-blind, multi-centre study that evaluated upadacitinib combined with TCS in adolescent and adult subjects in Japan with moderate to severe AD who were candidates for systemic therapy. Eligible subjects must have had a documented history of inadequate response to treatment with topical AD treatments or documented systemic treatment for AD within 6 months prior to the baseline visit.

The study was comprised of a 35-day screening period, a 16-week Double-Blind Treatment Period, a 36-week blinded-extension Period (Week 16 to 52), an open label long-term extension (Week 52 to Week 160 or permanent withdrawal of the marketing application), and a 30-day Follow-Up Visit. The study was open label after all subjects completed the Week 52 visit.

Figure 1. Study design schematic



1. Topical calcineurin inhibitors permitted for use in areas where TCS generally not advisable.

An interim analysis was conducted when the last subject completed the Week 24 visit. After the Week 24 interim analysis, the sites and subjects remained blinded until Week 52. An additional interim analysis was conducted when the last ongoing subject completed the Week 52 visit, which included the safety data up to the timing of the database lock for the Week 52 CSR as well as all efficacy data up to Week 52.

An external Data Monitoring Committee (DMC) periodically reviewed unblinded safety data throughout the course of the study. The primary responsibility of the DMC was to protect the safety of the subjects participating in this study.

The study was performed at 42 study sites located in Japan. The first subjects first visit took place on 27 Oct 2018. The last subjects last visit was on 19 Aug 2022.

Methods

Study participants

A total of 272 subjects, including 29 adolescents, were randomized at 42 study sites. At baseline, male and female subjects enrolled in this study were ≥ 12 and ≤ 75 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, and weekly average of daily worst pruritus numerical rating scale ≥ 4. Additionally, subjects must have applied a topical emollient (moisturizer) twice daily for at least 7 days before the baseline visit. Also, subjects were required to have a documented history (within 6 months prior to the baseline visit) of inadequate response to TCS or TCI or documented systemic treatment for AD within 6 months prior to the baseline visit.

Subjects were excluded if they received systemic therapy for AD within 4 weeks; targeted biologic treatment within 5 half-lives (if known) or 12 weeks, whichever is longer; phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks; oral or parenteral traditional Chinese medicine within 4 weeks; marijuana use within 2 weeks; or topical treatments (with the exception of topical emollient treatments) including but not limited to TCS, TCI, or topical phosphodiesterase type 4-inhibitors within 7 days.

In addition, to ensure subject safety, any subject laboratory values that met the following criteria at screening were excluded: serum aspartate transaminase (AST) > 2 × upper limit of normal (ULN); serum alanine aminotransferase (ALT) > 2 × ULN; estimated glomerular filtration rate of < 40 mL/min/1.73 m2 by simplified 4-variable Modification of Diet in Renal Disease formula < 40 mL/min/1.73 m2 for adult subjects or by Schwarz equation for adolescent subjects; total white blood cell count < 2,500/µL; absolute neutrophil count < 1,500/µL; platelet count < 100,000/µL; absolute lymphocyte count < 800/µL; and hemoglobin < 10 g/dL.

Randomisation and treatments

Subjects who met eligibility criteria were randomized in a 1:1:1 ratio to receive, in combination with TCS, either daily oral doses of upadacitinib 15 mg, upadacitinib 30 mg, or placebo. Randomization was stratified by baseline disease severity (Validated Investigator Global Assessment for AD [vIGA-AD] 3 and 4) and age (< 18, 18 to 40, or > 40 years).

At the end of Week 16, subjects in the placebo group were re-randomized in a 1:1 ratio to receive daily oral doses of upadacitinib 15 mg or upadacitinib 30 mg. At Week 16, the re-randomization of the placebo treatment group was stratified by 50% reduction in Eczema Area and Severity Score (EASI) 50 responder (Yes or No) and age (< 18, 18 to 40, or > 40 years). Subjects originally in the upadacitinib 15 mg once-daily (QD) and upadacitinib 30 mg QD groups continued their treatment into the long-term extension period up to Week 160.

A TCS regimen in combination with study drug was mandatory until Week 16. After Week 16, the use of any concomitant topical medication for AD could be administered per investigator discretion and was no longer required. Additionally, high potency TCS was not considered as rescue treatment after Week 16.

At Week 4 through Week 24, rescue treatment for AD could be provided at the discretion of the investigator if medically necessary (i.e., to control intolerable AD symptoms) for subjects with < EASI 50 response at any 2 consecutive scheduled visits; after Week 24, systemic rescue treatment could be provided for subjects with < EASI 50 response at any scheduled or unscheduled visit.

Objective(s)

The objective of this study was to assess the safety of upadacitinib combined with topical corticosteroids (TCS) in adolescent and adult subjects in Japan with moderate to severe atopic dermatitis (AD) who are candidates for systemic therapy.

Outcomes/endpoints

Safety:
Adverse event (AE), changes in vital signs, physical examinations, electrocardiogram, laboratory tests (hematology, chemistry, and urinalysis), and collection of product complaints throughout the study.

Efficacy:

There were no primary or secondary efficacy endpoints.

Exploratory efficacy evaluations/endpoints included the following: proportion of subjects achieving vIGA-AD 0 or 1 with at least 2 grades of reduction from baseline; proportion of subjects achieving a 50%/75%/90% reduction in EASI; change and percent change from baseline in EASI; proportion of subjects achieving an improvement (reduction) in Worst Pruritus NRS ≥ 4 from baseline; change and percent change from baseline in Worst Pruritus NRS.

Sample size

The planned sample size were 264 subjects, 272 subjects were analysed.

Statistical Methods

Safety:

The safety analyses were carried out using the Safety Population in the DB, BE, and OL Periods, and across periods, and was based on treatments the subjects received. Safety data were also summarized separately for adult and adolescent populations. Safety was assessed by AEs, physical examination, laboratory assessments, and vital signs. Missing safety data were not imputed.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA).
Treatment-emergent adverse events (TEAEs) were defined as those that began or worsened in severity after the first dose of study drug but within 30 days after the last dose of study drug. The number and percentage of subjects experiencing TEAEs were tabulated using the MedDRA system organ class (SOC) and preferred term (PT) by severity and by relationship to the study drug as assessed by the investigator. Summaries (including percentages and events per 100 patient-years) of serious AEs (SAEs), deaths, AEs leading to discontinuation, and AEs of special interest (AESIs) were provided as well. Pre-treatment AEs were summarized separately.

For laboratory and vital signs, mean change from baseline and percentage of subjects with evaluations meeting pre-defined potentially clinically significant values were summarized.

Efficacy:

The efficacy analysis was exploratory and was conducted in the Intent-to-Treat Population.
In the DB Period, categorical endpoints were analysed using a Cochran-Mantel-Haenszel test stratified by vIGA-AD categories (<4; 4) and age (adolescent; adults). Non-responder imputation (NRI) was used to handle the intercurrent events and missing data. For the categorical endpoints, NRI was used for handling the intercurrent events (composite variable strategy) and missing data. For continuous endpoints, MMRM was used for handling the intercurrent events (hypothetical strategy) and missing data. In the DB Period, efficacy was also analysed using the observed case (OC) approach (for subjects who stayed on treatment): for the continuous endpoints, the least-squares mean and standard error were provided based on the analysis of covariance (ANCOVA); for the categorical endpoints, the response rate and the 95% CI based on the normal approximation were provided.
The long-term efficacy in the BE and OL periods was summarized using the OC approach (for subjects who stayed on treatment), the NRI approach (categorical endpoints only), and the MMRM approach (continuous endpoints only).

Efficacy Results

In the All Upadacitinib Treated Population overall, improvements in exploratory efficacy endpoints were observed for subjects randomized at the start of the study to receive upadacitinib 15 mg or 30 mg, generally with long-term maintenance of improvement through Week 160. For subjects initially randomized to receive placebo during the DB Period and then randomized to receive upadacitinib at either 15 mg or 30 mg dose during the BE/OL Period, trends in efficacy variables from initiation of treatment through Week 160 were generally similar to the trends observed for subjects randomized to upadacitinib at baseline.

Safety results

In the All_UPA Population overall (adults and adolescents), the exposure adjusted rate of treatment-emergent adverse events (TEAEs) was slightly higher in the upadacitinib 30 mg group compared with the 15 mg group.

The most common TEAEs (≥ 5 E/100 patient years [PY]) were nasopharyngitis, acne, herpes zoster, pyrexia, AD, herpes simplex, oral herpes, and injection site pain (due to COVID-19 vaccination). The rates of serious adverse events (SAEs) and TEAEs leading to study drug discontinuation were low (< 5 E/100 PY) and similar between the two treatment groups. Most SAEs or AEs leading to discontinuation of study drug were reported with a single preferred term (PT). No deaths were reported during the study.

In the All_UPA Population overall, most AESIs reported in adolescents were infrequent. The event rates of adverse events of special interest (AESIs) of serious infection, herpes zoster, anemia, neutropenia, lymphopenia, and creatine phosphokinase (CPK) elevation were slightly higher with upadacitinib 30 mg compared to upadacitinib 15 mg. The characteristics of these events were generally similar to what was observed in the other AD studies for upadacitinib. One rectal cancer was reported in a 36-year-old subject receiving upadacitinib 15 mg that was considered by the investigator to be not related to study drug. One event of adjudicated major adverse cardiovascular even (MACE) (cerebellar hemorrhage) was reported in a 22-year-old subject receiving upadacitinib 15 mg and the event was considered by the investigator to have a reasonable possibility of being related to study drug. No events of active tuberculosis, gastrointestinal perforation, non-melanoma skin cancer, confirmed lymphoma, adjudicated venous thromboembolism, and renal dysfunction were observed in the study.

Similar to other AD studies for upadacitinib, acne was reported at a higher dose with upadacitinib 30 mg compared to upadacitinib 15 mg. All acne events were mild or moderate and nonserious. Fractures were reported slightly more frequently in the upadacitinib 30 mg group (10 events) compared to the 15 mg group (6 events). No pattern in terms of fracture types was observed. All but one event of fractures were nonserious. The serious event of fracture was considered by investigator to be not related to study drug. No events of fracture led to interruption of study drug and all but one event of fractures resolved by the end of the study.

Evaluation of laboratory values and vital signs did not reveal any new safety concerns. No subject was identified as having a Hy's Law case during the study. Similar to other AD studies, weight increases were observed in both upadacitinib treatment groups.

Overall, no new safety risks were identified in this study and the safety profile of upadacitinib was consistent with what was observed in other AD studies.

Paediatric Data

In Study M17-377, 29 patients were ≤ 18 years of age, comprising the adolescent group. Both upadacitinib 15 mg and 30 mg showed improvements in exploratory efficacy endpoints, with long-term

maintenance through Week 160. Adolescent subjects comprised a small proportion (29/272) of the total population during the DB Period. Of these, 8/9 adolescents in the placebo group and all adolescents in both upadacitinib treatment groups completed the DB Period and entered the BE/OL Period.

In the All_UPA Population adolescent group (28 adolescent subjects), the exposure-adjusted event rate of TEAEs was numerically higher in the upadacitinib 30 mg group, and the rate of TEAEs assessed by the investigator as having a reasonable possibility of being related to study drug was higher in the upadacitinib 15 mg group. A total of 2 TEAEs (worsening of atopic dermatitis, abnormal lymphocyte morphology) led to discontinuation of study drug. Overall, there were 4 SAEs reported among adolescents (appendicitis, irritable bowel syndrome, concussion, and meniscus injury). One SAE was assessed as having a reasonable possibility of being related to study drug (appendicitis in the upadacitinib 15 mg group). Note, however, that the total number of adolescents included in this study was small; thus, the interpretation of safety data in the adolescent group should be made with caution.

Evaluation of available height data in the Safety_A Population indicated subjects had reached the decline phase of pubertal growth at the time of treatment initiation with upadacitinib. Growth curves generally stayed within the standards for the general population, except for a single male subject on upadacitinib 30 mg. This subject's height was already below -2 standard deviations of the general growth curve prior to initiating treatment and may have already reached adult height by the time of entry into the study at 17 years of age.

The MAH's conclusions

The efficacy of upadacitinib for subjects with moderate to severe AD was supported by improvement and maintenance of improvement in exploratory efficacy variables through Week 160 for subjects who were randomized to receive upadacitinib at baseline. Similar trends in improvement were observed in subjects switched to receive upadacitinib in the BE/OL Period of the study.

Safety results showed that upadacitinib 15 mg and 30 mg QD doses were well tolerated. No new safety risks were observed in this AD clinical study.

The benefit-risk profile of both doses of upadacitinib in this study is assessed as favourable based on the safety and exploratory efficacy outcomes of the study. No updates to the Summary of Product Characteristics have been proposed based on these data.

2.3.2. Discussion on clinical aspects

The results of the performed study support the clinical safety and efficacy of Rinvoq used in treatment of patients with atopic dermatitis in Japan. Safety and clinical efficacy were also demonstrated in less than 30 paediatric patients enrolled in the study. The total number of adolescents included in this study was small; thus, the interpretation of safety data in the adolescent group should be made with caution.

The safety results were consistent with the currently documented safety profile of the product, as described in the label. The benefit-risk of upadacitinib is unchanged and no update to the Summary of Product Characteristics has been proposed based on these data and will not be requested.

3. CHMP overall conclusion and recommendation

No new findings of clinical efficacy and safety were observed in the performed Post-Marketing Study. The MAH has not suggested any update to the Summary of Product Characteristics based on the performed study, a view which is supported by the CHMP.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

None.