19 August 2022
EMA/602548/2022
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/P46/015

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	21 June 2022	21 June 2022	☐
☐	CHMP Rapporteur Assessment Report	25 July 2022	21 June 2022	☐
☐	CHMP members comments	08 Aug 2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	11 Aug 2022	n/a	☐
☒	CHMP adoption of conclusions:	19 Aug 2022	19 Aug 2022	☐

[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 06 May 2022, 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

Study M14-234 is part of the ulcerative colitis clinical development program.

An interim clinical study report of M14-234 Substudy 3 (data cut-off date 30 April 2021) was submitted as part of the grouped extension application with Type II variation for ulcerative colitis (UC, EMEA/H/C/004760/X/0012/G). This submission includes the final study report, with last subject last visit 13 Dec 2021.

2.2. Information on the pharmaceutical formulation used in the study

Patients were treated with oral upadacitinib 7.5 mg QD, upadacitinib 15 mg QD, upadacitinib 30 mg QD or placebo. There are no specific paediatric formulations.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study M14-234 Substudy 3
  A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis. Substudy 3 includes the phase 3 maintenance part of the study.

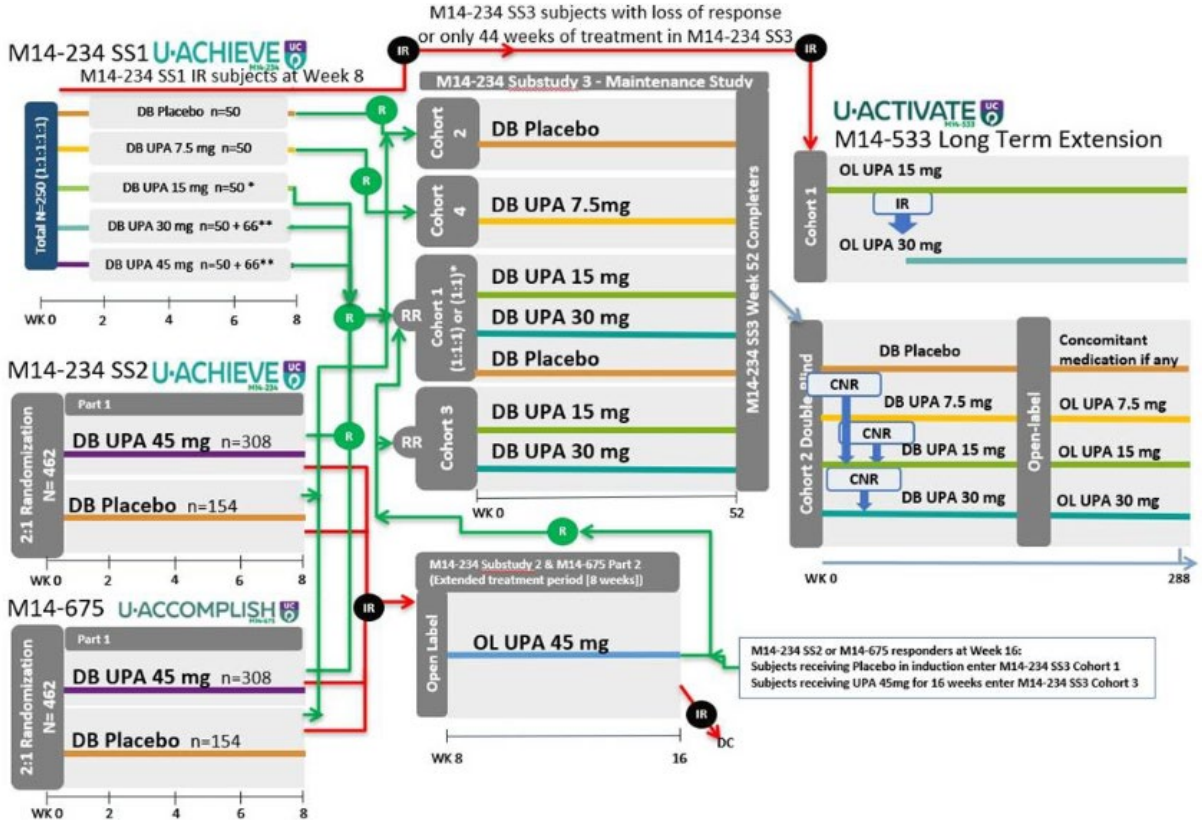
2.3.2. Clinical study

Study M14-234 Substudy 3

Description

A summary of the overall ulcerative colitis clinical programme is shown below.

Figure 1. Ulcerative colitis clinical trial programme



Study M14-234 Substudy 3 was a Phase 3 maintenance study with a primary objective to evaluate the efficacy and safety of upadacitinib 15 and 30 mg once daily (QD) compared with placebo in subjects with moderately to severely active UC who achieved clinical response per Adapted Mayo score following induction therapy from the Phase 2 induction Study M14-234 Substudy 1 and the two identical Phase 3 induction Studies M14-234 Substudy 2, and Study M14-675.

Methods

Study participants

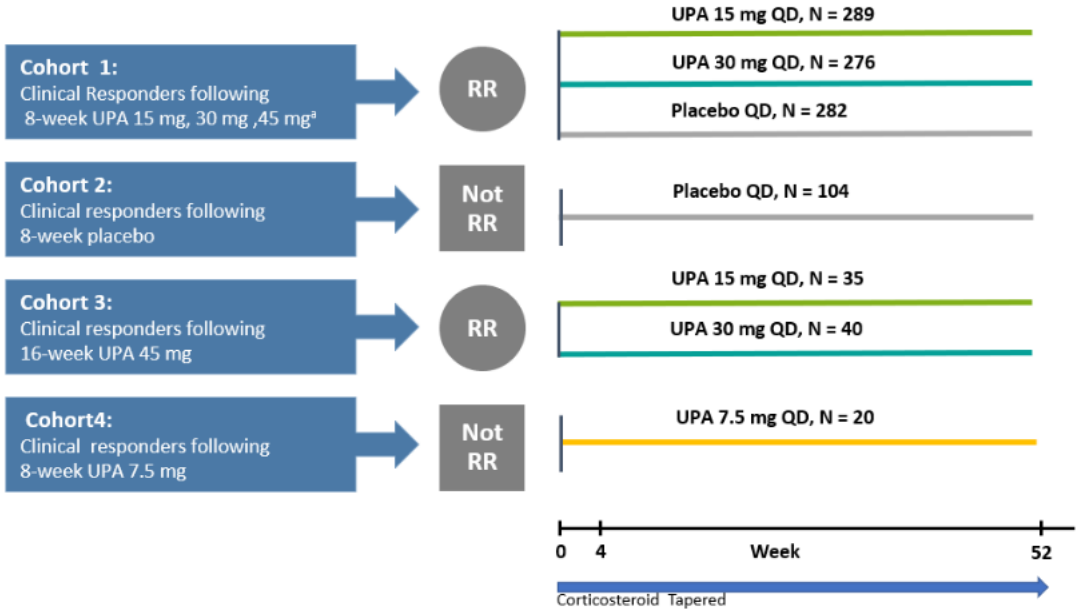
Study M14-234 enrolled adult subjects 18 to 75 years of age with moderately to severely active UC defined as an Adapted Mayo score of 5 to 9 (consisting of stool frequency subscore [SFS], rectal bleeding subscore [RBS], and endoscopy subscore) with endoscopy subscore of 2 or 3 (confirmed by a central reader).

In addition to adult subjects, adolescent subjects 16 and 17 years of age with body weight ≥ 40 kg who met the definition of Tanner Stage 5 were also eligible if allowed by local regulations/institutional review boards/independent ethics committees.

Treatments

For the treatments given in the study, please see figure below.

Figure 2. M14-234 Substudy 3 design



QD = once daily; RR = re-randomized; UPA = upadacitinib

Notes: Approximately 525 subjects were planned for Cohort 1 groups, N = 175/group. Approximately 60 subjects were planned for Cohort 2; approximately 150 subjects, N = 75/group were planned for Cohort 3; and approximately 15 subjects were planned for Cohort 4.

Responders who received upadacitinib 15 mg in Study M14-234 Substudy 1 were randomized only to receive upadacitinib 15 mg or placebo.

A total of 1044 subjects were dosed. Two subjects in Cohort 1 who were enrolled were not dosed: 1 subject in the upadacitinib 15 mg group and 1 subject in the placebo group.

Objectives

The primary objective of Substudy 3 (Phase 3 maintenance) was to evaluate the efficacy and safety of upadacitinib 30 mg and 15 mg compared to placebo in achieving clinical remission per Adapted Mayo score in subjects with moderately to severely active UC who achieved clinical response per Adapted Mayo score following induction therapy from Study M14-234 Substudy 1, Substudy 2, or Study M14-675.

The secondary objective of Substudy 3 was to evaluate the efficacy of upadacitinib 15 and 30 mg compared to placebo in the multiplicity-controlled secondary endpoints at Week 52 including endoscopic improvement, maintaining clinical remission, corticosteroid-free remission, maintaining endoscopic improvement, endoscopic remission, maintaining clinical response, mucosal healing, no bowel urgency, no abdominal pain, histologic-endoscopic mucosal improvement, change in Inflammatory Bowel Disease Questionnaire (IBDQ) total score, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score.

Outcomes/endpoints

This final clinical study report summarizes the safety of upadacitinib as maintenance therapy in Study M14-234 Substudy 3 (Phase 3 maintenance). The only and final analysis for the 52-week efficacy data of Study M14-234 Substudy 3 was performed at a database lock and unblinded analysis conducted in June 2021 for the purpose of regulatory submission has been previously submitted as part of variation X/12.

Sample size

Study M14-234 Substudy 3 was planned for approximately 750 subjects who achieved clinical response per Adapted Mayo Score after completion of induction treatment or Extended Treatment Period in Study M14-234 Substudy 1, Substudy 2, or Study M14-675 were eligible to enter Substudy 3 and treated with a blinded treatment assignment for up to 52 weeks.

Randomisation and blinding (masking)

An overview of the randomisation is showed in Figure 1. The rationale for re-randomizing only induction responders who received upadacitinib 15, 30 or 45 mg QD was to ensure that no subject received a dose during maintenance that was higher than what was received in the induction period.

Statistical Methods

The primary focus of the safety presentations was the SA_C population, a subset of the Safety population (all subjects who received study drug) who were upadacitinib 45 mg 8-week induction responders and who were enrolled under the protocol for 44- or 52-week maintenance treatment period in Cohort 1. In addition, safety summaries were provided for other safety populations. The standard safety analyses included reporting of AEs, adverse events of special interest (AESIs), laboratory measurements, and vital signs measurements.

Frequency tables and exposure-adjusted event rate (EAER) per 100 patient-years (PYs) tables of subjects with treatment-emergent adverse events (TEAEs) by system organ class (SOC) and by preferred term (PT) as in the Medical Dictionary for Regulatory Activities (MedDRA) dictionary were provided by treatment group. All continuous laboratory parameters and vital signs variables at each visit were summarized by treatment group. Frequency tables of subjects meeting criteria for potentially clinically significant (PCS) laboratory values and for PCS vital sign values were provided by treatment group.

Results

Participant flow

A total of 1,046 patients were enrolled in the study. Among all enrolled subjects, 617 subjects had completed the study and 429 subjects had prematurely discontinued from the study. Among the 1,044 subjects who received at least 1 dose of study drug, 6 were excluded from the ITT population due to site non-compliance.

Recruitment

A total of 1,046 subjects were enrolled from 299 sites in 43 countries.

First Subject First Visit: 14 December 2016
Last Subject Last Visit: 13 December 2021

Baseline data

Key demographics and baseline characteristics were generally balanced between the placebo and upadacitinib treatment groups. Approximately 45% of subjects in each group were ≥ 18 years to < 40 years, and another 45% of subjects in each group were ≥ 40 years to < 65 years and approximately half of subjects were biologic therapy-intolerant or inadequate responder (Bio-IR).

Number analysed

A total of 6 adolescent subjects were enrolled, all of whom came from induction Study M14-675. Of the 6 adolescent subjects, 2 (1 male and 1 female) were randomized to the upadacitinib 30 mg group and 4 were randomized to the placebo group (2 males and 2 females). In Study M14-234 Substudy 3, all 6 adolescent subjects were enrolled in Cohort 1.

Efficacy results

According to the MAH, no efficacy conclusions can be drawn based on the small number of adolescents enrolled.

Safety results

Summary of the overall safety data presented in the final CSR

Upadacitinib is known to be associated with an increased risk of serious infections, opportunistic infections, herpes zoster, hepatic transaminase elevations, anemia, neutropenia, creatinine phosphokinase (CPK) elevations, and increases in lipid parameters and weight. There is general concern on the risk for malignancy, major adverse cardiac event (MACE), venous thromboembolic event (VTE), and gastrointestinal (GI) perforations based on potential class effects for the JAK inhibitors. A class referral is currently ongoing (EMEA/H/A-20/1517).

Since this submission not only includes paediatric data but also the final study report from Study M14-234, a summary of the overall safety data was presented. According to the MAH, upadacitinib 15 and 30 mg were generally safe and well-tolerated in the maintenance treatment for UC subjects, and no new safety risk was observed compared with the known safety profile of upadacitinib.

Table 1. Overview of Treatment-Emergent Adverse Events and All Deaths per 100 Patient-Years (SA-C population)

	Placebo (N=245) (PYS=135.0) Events (E/100PY) [SSA E/100PY]	UPA 15 mg QD (N=250) (PYS=199.4) Events (E/100PY) [SSA E/100PY]	UPA 30 mg QD (N=251) (PYS=218.5) Events (E/100PY) [SSA E/100PY]
Any treatment-emergent:			
Any adverse event (AE)	674 (499.4) [494.1]	626 (313.9) [314.1]	691 (316.2) [315.6]
Any AE with reasonable possibility of being related to study drug$	192 (142.3) [137.5]	178 (89.3) [91.1]	233 (106.6) [106.6]
Any severe AE	29 (21.5) [21.3]	18 (9.0) [8.9]	23 (10.5) [10.5]
Any serious AE	28 (20.7) [20.8]	24 (12.0) [12.0]	22 (10.1) [10.0]
Any AE leading to discontinuation of study drug	26 (19.3) [19.1]	11 (5.5) [5.5]	19 (8.7) [8.7]
Any AE leading to death	0	0	0
Deaths#	0	0	0
Occurring <= 30 days after last dose	0	0	0
Occurring > 30 days after last dose	0	0	0

No death was reported in the maintenance treatment period. In the primary analysis data set (SA_C, subjects who received at least 1 dose of the study drug and who were 8-week clinical responders to upadacitinib 45 mg induction therapy), the most frequently reported treatment-emergent adverse

events (TEAEs) included nasopharyngitis in all treatment groups. The most frequently reported TEAEs also included worsening of UC (preferred term [PT]: colitis ulcerative) and arthralgia in the placebo group, worsening of UC in the upadacitinib 15 mg group, and blood CPK increased in the upadacitinib 30 mg group.

No adverse events of special interest in the categories of active tuberculosis (TB) and lymphoma were reported in the maintenance treatment period (Table 2). In the SA_C population, the event rates of serious infection and opportunistic infection (excluding TB and herpes zoster) were not higher in the upadacitinib treatment groups compared with the placebo group. Herpes zoster was reported in subjects in the 2 upadacitinib treatment groups with higher event rates on upadacitinib 30 mg; no events were reported in placebo group. Malignancy excluding non-melanoma skin cancer (NMSC) was reported infrequently across all treatment groups. Three NMSC events were reported, all in the upadacitinib 30 mg group. No adjudicated GI perforation was reported in subjects on upadacitinib. One event of adjudicated MACE was reported in the upadacitinib 30 mg group, and 2 events of adjudicated VTE were each reported in the upadacitinib 15 mg and 30 mg groups.

Table 2. Overview of Treatment-Emergent Adverse Events of Special Interest per 100 Patient-Years (SA-C population)

	Placebo (N=245) (PYS=135.0) Events (E/100PY) [SSA E/100PY]	UPA 15 mg QD (N=250) (PYS=199.4) Events (E/100PY) [SSA E/100PY]	UPA 30 mg QD (N=251) (PYS=218.5) Events (E/100PY) [SSA E/100PY]
Any treatment-emergent:			
Any serious infections	8 (5.9) [5.9]	10 (5.0) [5.0]	7 (3.2) [3.2]
Any opportunistic infection excluding tuberculosis and herpes zoster	2 (1.5) [1.6]	2 (1.0) [0.9]	2 (0.9) [0.9]
Any active tuberculosis	0	0	0
Any herpes zoster	0	12 (6.0) [5.8]	16 (7.3) [7.3]
Any neutropenia	7 (5.2) [5.1]	11 (5.5) [5.5]	19 (8.7) [8.7]
Any creatine phosphokinase (CPK) elevation	5 (3.7) [3.9]	16 (8.0) [8.1]	22 (10.1) [10.1]
Any possible malignancies	2 (1.5) [1.6]	1 (0.5) [0.5]	5 (2.3) [2.3]
Any malignancy	1 (0.7) [0.8]	1 (0.5) [0.5]	5 (2.3) [2.3]
Any malignancies excluding NMSC	1 (0.7) [0.8]	1 (0.5) [0.5]	2 (0.9) [0.9]
Any non-melanoma skin cancer (NMSC)	0	0	3 (1.4) [1.4]
Any lymphoma	0	0	0

Consistent with other indications, the events of neutropenia, CPK elevation, and transaminase increases were generally reported more frequently in subjects on upadacitinib than those on placebo. Most of the laboratory-related TEAEs were mild or moderate in severity, nonserious, and uncommonly led to study drug discontinuation.

Common Terminology Criteria for Adverse Events Grade 3 or 4 laboratory values and potentially clinically significant vital signs were generally infrequent. In the SA_C population, worsening of UC and anemia were more frequently reported in subjects treated with placebo than those on upadacitinib, which may be related to the improvement of underlying disease of UC in upadacitinib-treated subjects.

Summary of the paediatric data

Five of the 6 adolescent subjects reported TEAEs during Study M14-234 Substudy 3 with events reported during placebo treatment for 3 subjects and during upadacitinib treatment for 2 subjects (Table 3). No treatment-emergent SAEs were reported and no action was

taken with the study drug based on TEAEs for any of the adolescent subjects. According to the MAH, TEAEs were mild to moderate in severity.

Table 3. Treatment-emergent AEs and SAEs in Paediatric Subjects, by Study Treatment

Study Treatment Sex	Study Start / Stop Days Duration (days)	MedDRA PT	Serious?	Action with Study Drug	Relationship to Study Drug	Severity
Substudy 3 Treatment						
30 mg Upadacitinib QD						
Male	15/22 8	Influenza like illness	No	None	Reasonable possibility	Mild
	71 / ongoing	Fatigue	No	None	No reasonable possibility	Mild
	223 / ongoing	Acne	No	None	Reasonable possibility	Mild
Female	252 / 364 113	Mouth ulceration	No	None	No reasonable possibility	Mild
Placebo QD						
Female	177 / ongoing	Colitis ulcerative	No	None	No reasonable possibility	Moderate
Male	31 / 54 24	Urinary tract infection	No	None	No reasonable possibility	Mild
Female	214 / ongoing	Arthralgia	No	None	No reasonable possibility	Mild

AE = adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; SAE = serious adverse event.

NOTE: All yellow highlighted subject numbers (and this note) will be removed after QC.

2.3.3. Discussion on clinical aspects

This report includes the submission of a completed paediatric study for Rinvoq, in accordance with Article 46 of Regulation (EC) No1901/2006.

Study M14-234 is part of the ulcerative colitis clinical development program. Study M14-234 substudy 3 was a phase 3 maintenance study with the primary objective to evaluate the efficacy and safety of upadacitinib 15 and 30 mg once daily compared with placebo in subjects with moderately to severely active UC who achieved clinical response following induction therapy from the phase 2 and phase 3 induction studies.

An interim report of M14-234 substudy 3 (data cut-off date 30 April 2021) was submitted as part of the grouped extension application with Type II variation for ulcerative colitis (UC, EMEA/H/C/004760/X/0012/G). This submission includes the final study report, with last subject last visit 13 Dec 2021.

Study M14-234 enrolled adult subjects 18 to 75 years of age. In addition, adolescent subjects 16 and 17 years of age with body weight ≥ 40 kg who met the definition of Tanner Stage 5 were also eligible if allowed by local regulations/institutional review boards/independent ethics committees.

A total of 1,046 patients were enrolled in the study, including **6 adolescent subjects**. According to the MAH, no efficacy conclusions can be drawn based on the small number of adolescents enrolled. This is agreed on.

Summary of the overall safety data presented in the final CSR

Since this submission not only includes paediatric data but also the final study report from Study M14-234, a summary of the overall safety data was presented. No death was reported in the maintenance treatment period. The most frequently reported treatment-emergent adverse events included nasopharyngitis, worsening of UC, and blood CPK increased. Among adverse events of special interest, no cases of active tuberculosis or lymphoma were reported. The event rates of serious infection and opportunistic infection (excluding TB and herpes zoster) were similar in the upadacitinib and placebo group. Herpes zoster was more frequent in the upadacitinib treatment groups than in the placebo group. There were seven cases of malignancy reported, one in the placebo and upadacitinib 15 mg groups, respectively, and 5 in the upadacitinib 30 mg group. Among these, three were NMSC, all reported in the upadacitinib 30 mg group. No adjudicated GI perforation was reported in subjects on upadacitinib. One event of adjudicated MACE was reported in the upadacitinib 30 mg group, and 2 events of adjudicated VTE were each reported in the upadacitinib 15 mg and 30 mg groups. No additional cases of malignancy, MACE or VTE was reported compared to the data assessed within X/12/G. The risk for malignancy, MACE and VTE is currently under review in the class referral (EMEA/H/A-20/1517), and although the recent findings confer some concern, no actions are warranted within the current procedure.

Summary of the paediatric data

Among the 6 adolescent patients, treatment-emergent adverse events were reported in 5/6 patients (3 during treatment with placebo and 2 during treatment with upadacitinib; these were influenza-like illness, fatigue, and acne in one patient and mouth ulceration in one patient). No SAEs were reported. The presented data does not constitute any new safety concerns, and no actions are warranted.

3. CHMP overall conclusion and recommendation

This report includes the submission of a completed paediatric study for Rinvoq, in accordance with Article 46 of Regulation (EC) No1901/2006.

Within this procedure, the MAH submitted in accordance with Article 46 of Regulation (EC) No1901/2006 the final study report for the ulcerative colitis M14-234 maintenance substudy, including 6 adolescent subjects.

Since this submission not only includes paediatric data but also the final study report from Study M14-234, a summary of the overall safety data was presented. Among the AESIs, herpes zoster was more frequent in the upadacitinib treatment groups than in the placebo group. This is a known safety concern for upadacitinib. A dose-dependent association was observed for malignancy, in particular NMSC. Further, one event of adjudicated MACE was reported in the upadacitinib 30 mg group, and 2 events of adjudicated VTE were each reported in the upadacitinib 15 mg and 30 mg groups. The risk for malignancy, MACE and VTE is currently under review in a class referral (EMEA/H/A-20/1517), and although the recent findings confer some concern, no actions are warranted within the current procedure.

Among the 6 adolescent patients, no new safety concerns were identified.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

4. Request for supplementary information

None.