Amsterdam, 14 October 2021
EMA/527511/2021
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/P46/011

Note

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

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Table of contents

1. Introduction

On 08 July 2021, the MAH submitted data available from patients less than 18 years of age recruited to a Phase 3 induction study in ulcerative colitis (M14-675) for upadacitinib, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The indications approved for Rinvoq are Rheumatoid arthritis, Psoriatic arthritis and Ankylosing spondylitis (all in adult patients); and Atopic dermatitis (in adults and adolescents 12 years and older).

2. Scientific discussion

2.1. Information on the development program

Ulcerative colitis (UC) is a chronic, relapsing inflammatory disease of the large intestine characterised by inflammation and ulceration of mainly the mucosal and occasionally submucosal intestinal layers. Patients with UC are at an increased risk for colon cancer, and the risk increases with the duration of disease as well as extent of colon affected by the disease.

The MAH submitted a clinical study report for a Phase 3 induction study:

Study M14-675: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Evaluate the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Ulcerative Colitis

The MAH stated that the purpose of this submission is to comply with Article 46 of Regulation (EC) No1901/2006, as amended, by submitting data available from patients less than 18 years of age recruited to the study M14-675.

The MAH also stated that the study M14-675 clinical study report will also be submitted to support the Grouped Extension Application with Type II variation for Ulcerative Colitis in September 2021.

2.2. Information on the pharmaceutical formulation used in the study

The study agent (1 tablet of upadacitinib 45 mg or matched placebo) was administered orally once daily for 8 weeks in Part 1, and additional 8 weeks in Part 2 (see study design below).

2.3. Clinical aspects

2.3.1. Clinical study

Study M14-675: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Evaluate the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Ulcerative Colitis

Description

Study M14-675 was a two-part Phase 3, multicenter, randomised, placebo-controlled, double-blind induction study evaluating the efficacy and safety of upadacitinib 45 mg once daily (QD) compared to placebo in subjects with moderately to severely active UC. In addition to adult subjects, adolescent subjects with body weight ≥ 40 kg who met the definition of Tanner Stage 5 were also enrolled if allowed by local regulations/institutional review boards/independent ethics committees.

In Part 1, 522 subjects were randomized 2:1 to double-blind (DB) upadacitinib (n=345) or matching placebo (n=177) for an 8-week induction period. Subjects who did not achieve clinical response per Adapted Mayo score at Week 8 in Part 1 could continue in Part 2 (an open-label 8-week extended treatment period for clinical non-responders from Part 1), in which all subjects received upadacitinib 45 mg QD.

Methods

Objective(s)

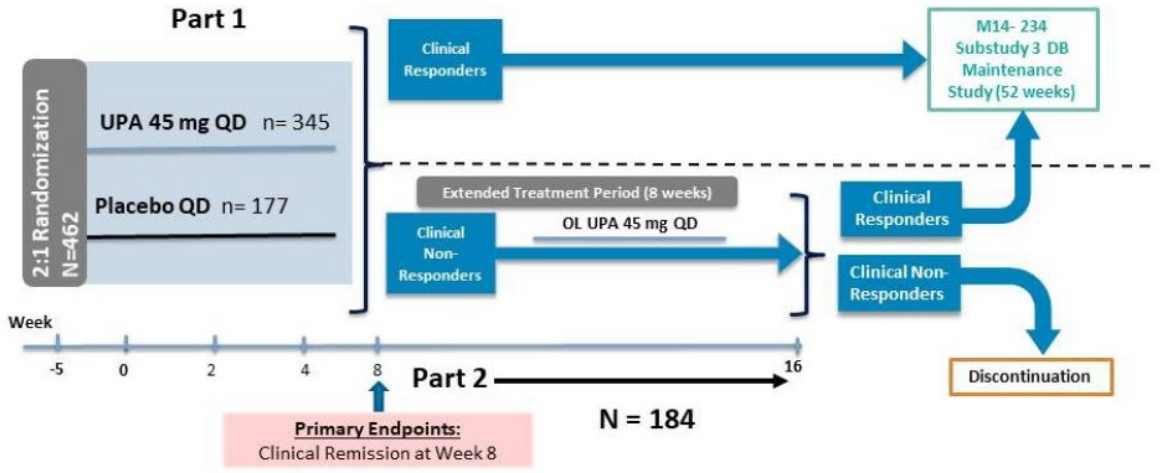
The **primary objective** of this study was to evaluate the efficacy and safety of upadacitinib 45 mg QD compared to placebo in inducing clinical remission (per Adapted Mayo score) in subjects with moderately to severely active UC who have demonstrated inadequate response, loss of response, or intolerance to oral aminosalicylates, immunosuppressants, corticosteroids, and/or biologic therapies.

The **secondary objectives** of the study were to evaluate the efficacy of upadacitinib 45 mg QD comparing with placebo in ranked secondary endpoints of achieving endoscopic improvement, endoscopic remission, clinical response per Adapted Mayo score, clinical response per Partial Adapted Mayo score, histologic-endoscopic mucosal improvement, no bowel urgency, no abdominal pain, histologic improvement, mucosal healing, and change in Inflammatory Bowel Disease Questionnaire (IBDQ) total score and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score.

Study design

Study M14-675 was a two-part Phase 3, multicenter, randomised, placebo-controlled, double-blind induction study designed to evaluate the efficacy and safety of oral administration of upadacitinib 45 mg once daily compared to placebo as induction therapy for up to 16 weeks in subjects with moderately to severely active UC.

Figure 1. Design Schematic



DB = double-blind; OL = open label; QD = once daily; UPA = upadacitinib

Note: Planned numbers were 308 subjects in the upadacitinib 45 mg group and 154 subjects in the placebo group.

In **Part 1**, 522 subjects were randomized 2:1 to double-blind (DB) upadacitinib (n = 345) or matching placebo (n = 177) for an 8-week induction period.

Randomization was stratified by biologic inadequate responders (Bio-IR) status (bio-IR vs non-bio-IR), corticosteroid use (yes or no), and Adapted Mayo score (≤ 7 or > 7) at Baseline. Within bio-IR stratum, the randomization was further stratified by number of prior biologic treatments (≤ 1 or > 1). Within non-bio-IR stratum, the randomization was further stratified by previous biologic use (yes or no). Subjects who did not achieve clinical response per Adapted Mayo score at Week 8 in Part 1 could continue in Part 2.

The **Part 2** was an open-label 8-week Extended Treatment Period for clinical non-responders from Part 1, in which all subjects received open-label treatment with upadacitinib 45 mg QD for 8 additional weeks (until Week 16).

Subjects who achieved clinical response at Week 8 or Week 16 were eligible to enroll into the Phase 3 maintenance study (M14-234 Substudy 3) in the upadacitinib UC program. Subjects who did not achieve clinical response at Week 16 were discontinued from the induction study.

Study population

Study M14-675 enrolled adult Subjects 18 to 75 years of age with moderately to severely active UC defined as an Adapted Mayo score of 5 to 9 (consisting of stool frequency subscore [SFS], rectal bleeding subscore [RBS] and endoscopy subscore) with endoscopy subscore of 2 or 3 (confirmed by a central reader).

In addition to adult subjects, adolescent subjects with body weight ≥ 40 kg who met the definition of Tanner Stage 5 were also enrolled if allowed by local regulations/institutional review boards/independent ethics committees.

Subjects were diagnosed with UC for ≥ 90 days prior to Baseline, confirmed by colonoscopy during the Screening Period. Subjects demonstrated an inadequate response, loss of response, or intolerance to at least one of the following treatments including oral aminosalicylates, corticosteroids, immunosuppressants, and/or biologic therapies.

Treatments

Study drug was to be taken orally once daily with or without food at approximately the same time each day, beginning at the Baseline Visit. All subjects received 1 tablet daily.

In Part 1 of the study, subjects were randomised in a 2:1 ratio to receive double-blind 1 tablet of upadacitinib 45 mg or matching placebo QD therapy for 8 weeks.

In Part 2 of the study, subjects who did not achieve clinical response per Adapted Mayo score (defined as a decrease from Baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from Baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1) at Week 8 in Part 1 received 1 tablet open-label treatment with upadacitinib 45 mg QD for 8 additional weeks (until Week 16).

Outcomes/endpoints

<u>The primary endpoint</u> was the proportion of subjects who achieved clinical remission per Adapted Mayo score (defined as SFS ≤ 1 and not greater than Baseline, RBS of 0, and endoscopic subscore ≤ 1) at Week 8. Note: evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity conferred an endoscopic subscore of 2.

<u>Ranked secondary</u> were evaluated at Week 8 or Week 2 (only clinical response per Partial Adapted Mayo score):

- Proportion of subjects with endoscopic improvement (defined as an endoscopic subscore ≤ 1)
- Proportion of subjects with endoscopic remission (defined as an endoscopic subscore of 0)
- Proportion of subjects achieving clinical response per Adapted Mayo score (defined as decrease from baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1)
- Proportion of subjects achieving clinical response per Partial Adapted Mayo score (defined as decrease from Baseline ≥ 1 points and ≥ 30% from Baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1)
- Proportion of subjects achieving histologic-endoscopic mucosal improvement (endoscopic subscore ≤ 1 and Geboes score ≤ 3.1)
- Proportion of subjects who reported no bowel urgency
- Proportion of subjects who reported no abdominal pain
- Proportion of subjects who achieved histologic improvement
- Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) total score
- Proportion of subjects with mucosal healing (endoscopic subscore = 0 and Geboes score < 2)
- Change from Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) score

Statistical Methods

Efficacy

The primary estimand was the difference in the percentage of subjects achieving clinical remission per Adapted Mayo score at Week 8 regardless of premature discontinuation of study drug and without initiation or dose escalation of UC-related corticosteroids in the upadacitinib 45 mg QD and placebo groups in the Intent-to-Treat (ITT) population. The primary analysis compared the proportion of subjects achieving clinical remission in upadacitinib treatment group and placebo group in the ITT1 population. The difference between the treatment groups in the primary efficacy endpoint were assessed using the Cochran-Mantel-Haenszel (CMH) test and were stratified by bio-IR status (bio-IR vs. non-bio-IR), Baseline corticosteroid use (yes vs. no) and Baseline Adapted Mayo score (≤ 7 vs. > 7). A CMH based two-sided 95% confidence interval for the difference between treatment groups was calculated.

Safety

Standard safety analyses included reporting of AEs, adverse events of special interest (AESIs), laboratory, and vital signs measurements. All safety comparisons were performed between the upadacitinib group and the placebo group using the safety analysis sets. The safety variable was summarized by treatment according to the treatment a subject actually received. The number and percent of subjects experiencing treatment-emergent adverse events were summarized. The treatment group differences in continuous safety variables (e.g., change from Baseline on laboratory tests and vital signs) were assessed using an ANOVA model with the term of treatment.

Results

Recruitment/ Number analysed

In Study M14-675, subjects were enrolled from 204 sites in 40 countries. In Part 1, a total of 522 subjects were randomised and 521 subjects, including 9 adolescent subjects, received at least one dose of study drug.

Baseline data

Key demographics and baseline characteristics were generally balanced between the placebo and upadacitinib 45 mg QD groups, according to the MAH. Approximately half of subjects were Bio-IR (biologic therapy-intolerant or inadequate responder).

Efficacy results

CHMP's comment:

The MAH submitted data available from patients less than 18 years of age recruited to the Phase 3 induction study (M14-675) for Upadacitinib, in accordance with Article 46 of Regulation (EC) No1901/2006.

A total of 521 subjects, including 9 adolescent subjects, received at least one dose of study drug in the study (M14-675).

No conclusion could be drawn for the efficacy of upadacitinib for induction treatment in adolescent subjects with Ulcerative Colitis, based on 9 adolescent subjects enrolled in the study M14-675 (6 randomised to the upadacitinib 45 mg QD group and 3 to the placebo group).

Safety results

According to the MAH:

Upadacitinib 45 mg QD as induction treatment for 8 weeks was well tolerated. No new safety risks were observed with upadacitinib 45 mg treatment compared with the known safety profiles of upadacitinib 15 mg and 30 mg doses as observed in the upadacitinib clinical programs for other indications.

No events of adjudicated major adverse cardiac events (MACE), venous thromboembolic events (VTE) or gastrointestinal perforation or active tuberculosis, malignancy, or death were reported in the upadacitinib group. Rates of serious adverse events (SAEs) and adverse events (AEs) leading to treatment discontinuation were higher in the placebo group compared to the upadacitinib group.

The most commonly reported AEs (≥ 4% of subjects) were acne, creatine phosphokinase (CPK) elevations and anemia in the upadacitinib group, and headache and worsening ulcerative colitis in the placebo group. Both herpes zoster and opportunistic infection (cytomegalovirus infection) were each reported in 2 subjects on upadacitinib.

The incidences of neutropenia, CPK elevation, hepatic disorder (most were elevations of transaminases), anemia, and lymphopenia were higher with upadacitinib 45 mg QD compared with placebo, and most were mild or moderate; all AE of special interest events were non-serious except for 1 serious event of anemia. One event of lymphopenia in the upadacitinib 45 mg group led to study drug discontinuation. Rates of Common Terminology Criteria for Adverse Events Grade 3 or 4 laboratory values and potentially clinically significant vital signs were generally infrequent.

Extended treatment of up to 16 weeks of upadacitinib 45 mg QD did not result in an overall increased or new safety risk.

Paediatric Data

Study M14-675 enrolled 9 adolescent subjects (5 male and 4 female).

Of the 9 subjects, 6 were randomised to receive upadacitinib 45 mg QD and 3 were randomised to receive matching placebo.

- Part 1 (randomised, double-blind, placebo-controlled 8-week induction period):
    - Upadacitinib 45 mg QD: All 6 subjects completed treatment, ranging in duration from 54 to 58 days.
    - Placebo: All 3 subjects completed treatment, ranging in duration from 56 to 58 days.
- Part 2 (open-label, 8-week extended treatment period for clinical non-responders from Part 1):
    - Upadacitinib 45 mg QD (Part 1)/upadacitinib 45 mg QD (Part 2) sequence: The one subject assigned to this sequence discontinued the Part 2 treatment after 35 days due to an SAE of colitis ulcerative (worsening of UC).
    - Placebo (Part 1)/upadacitinib 45 mg QD (Part 2) sequence: All 3 subjects assigned to this sequence completed the Part 2 treatment (duration: 56 days).

Five of the 9 adolescent subjects reported treatment-emergent adverse events (TEAEs), with events reported during placebo treatment for 1 subject, during upadacitinib treatment for 3 subjects, and during both placebo and upadacitinib treatment for 1 subject (Table 2). Of the 4 subjects with TEAEs during upadacitinib treatment, 1 subject reported TEAEs in Part 1, 2 subjects in reported TEAEs in Part 2, and 1 subject reported TEAEs in Parts 1 and 2.

Table 2. Treatment-emergent AEs and SAEs in Paediatric Subjects, by Study Part and Treatment

Study Part(s) Treatment	Study Period	Study Start / Stop Days	MedDRA PT	Serious?	Action with Study Drug	Relationship to Study Drug	Severity
DB Part 1 Treatment							
DB UPA 45 mg QD							
5	DB	15 / 29	Aphthous ulcer	No	None	Possibly related	Mild
	DB	28 / 29	Oral pain	No	None	Not related	Moderate
DB Part 1 Treatment / OL Part 2 Treatment							
DB Placebo / OL UPA 45 mg QD							
6	DB	31 / 59	Anaemia	No	None	Possibly related	Moderate
	DB	31 / 118	Thrombo-cytosis	No	None	Not related	Moderate
	OL	87 / 120	Anaemia	No	None	Not related	Moderate
	FU	115 / 126	Colitis ulcerative	Yes	None	Not related	Moderate
7	DB	17 / ongoing	Anaemia	Yes	None	Possibly related	Moderate
	DB	31 / 45	Blood creatinine increased	No	None	Possibly related	Mild
8	OL	71 / 97	Mouth ulceration	No	None	Not related	Mild
DB UPA 45 mg QD / OL UPA 45 mg QD							
9	DB	31 / 45	Anaemia	No	None	Not related	Mild
	OL	73 / ongoing	Anaemia	No	None	Not related	Moderate
	OL	93 / ongoing	Colitis ulcerative	Yes	Withdrawn	Not related	Moderate

AE = adverse event; DB = double-blind treatment; FU = follow-up; MedDRA: Medical Dictionary for Regulatory Activities; OL = open-label treatment; PT = preferred term; QD = once daily; SAE = serious adverse event; UPA = upadacitinib

Treatment-emergent SAEs were reported in 3 subjects, according to the MAH:

• Placebo (Part 1)/upadacitinib 45 mg QD (Part 2) sequence: A subject reported an SAE of colitis ulcerative during the 30-day follow-up period after the last dose of study drug. The event, which was assessed by the investigator as unrelated to study drug, resolved after 12 days.

• Placebo (Part 1)/upadacitinib 45 mg QD (Part 2) sequence: A subject with history of anemia and receiving treatment with iron supplementation.

During Part 1 (placebo) on Study Day 35, the subject developed pale skin, anemia and was admitted to the hospital due to anemia. The subject was transfused with 1 unit of red blood cell concentrate. On Study Day 37, the subject was discharged from the hospital. Study drug was not interrupted.

The event, which was assessed by the investigator as possibly related to study drug, was ongoing at the end of the study.

• Upadacitinib 45 mg QD (Part 1)/upadacitinib 45 mg QD (Part 2) sequence: A subject, with 4-year history of UC and anemia. During Part 2 on Study Day 93, the subject was admitted to the hospital with an exacerbation of UC.

On Day 100, the subject underwent a subtotal colectomy with emergence of a stoma. On Day 113, the subject was discharged from the hospital. The study drug was withdrawn due to the event on Study Day 93. The event, which was assessed by the investigator as not related to study drug, was ongoing at the end of the study.

CHMP's comment:

A total of 521 subjects, including 9 adolescent subjects, received at least one dose of study drug in the study (M14-675).

All the 9 adolescent subjects (6 in the upadacitinib 45 mg QD group and 3 in the placebo group) completed 8-week treatment in the Part 1 (randomised, double-blind, placebo-controlled 8-week induction period).

One subject assigned to the 45 mg QD (Part 1)/upadacitinib 45 mg QD (Part 2) group discontinued the Part 2 treatment (an open-label 8-week extended treatment period for clinical non-responders from Part 1) after 35 days (study Day 93) due to a SAE of colitis ulcerative (worsening of UC).

Five of the 9 adolescent subjects reported treatment-emergent AEs.

Treatment-emergent SAEs were reported in 3 adolescent subjects:
- one SAE of anemia (moderate) reported in a subject in the placebo group (Part 1)
- one SAE of colitis ulcerative (worsening of UC, moderate) reported in a subject assigned to the placebo (Part 1)/upadacitinib 45 mg QD (Part 2) group during the 30-day follow-up period (assessed by the investigator as unrelated to study drug)
- one SAE of colitis ulcerative (worsening of UC, moderate) reported in a subject assigned to the 45 mg QD (Part 1)/upadacitinib 45 mg QD (Part 2) group on study Day 93 (assessed by the investigator as not related to study drug). This subject discontinued the Part 2 treatment due to the SAE.

Other treatment-emergent AEs (non-SAEs) reported during Part 1 and/or Part 2 were aphthous ulcer (mild) and oral pain (moderate) in one subject, anaemia in two subjects (moderate in 1 subject, mild/moderate in 1 subject), thrombocytosis in one subject (moderate), blood creatinine increased in one subject (mild), and mouth ulceration in one subject (mild).

No new safety signals were identified by the MAH.

No firm conclusions could be drawn for the safety of upadacitinib for induction treatment in adolescent subjects with Ulcerative Colitis, based on 9 adolescent subjects enrolled in the study M14-675 (6 in the upadacitinib 45 mg QD group and 3 in the placebo group).

No update to the product information has been proposed by the MAH as part of this Article 46 submission, which is endorsed.

2.3.2. Discussion on clinical aspects

The MAH submitted data available from patients less than 18 years of age recruited to a Phase 3 ulcerative colitis induction study (M14-675) for upadacitinib, in accordance with Article 46 of Regulation (EC) No1901/2006.

The study M14-675 was a two-part Phase 3, multicenter, randomised, placebo-controlled, double-blind induction study evaluating the efficacy and safety of upadacitinib 45 mg once daily compared to placebo in subjects with moderately to severely active Ulcerative colitis (UC). In Part 1, 522 subjects were randomized 2:1 to double-blind upadacitinib (n=345) or matching placebo (n=177) for an 8-week induction period. Subjects who did not achieve clinical response per Adapted Mayo score at Week

8 in Part 1 could continue in Part 2 *(*an open-label 8-week extended treatment period for clinical non-responders from Part 1), in which all subjects received upadacitinib 45 mg once daily.

The primary objective was to assess the efficacy and safety of upadacitinib compared to placebo in inducing clinical remission (per Adapted Mayo score) in subjects with moderately to severely active UC who have demonstrated inadequate response, loss of response, or intolerance to oral aminosalicylates, immunosuppressants, corticosteroids, and/or biologic therapies.

A total of 521 subjects, including 9 adolescent subjects, received at least one dose of study drug in the study M14-675.

Efficacy

Nine adolescent subjects (6 randomised to the upadacitinib 45 mg QD group and 3 to the placebo group) were enrolled in the study M14-675. No conclusion could be drawn for the efficacy of upadacitinib for induction treatment in adolescent subjects with Ulcerative Colitis.

Safety

All the 9 adolescent subjects (6 in the upadacitinib 45 mg QD group and 3 in the placebo group) completed 8-week treatment in the Part 1. One subject assigned to 45 mg QD (Part 1)/upadacitinib 45 mg QD (Part 2) group discontinued the Part 2 treatment after 35 days due to a SAE of colitis ulcerative (worsening of UC).

Five of the 9 adolescent subjects reported treatment-emergent AEs (mild or moderate). Treatment-emergent SAEs (all moderate) were reported in 3 adolescent subjects (anemia reported in 1 subject in the placebo group; colitis ulcerative (worsening of UC) reported in 2 subjects, both assessed by the investigator as unrelated to study drug). No new safety signals were identified by the MAH.

Overall, no new safety concerns have emerged in the adolescent subjects participated in the study M14-675 with oral administration of upadacitinib 45 mg QD as induction therapy up to 16 weeks.

No firm conclusions could be drawn for the safety of upadacitinib for induction treatment in adolescent subjects with Ulcerative Colitis, based on 9 adolescent subjects enrolled in the study M14-675 (6 in the upadacitinib 45 mg QD group and 3 in the placebo group).

No update to the product information has been proposed by the MAH as part of this Article 46 submission, which is endorsed.

3. CHMP overall conclusion and recommendation

A total of 9 adolescent subjects with Ulcerative Colitis (6 in the upadacitinib 45 mg QD group and 3 in the placebo group) were enrolled in the Phase 3 induction study (M14-675). No new safety signals have emerged.

The benefit-risk balance of upadacitinib remains unchanged and no update of the SmPC is warranted.

☒ Fulfilled:

No regulatory action required. According to the MAH, the study M14-675 clinical study report will also be submitted to support the Grouped Extension Application with Type II variation for Ulcerative Colitis in September 2021.