EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 February 2023
EMA/113995/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RINVOQ

International non-proprietary name: upadacitinib

Procedure No. EMEA/H/C/004760/II/0027

Note

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

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
AO	as observed
AP	abdominal pain
APS	abdominal pain score
BMI	body mass index
CAC	Cardiovascular Adjudication Committee
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CMH	Cochran-Mantel-Haenszel
CMQ	Company MedDRA query
COVID-19	coronavirus disease
CR-100	clinical response 100
CRF	case report form
CRO	contract research organization
CSS	Crohn's Symptom Severity
CTCAE	Common Toxicity Criteria for Adverse Events
DBL	database lock
DMC	Data Monitoring Committee
ECG	electrocardiogram
EIM	extra-intestinal manifestation
ePRO	electronic patient reported outcome
EQ-5D-5L	European Quality of Life 5 Dimensions
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FCP	fecal calprotectin
FDA	Food and Drug Administration
hs-CRP	high sensitivity C-reactive protein
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation42IEC Independent Ethics Committee
ITT	Intent-to-Treat
MACE	major adverse cardiac event
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effect model repeat measurement
NMSC	nonmelanoma skin cancer

NRI-C	Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19
NRI-NC	NRI with No special data handling for missing due to COVID-19
PD	premature discontinuation
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PRO	patient reported outcome
PT	preferred term
PY	patient-years
QoL	quality of life
SA	Safety population
SAE	serious adverse event
SAP	Statistical Analysis Plan
SES-CD	Simple Endoscopic Score for Crohn's disease
SF	stool frequency
SF-36	36-Item Short Form Health Survey
SMQ	Standardized MedDRA query
SOC	system organ class
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
US	United States
WPAI-CD	Work Productivity and Impairment Questionnaire – Crohn's disease

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AbbVie Deutschland GmbH & Co. KG submitted to the European Medicines Agency on 25 July 2022 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of moderately to severely active Crohn's disease in adult patients for RINVOQ, based on final results from three Phase III studies, two confirmatory placebo-controlled induction studies (Study M14 431/U-EXCEED/CD-1) and Study M14 433/U-EXCEL/CD-2) and a placebo-controlled maintenance/long-term extension study (Study M14-430/U-ENDURE/CD-3).
M14-431 study is a Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Biologic Therapy.
M14-433 study is a Phase III, Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Conventional and/or Biologic Therapies.
M14-430 study is an ongoing Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Maintenance and Long-Term Extension Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Crohn's Disease Who Completed the Studies M14-431 or M14-433.
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated.
The Package Leaflet is updated in accordance. Version 11 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0263/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0263/2022 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition

related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 12 October 2018 (EMEA/H/SA/3190/5/2017/II)18 May 2017 (EMEA/H/SA/3190/5/2017/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:　　Kristina Dunder　　　Co-Rapporteur:　　　　n/a

Timetable	Actual dates
Submission date	25 July 2022
Start of procedure:	13 August 2022
CHMP Rapporteur Assessment Report	7 October 2022
PRAC Rapporteur Assessment Report	14 October 2022
PRAC members comments	19 October 2022
Updated PRAC Rapporteur Assessment Report	20 October 2022
PRAC Outcome	27 October 2022
CHMP members comments	28 October 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 November 2022
Request for supplementary information (RSI)	10 November 2022
CHMP Rapporteur Assessment Report	20 December 2022
PRAC Rapporteur Assessment Report	3 January 2023
PRAC members comments	4 January 2023
Updated PRAC Rapporteur Assessment Report	5 January 2023
PRAC Outcome	12 January 2023
CHMP members comments	16 January 2023
Updated CHMP Rapporteur Assessment Report	19 January 2023
Request for supplementary information	26 January 2023
CHMP Rapporteur Assessment Report	8 February 2023
PRAC Rapporteur Assessment Report	13 February 2023
PRAC members comments	n/a
CHMP members comments	n/a
Updated PRAC Rapporteur Assessment Report	17 February 2023
Updated CHMP Rapporteur Assessment Report	17 February 2023
CHMP opinion:	23 February 2023

2. Scientific discussion

2.1. Introduction

The upadacitinib Crohn's disease (CD) clinical development program was designed to evaluate the efficacy and safety of upadacitinib in moderately to severely active CD in adult subjects who have primary or secondary inadequate response or intolerance to any of the currently available treatments for CD, including biologic treatments (Bio-IR) and conventional treatments except biologics (Non-Bio-IR).

2.1.1. Problem statement

Disease or condition

Crohn's disease (CD) is chronic inflammatory bowel disease with focal asymmetric, transmural, and occasionally granulomatous inflammation which can affect any segment of the gastrointestinal (GI) tract. CD may present with symptoms of fatigue, prolonged diarrhea with or without gross bleeding, abdominal pain, weight loss, and fever but the most common clinical symptoms are abdominal pain and diarrhoea.

The MAH applied for the following indication:

"RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent, or for whom such therapies are not advisable."

Epidemiology

Crohn disease is most common in western Europe and North America, where it has a prevalence of 100 to 300 per 100,000 people. (NIH)

Crohn's disease may present at any age though it more commonly presents in young adults. Both sexes are affected equally. It is more common in the presence of a family history in first degree relatives.

Biologic features

The exact cause of CD is still unknown but is hypothesized to be the result of a dysregulated immune system in the context of a genetically susceptible individual. It is thought that a combination of a patient's genetics, microbiome, immune response, and the environment result in an excessive and abnormal immune response in the gut that results in pathology seen in CD.

Clinical presentation, diagnosis and stage/prognosis

Any part of the GI tract may be affected from the mouth to the anus, with the ileum, colon and perineum most frequently involved. Affected tissue is identified by well-demarcated areas of thickened bowel, stenosis, adhesions, local lympho-adenopathy and fistulae. Typical endoscopic features include

isolated aphthous ulcers, deep ulceration, a cobblestone appearance of the gut lining and polyp formation. Histologically, Crohn's disease is characterised by trans-mural inflammation of the intestine. Inflammation may be non-specific or may be present as focal or diffuse granulomata. Extra-intestinal manifestations may affect the skin, joints, liver, biliary tree and eyes.

Diagnosis is achieved by a combination of clinical, laboratory, radiological, endoscopic and histological findings.

The natural history of CD is progressive for several patients, ultimately requiring hospitalisation and surgery, and lifelong treatment is required.

Crohn's disease is a chronic condition that relapses and remits. It has a global impact on patients' education, work, social and family life.

Management

The aim of medical treatment in CD has been focused on controlling inflammation and reducing symptoms. In addition to improving symptoms, an emerging goal of therapy is to heal the gut mucosa. Resolution of intestinal ulcers and endoscopic remission have been associated with positive clinical benefits, including higher rates of clinical remission, fewer hospitalizations, and few abdominal surgeries. However, improvement of the appearance of the intestinal mucosa may be more difficult to achieve than symptomatic improvement alone.

Treatment of moderately to severely active CD consists of conventional pharmaceutical therapies such as corticosteroids (for short term use) and immunomodulators [e.g., thiopurines and methotrexate], as well as biologic therapies. Contrary to the case in Ulcerative colitis (UC), aminosalicylates has shown limited efficacy in CD and is not recommended.

The approval of the first biologic infliximab over two decades ago and a few years later adalimumab greatly improved the treatment possibilities in CD. More recently, vedolizumab an anti-integrin and ustekinumab an inhibitor of IL-12 and IL-23 has been approved for use in CD.

Still, a proportion of CD patients have limited efficacy of approved treatments due to failing to respond (primary non-response), losing response over time (secondary non-response) or having contra-indications or intolerance to these medications. Regarding anti-TNF agents, data from clinical trials demonstrate that approximately 40% of patients experience primary non-response and secondary loss of response has occurred in 38% of patients at 6 months and 50% of patients at 1 year.

Therefore, there are unmet clinical need for new effective treatments in CD.

2.1.2. About the product

Upadacitinib is a selective and reversible Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, hematopoiesis, and immune surveillance. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and TYK2 which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, modulates gene expression and cellular function. JAK1 is important in inflammatory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function.

In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Atopic dermatitis is driven

by pro-inflammatory cytokines (including IL-4, IL-13, IL-22, TSLP, IL-31 and IFN-γ) that transduce signals via the JAK1 pathway. Inhibiting JAK1 with upadacitinib reduces the signaling of many mediators which drive the signs and symptoms of atopic dermatitis such as eczematous skin lesions and pruritus. Pro inflammatory cytokines (primarily IL 6, IL 7, IL 15 and IFNγ) transduce signals via the JAK1 pathway and are involved in the pathology of inflammatory bowel disease. JAK1 inhibition with upadacitinib modulates the signalling of the JAK-dependent cytokines underlying the inflammatory burden and signs and symptoms of inflammatory bowel diseases.

Upadacitinib is indicated in Rheumatoid arthritis, Psoriatic arthritis, Axial spondyloarthritis, Atopic dermatitis and Ulcerative colitis.

In 2022, a review of JAK inhibitors in the treatment of inflammatory disorders was initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004. On 23 January 2023, EMA's human medicines committee (CHMP) endorsed the measures recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to minimise the risk of serious side effects with Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders. These side effects include cardiovascular conditions, blood clots, cancer and serious infections.

These medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer.

JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Upadacitinib Crohn's Disease application is supported by data from one phase 2 dose ranging study, two replicate phase 3 induction studies (M14-431 and M14-433) and one phase 3 maintenance study (M14-430) which were all double-blind, randomised, placebo-controlled multi-centre studies. As stated in the EMA Guideline (CPMP/EWP/2284/99 Rev. 2 Guideline on the development of new medicinal products for the treatment of Crohn's disease) "to fulfil a claim for the treatment of Crohn's disease, it is expected that at least two confirmatory trials are provided". This is considered as fulfilled. The MAH also received Scientific Advice at the CHMP (EMEA/H/SA/3190/5/2017/II and clarification letter EMA/660515/2018). Most of the advice from the CHMP were followed with some minor deviation that are discussed in relevant sections.

2.1.4. General comments on compliance with GCP

According to the MAH, all clinical studies have been/are being conducted in accordance with the ICH and Good Clinical Practice guidelines and relevant regulatory requirements. Subjects were/are being accorded all rights granted by the Declaration of Helsinki. All protocols received approval by the appropriate governing investigational review board, ethics committee, or similar authority. Standard research methodology was/is utilized for the conduct and performance of each clinical study.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH has provided an ERA to include the new indication of Crohn´s disease; however, no new data for the environmental risk assessment were included with this application. The submitted ERA was updated from the original ERA submitted for the MAA for RA approval, and the updates to support the indications psoriatic arthritis (PsA), ankylosing spondylitis (AS), atopic dermatitis (AD), active ulcerative colitis (UC) and non-Radiographic Axial Spondylarthritis (nr-axSpA) in adult patients.

In the original ERA the results of the Phase I assessment triggered a Phase II Tier A assessment and the standard suite of fate and effect studies were completed.

Upadacitinib is very persistent in sediment according to the OECD 308 study. A Phase II Tier B extended effects on water sediment was thus triggered.

Regarding the original ERA, the MAH submitted a final report an OECD TG107 study post-approval. The overall log Kow of the test substance was determined to be 1.81 (pH4), 2.50 (pH7), and 2.48 (pH9) at 25°C. The conclusion of the assessment was that the study report provided had an acceptable experimental design and fulfilled the quality/validation criteria and that the data was also included in the updated ERA in a satisfactory manner.

Phase I

The maximum daily dose for the indication CD is 45 mg/day, resulting in $PEC_{SURFACEWATER}$ value of 0.225 µg/L, for each of the indications RA, PsA, AS and nr-axSpA with the maximum daily dose of 15 mg/day, the $PEC_{SURFACEWATER}$ values was 0.075 µg/L, for the indication AD with the maximum daily dose of 15 mg/day, the $PEC_{SURFACEWATER}$ values was 0.15 µg/L and for the indication UC with the maximum daily dose of 45 mg/day, the $PEC_{SURFACEWATER}$ values was 0.225 µg/L, when using the default Fpen value of 0.01.

A $PEC_{SW-TOTAL}$ was calculated (0.9 µg/L) and was used to re-calculate the Phase II Tier A and Tier B PEC/PNEC ratios.

The Log Pow and Log D were 2.50 (pH 7) using the shake flask method (OECD 107). Since the values were below the criteria of 3 no PBT assessment was needed.

Phase II

For this application, the same PNEC values were presented as for the original ERA submitted for the MAA. In the table below the updated PEC/PNEC ratios are presented, based on the PEC value obtained for all seven indications. These ratios remain far below 0.1, and the conclusion remains: the clinical use of upadacitinib is not expected to be a risk for the environment.

The PEC values in relevant environmental compartments are compared to the PNEC values for these compartments by calculation of PEC/PNEC ratios.

Compartment	PEC	PNEC	PEC/PNEC (action limit)
Surface water	0.9 µg/L	63 µg/L	0.014 (<1)
Groundwater	0.23 µg/L	160 µg/L	0.0014 (<1)
Microorganism	0.9 µg/L	100000 µg/L	0.000009 (<0.1)

Phase II Tier B

The PEC value in sediment (dry) was recalculated with the updated $PEC_{SURFACEWATER}$ and compared to the PNEC values for this compartment.

Compartment	PEC	PNEC	PEC/PNEC (action limit)
Sediment	1.02 mg/kg	15.6 mg/kg	0.065 (<1)

Conclusion

Considering the above data, upadacitinib is not expected to pose a risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

No additional toxicology studies were conducted to support this application; however, the MAH has proposed changes in Section 5.3 of the SmPC to correct some of the figures. These proposals are acceptable to the CHMP. There are no objections from a non-clinical point of view concerning the application for Rinvoq (upadacitinib) to include a new indication; treatment of Crohn´s disease in adults.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of updacitinib.

Considering the above data, upadacitinib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol Number/Phase Study Periods Status	Population Treatment Groups	Objectives	Sample Size[a]
M13-740/Phase 2 Induction: 16-week DB Extension: 36-week DB and OL Completed	Subjects with moderately to severely active CD who failed prior immunomodulators or biologic therapy **Induction:** UPA 3 mg BID; 6 mg BID; 12 mg BID; 24 mg BID; 24 mg QD, PBO **Extension:** UPA 3 mg BID; 6 mg BID; 12 mg BID; 24 mg QD	To evaluate the efficacy and safety of multiple doses of UPA immediate-release formulation vs PBO and assess the pharmacokinetics of UPA following oral administration in subjects with moderate to severe active CD	220
M14-327/Phase 2 96-month OL Ongoing	Subjects who completed Study M13-740 UPA 15 mg QD; UPA 30 mg QD	To evaluate the long-term efficacy, safety, and tolerability of UPA modified-release formulation in subjects who completed Study M13-740	107
M14-431/Phase 3 **Part 1:** randomized DB, PBO-controlled 12-wk induction **Part 2:** OL, single-arm, 12-wk induction **Part 3:** DB or OL, 12-wk Extended Treatment Period for subjects not achieving response at Wk 12 of Part 1 or Part 2 Completed	Subjects with moderately to severely active CD who failed prior biologic therapy **Part 1:** UPA 45 mg QD, PBO QD **Part 2:** UPA 45 mg QD **Part 3:** Cohort 1 (PBO non-responders; DB): UPA 45 mg QD Cohort 2 (non-responders to UPA 45 mg in Part 1; DB): UPA 30 mg QD Cohort 3 (non-responders to UPA 45 mg on Part 2; OL): UPA 30 mg QD	**Part 1:** To evaluate the efficacy and safety of UPA induction therapy compared to PBO in subjects with moderate to severe active CD **Part 2:** To obtain sufficient responders to achieve the required sample size for the maintenance study **Part 3:** To offer UPA 45 mg induction treatment to PBO non-responders and assess delayed response in non-responders to UPA 45 mg induction treatment in Part 1 and Part 2	**Part 1:** UPA 45 mg = 324 PBO = 171 **Part 2:** UPA 45 mg = 129 **Part 3:** Cohort 1: UPA 45 mg = 78 Cohort 2: UPA 30 mg = 69 Cohort 3: UPA 30 mg = 14

Protocol Number/Phase Study Periods Status	Population Treatment Groups	Objectives	Sample Size[a]
M14-433/Phase 3 **Part 1:** randomized, DB, PBO-controlled 12-week Induction **Part 2:** DB, 12-week Extended Treatment Period for subjects not achieving response at Week 12 of Part 1 Completed	Subjects with moderately to severely active CD who failed prior conventional or biologic therapy **Part 1:** UPA 45 mg QD, PBO QD **Part 2:** Cohort 1 (PBO-non-responders): UPA 45 mg QD Cohort 2 (UPA 45 mg non-responders): UPA 30 mg QD	**Part 1:** Evaluate the efficacy and safety of UPA compared to PBO as induction therapy in subjects with moderate to severe active CD **Part 2:** Offer UPA 45 mg induction treatment for PBO non-responders and to assess delayed response in non-responders to UPA 45 mg induction treatment in Part 1	**Part 1:** UPA 45 mg = 350 PBO = 176 **Part 2:** Cohort 1: UPA 45 mg = 57 Cohort 2: UPA 30 mg = 59
M14-430/Phase 3 **Substudy 1 (SS1):** DB, 52-week Maintenance Study **Cohort 1:** randomized, PBO-controlled for UPA 45 mg induction responders **Cohort 2:** single-arm for PBO induction responders **Cohort 3:** single-arm for UPA 30 mg responders in the Extended Treatment Period of the induction studies Completed	**SS1:** Subjects who achieved clinical response at Wk 12 or after the Extended Treatment Period of Studies M14-431 or M14-433 **Cohort 1:** UPA 15 mg QD or UPA 30 mg QD versus PBO QD **Cohort 2:** PBO QD **Cohort 3:** UPA 30 mg QD	**SS1:** **Cohort 1:** To evaluate the efficacy and safety of UPA 15 mg and 30 mg QD versus PBO as maintenance therapy in subjects with moderately to severely active CD who responded to treatment in induction studies **Cohort 2:** To describe the efficacy and safety of subjects receiving PBO treatment **Cohort 3:** To describe the efficacy and safety of subjects receiving UPA 30 mg maintenance treatment	**SS1:** **Cohort 1[b]:** PBO = 165 UPA 15 mg = 169 UPA 30 mg = 168 **Cohort 2[b]:** PBO = 130 **Cohort 3[b]:** UPA 30 mg = 51
M14-430/Phase 3 **Substudy 2 (SS2):** 240-week LTE Study **Cohort 4:** OL, single-arm for OL UPA 45 mg/30 mg responders at Week 24 of M14-431 Part 3, Cohort 3 **Cohort 5:** LTE for SS1 completers Ongoing	**SS2:** Evaluate safety and efficacy of long-term administration of UPA in subjects who participated in the Phase 3 UPA induction and maintenance studies **Cohort 4:** UPA 30 mg QD **Cohort 5:** PBO QD, UPA 15 mg QD, UPA 30 mg QD	**SS2:** **Cohort 4:** To describe the efficacy and safety of subjects receiving UPA 30 mg OL treatment **Cohort 5:** To describe the efficacy and safety of subjects receiving long-term treatment with UPA 15 or 30 mg QD	**SS2:** **Cohort 4:** UPA 30 mg = 5 **Cohort 5[c]:** PBO = 74 UPA 15 mg = 88 UPA 30 mg = 132 OL/RESC[d] 30 mg = 258

a. Subjects enrolled/exposed to at least 1 dose of study drug included in the analyses (N).

b. Substudy 1: Cohort 1: A total of 673 subjects were re-randomized and received at least 1 dose of study drug; of these, the first 502 subjects randomized on or prior to 29 Mar 2021 were included in the primary efficacy analysis for Study M14-430; Cohort 2 and 3: A total of 161 and 66 subjects were enrolled, respectively; of these, 130 and 51 subjects who either (i) completed Substudy 1 or (ii) entered Substudy 1 on or prior to 29 Mar 2021 and prematurely discontinued were included in the primary efficacy analysis for Study M14-430.

c. Substudy 2: Cohort 5: subjects who completed Substudy 1 continued to receive their originally assigned DB treatment. Current sample size shown as of 30 Mar 2022. The treatment assignment will be unblinded when the last subject in Substudy 1 completes Week 52 (expected in 2023). Planned approximately 573 subjects to complete Substudy 1 and enter Cohort 5.

d. Includes exposure time and events from subjects rescued in Substudy 1 (and were on OL/RESC 30 mg at the start of Substudy 2), rescued in Substudy 2 (and switched to OL/RESC 30 mg during Substudy 2; these are also counted in their previous DB treatment group); enrolled directly from M14-431 Part 3 and entered Cohort 4 in M14-430 Substudy 2.

In addition, the following biopharmaceutical study is submitted as part of the variation:

Protocol Number/Phase Status	Population Treatment Groups	Objective	Sample size
M21-561/Phase 1 Single-dose, open-label, randomized, four-period, four-sequence, multi-center crossover study. Completed	Healthy subjects	Evaluating the bioavailability of UPA 45 mg dose administered as 3 x 15 mg tablets relative to 1 x 45 mg tablet under fasting conditions and after a high-fat/high-calorie meal.	60

2.3.2. Pharmacokinetics

Methods

Analytical methods

A salt-assisted liquid/liquid extraction HPLC tandem Mass Spectrometric method was used for the determination of upadacitinib in human plasma. The analytical method is the same as used in previous applications. The following validation reports are applicable: R&D/12/654 (issued Jul-2012, amended Mar-2018), R&D/16/0683 (issued Mar-2018, amended May-2018 and Sep-2020) and R&D/18/1039 (issued Oct-2018).

Pharmacokinetic data analysis

Graphical assessment

Initially, the data was graphically explored. The dose-normalized observed upadacitinib concentration versus time since last dose profiles for the extended-release QD dosing regimens in subjects with moderately to severely active CD during the induction study, was comparable to dose-normalized exposures in subjects on extended-release formulation with UC, RA/AD in Phase 3 studies (Figure 1). The dose-normalized exposures in the maintenance study were comparable to the dose-normalized exposure in the induction studies.
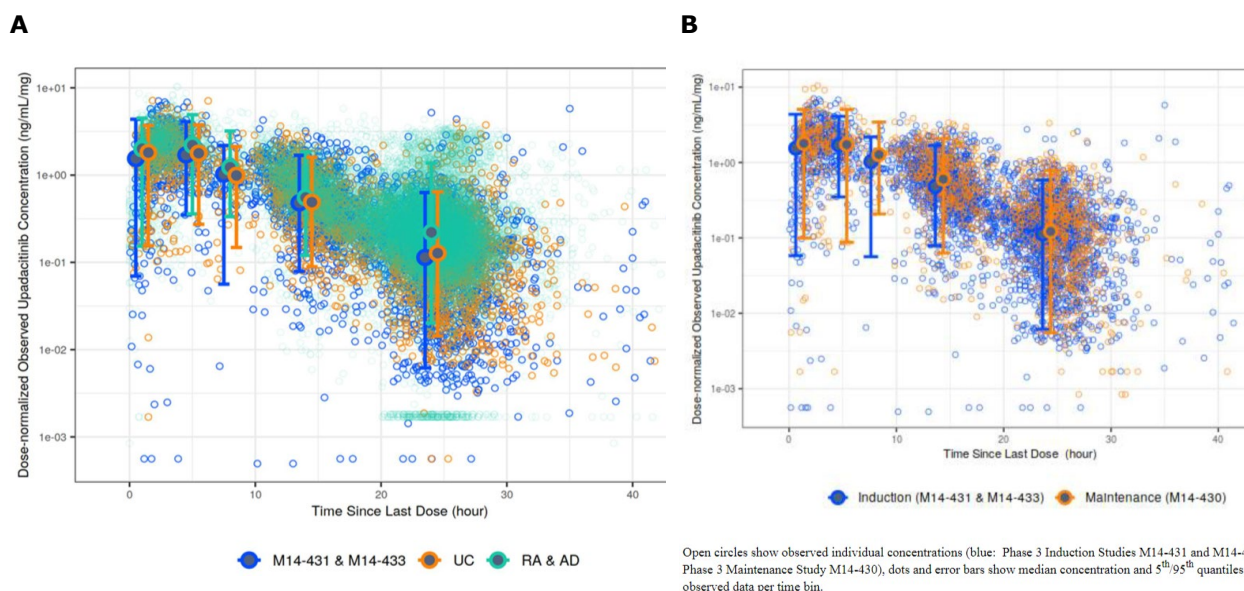
Figure 1. Dose-Normalized Observed Upadacitinib Concentrations in Subjects with CD in Phase 3 Induction studies (A) and maintenance Studies (B) Compared to Subjects with UC, RA, and AD in Phase 3 Studies on Extended-Release QD Dosing Regimens or the induction study respectively.

Population pharmacokinetic analysis

The MAH conducted two separate analyses of the data supporting this application with the objective to describe the PK of upadacitinib in subjects with Chron's disease. The data from studies M14-431 and M14-433 (induction period studies) were analysed separately (R&D/21/1457) from the results from study M14-430 (evaluation of efficacy and safety during the maintenance phase in subjects who were responders after 12 weeks of treatment in studies M14-431 and M14-433, R&D/21/1458).

The model developed using data from the induction studies was used for the description of data from the maintenance studies using a post hoc approach. Model parameters were not re-estimated. Exposures generated using the population PK model were used in exposure-response modelling.

All pharmacokinetic data from subjects enrolled in Studies M14-431, M14-433 and M14-430, who received at least one dose of upadacitinib and had at least one measurable upadacitinib concentration, were included in the population pharmacokinetic analysis. Samples were removed if dose/concentration was missing, if concentration was measured before first dose, if time since last dose (TSLD) was >140 hours (10 half-lives), timepoint was erroneous, if samples were BLQ or according to the outlier rule. In total 10.3% of the concentration data records from the induction study dataset and 19.6% of the concentration data records from the maintenance dose dataset were excluded. A total of 4.6% and 14.7% were removed due to the outlier rule from each study, respectively.

Evaluation and qualification of models

The upadacitinib population pharmacokinetic model was developed using non-linear mixed-effects modelling based on NONMEM (Version 7.4.4). A previously developed population pharmacokinetic model that described upadacitinib pharmacokinetics in healthy subjects and subjects with rheumatoid arthritis (RA), atopic dermatitis (AD), ulcerative colitis (UC), and CD (Phase 2 Study M13-740) served as the starting model for the analyses. The pharmacokinetic dataset from this previous model was

extended to include data from the CD Phase 3 induction studies (Studies M14-431 and M14-433) and used for the current analyses. The CD population constituted 53% of the total number of patients in the dataset. The dataset included data from the following covariates were already included in the starting model (R&D/18/10791) and therefore not investigated: CrCL, subject population (RA and healthy subjects), sex on CL/F and as well as sex and body weight on Vc/F.

Additional covariates (including CD-specific covariates (baseline disease severity, disease duration, baseline fecal calprotectin, and CRP) were tested to improve the model fit via stepwise forward inclusion and backward elimination (as implemented in Perl Speaks NONMEM stepwise covariate modelling (SCM) routine (PsN Version 4.8.1)). None of the additional covariates tested showed any clinically meaningful impact on the PK of upadacitinib. Model evaluation was performed using goodness-of-fit plots and visual predictive checks. The final parameter estimates are shown in Table 1, and the visual predictive check Figure 2.

Table 1 Parameter Estimates and Variability for Upadacitinib Population Pharmacokinetics: Updated Model with Data from Subjects with CD in Phase 3 Studies (Final Model) Compared to the Previously Developed Model Using Data from Phase 1 and 2 Studies Across Populations

| Parameter	Population Estimate	% RSE	95% Confidence Interval	Previous Model
CL/F (L/h)	38.8	1.76	(37.5, 40.2)	35.9
V_c/F (L)	165	2.24	(158, 173)	162
Extended-Release K_a (1/h)	0.114	6.35	(0.101, 0.129)	0.078
Immediate-Release K_a (1/h)	2.06	5.99	(1.83, 2.31)	2.80
Extended-Release Absorption Lag Time (h)	0.158	3.07	(0.149, 0.168)	0.157
Immediate-Release Absorption Lag Time (h)	0.239	0.667	(0.236, 0.242)	0.247
Fraction of Extended-Release Dose Absorbed through Zero-Order Process	0.719	0.522	(0.711, 0.726)	0.727
Zero-Order Absorption Duration (h)	3.33	0.99	(3.27, 3.40)	3.19
Bioavailability of the Extended-Release Formulation Relative to the Immediate-Release Formulation	0.791	0.786	(0.779, 0.803)	0.805
Q/F (L/h)	3.63	2.14	(3.48, 3.78)	3.60
V_p/F (L)	63.2	0.841	(62.2, 64.2)	71.5
Covariate Exponent Creatinine Clearance on CL/F	0.147	22.2	(0.0829, 0.210)	0.203
Ratio of CL/F in Subjects with RA Compared to Subjects with AD, CD, or UC	0.808	2.53	(0.769, 0.850)	0.896
Ratio of CL/F in Female Compared to Male Subjects	0.914	2.17	(0.876, 0.95)	0.828
Ratio of V_c/F in Female Compared to Male Subjects	0.842	2.79	(0.797, 0.889)	0.776
Covariate Exponent of Body Weight on V_c/F	0.632	10.8	(0.499, 0.765)	0.576
Ratio of CL/F in Healthy Subjects Compared to Subjects with AD, CD, or UC	1.11	5.37	(1.00, 1.24)	1.21
Ratio of V_c/F in Subjects with CD Compared to Healthy Subjects or Subjects with AD, UC, RA	1.24	2.9	(1.17, 1.31)	--
Covariate Exponent of Body Weight on CL/F	0.180	27.7	(0.0823, 0.278)	--
Scaling Factor on Residual Error	1.63	1.77	(1.57, 1.69)	--

Parameter	Population Estimate	% RSE	% Shrinkage	Previous Model
% IIV on CL/F	35.6	4.42	15.1	33.8
% IIV on V_c/F	25.4	10.3	51.9	29.1
% IIV on Extended-Release K_a	110	10.0	58.5	97.4
% IIV on Immediate-Release K_a	79	11.5	63.3	139
Proportional Error Phase 1, SD	0.266	1.22	--	0.320
Proportional Error Phase 2, SD	0.504	1.82	--	0.495
Additive Error, SD	0.103	5.09	--	0.103

SD = standard deviation; % RSE = % relative standard error (calculated as the standard deviation of the estimator divided by the mean of the estimator multiplied by 100); % IIV = % inter-individual variability (calculated as SQRT(ω^2)*100.); Q/F = apparent inter-compartmental clearance; V_p/F = apparent peripheral volume

$$CL/F = \left(\frac{\text{Body Weight [kg]}}{71\ kg}\right)^{0.180} \cdot \left(\frac{\text{CrCL [mL/min]}}{108.6\ mL/min}\right)^{0.147} \cdot \begin{cases} 0.914 \text{ for female subjects} \\ 1 \text{ for male subjects} \end{cases} \cdot \begin{cases} 38.8 \text{ for AD, CD and UC subjects} \\ 31.4 \text{ for RA subjects} \\ 43.2 \text{ for healthy subjects} \end{cases}$$

$$Vc/F = \left(\frac{\text{Body Weight [kg]}}{74\ kg}\right)^{0.632} \cdot \begin{cases} 0.842 \text{ for female subjects} \\ 1 \text{ for male subjects} \end{cases} \cdot \begin{cases} 165 \text{ for healthy, AD, UC and RA subjects} \\ 204 \text{ for CD subjects} \end{cases}$$

Note that continuous covariate effect parameters were centered by the reference values of the respective analysis population, i.e., R&D/18/1079[1] analysis population median values for body weight on V_c/F (74kg) and CrCL on CL/F (108.6 mL/min), and combined data including Phase 3 CD studies population for body weight on CL/F (71 kg).
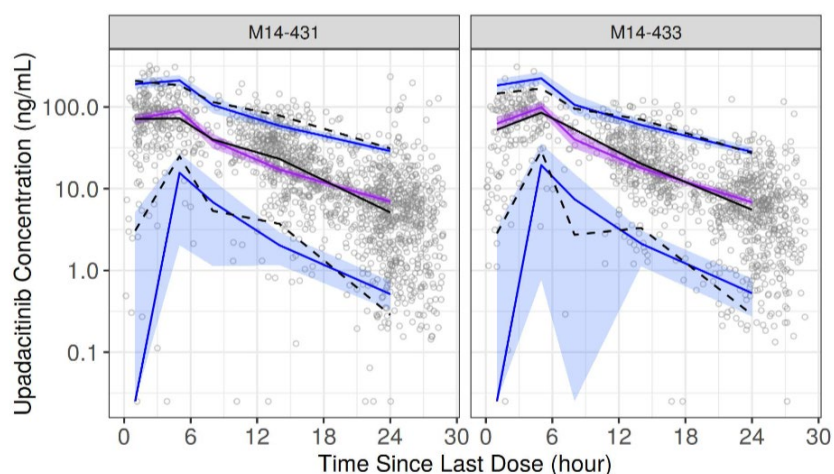
The blue lines represent the 90% prediction interval of the model, the shaded blue areas are the associated 90% confidence intervals of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% confidence interval. The solid black line and dashed black lines represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Circles denote observed concentrations. Note: Time bins were chosen at 1, 5, 8, 14, and 24 hours since last dose.

Figure 2   Visual Predictive Checks of Upadacitinib Concentration in Subjects with CD (Studies M14-431 and M14-433) Stratified by Study

The developed population pharmacokinetic model for upadacitinib based on CD Phase 3 induction studies (Study M14-431 and Study M14-433) was used to describe 80% of the observed upadacitinib plasma concentrations from Phase 3 Study M14-430 using a post hoc approach. Population parameter estimates of the fixed effects and estimates for the random effects (inter-individual variability) of the previously established population pharmacokinetic model were used to generate individual post hoc estimates for subjects in Study M14-430. Model parameters were not re-estimated. The model results were evaluated using goodness-of-fit and visual predictive check.

Absorption

Bioequivalence

Study **M21-561** was a Phase 1 single-dose, open-label, randomized, four-period, four-sequence, crossover study in 60 healthy subjects, aimed to assess the bioavailability of three upadacitinib 15 mg commercial formulation tablets (ER17) versus a single upadacitinib 45 mg commercial formulation tablet (ER19) under fasting conditions as well as after a high-fat/high-calorie meal.

Study drug was administered in the morning on Day 1 of each period as follows:

Regimen A	Single upadacitinib 45 mg dose administered as three 15 mg tablets of upadacitinib formulation (ER17) under fasting conditions (Test for B).
Regimen B	Single 45 mg upadacitinib tablet formulation (ER19) administered under fasting conditions (Reference for A).
Regimen C	Single upadacitinib 45 mg dose administered as three 15 mg tablets of upadacitinib formulation (ER17) after high-fat/high-calorie meal (Test for D).
Regimen D	Single 45 mg upadacitinib tablet formulation (ER19) administered after high-fat/high-calorie meal (Reference for C).

Blood samples for upadacitinib PK assay were collected up to 72 hours after dosing in each study period. A washout period of at least 4 days between doses were applied to ensure no drug carry-over.

All available data were used in the statistical analyses; hence data of all subjects (N = 60) were included in the pharmacokinetic analyses, with the following exemptions: one subject did not receive regimen D in period 2 (due to adverse event), one subject did not receive regimen B in period 4 (discontinuation upon subject´s own request) and one subject had upadacitinib plasma concentrations below LLOQ at all time points during Period 4 (Regimen D). Fifty-seven subjects completed all four periods of the study.

The point estimates and corresponding 90% confidence intervals, obtained from the analyses of the natural logarithms of C_{max}, AUC_{0-t}, AUC_{inf}, AUC_{0-12}, and AUC_{12-72}, are presented below. The results are all within the conventional acceptable range of 0.80-1.25.

Table 2 Point estimates and 90% Cis for the bioavailability of upadactinib 3 x 15 mg tablets relative to 1 x 15 mg tablet under fasting condition (regimen A versus B) and fed conditions (regimen C versus D)

Regimens Test vs. Reference	Pharmacokinetic Parameter (units)	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen A vs. B	C_{max} (ng/mL)	95.1	93.0	1.023	0.943, 1.110
	AUC_t (ng•h/mL)	792	763	1.037	0.989, 1.088
	AUC_{inf} (ng•h/mL)	812	785	1.034	0.983, 1.089
	AUC_{0-12} (ng•h/mL)	573	541	1.059	0.993, 1.130
	AUC_{12-72} (ng•h/mL)	209	210	0.998	0.914, 1.090
Regimen C vs. D	C_{max} (ng/mL)	125	138	0.905	0.846, 0.969
	AUC_t (ng•h/mL)	958	950	1.008	0.961, 1.057
	AUC_{inf} (ng•h/mL)	969	965	1.004	0.962, 1.049
	AUC_{0-12} (ng•h/mL)	757	762	0.993	0.938, 1.052
	AUC_{12-72} (ng•h/mL)	192	175	1.098	1.005, 1.199

2.3.3. Pharmacodynamics

Mechanism of action

Upadacitinib is a selective and reversible Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, hematopoiesis and immune surveillance.

Primary and secondary pharmacology

The exposure-response analyses were exploratory. The objectives were to characterize the relationships between upadacitinib plasma exposures and efficacy and safety in subjects with moderately to severely active CD during the 12-week induction period and the 52-week maintenance period. This analysis is supportive to the available clinical data. Model-estimated steady-state upadacitinib average concentration (Cavg) was derived using empirical Bayesian estimates and used as the primary exposure metric for exposure-response analyses.

Model-estimated steady-state Cmax was used to conduct supportive exposure-response analyses for safety. The exposure-safety analysis of the data from the induction studies was conducted using combined data from the Phase 3 induction studies in CD and UC (Study M14-324 and Study M14-675). For this analysis, the safety parameters were evaluated at the end of or during the induction period (Week 12 for CD and Week 8 for UC).

Exploratory graphical analysis (quartile plots) of exposure-response was first conducted, followed by logistic regression of response endpoints with > 10 events.

The study stratification variables were included as pre-specified variables in the efficacy exposure-response models: Population (biologic therapy-intolerant or inadequate responder [Bio-IR] versus non-Bio-IR), Baseline corticosteroid use (yes versus no), Endoscopic disease severity (SES-CD < 15, $\geq$ 15). Number of prior biologics (0, 1, > 1) was not included in the analyses as it was highly correlated with the population (Bio-IR versus non-Bio-IR) stratification factor. The following pre-specified relevant variables were included in the safety exposure-response models as recommended by the International Council for Harmonisation (ICH) E9 guidance: Hemoglobin (> 2 g/dL decrease from baseline, hemoglobin < 8 g/dL): baseline hemoglobin, Lymphopenia (Grade 3 or higher): baseline lymphocyte count, Neutropenia (Grade 3 or higher): baseline neutrophil count, Serious infections, pneumonia, herpes zoster: age.

The effect of significant covariates on exposure-response relationships was assessed and simulations using exposure-response models to generate the model-predicted efficacy of upadacitinib 45 mg QD compared to placebo were performed. Standard methods for model evaluation were used.

Exposure-efficacy analysis

The exposure-response analyses for efficacy from the induction studies did not show a trend for the percentage of subjects achieving clinical remission per CDAI with increasing upadacitinib Cavg within the range of plasma exposures associated with 45 mg QD. Bio-IR status, clinical remission per PROs at Week 0, and endoscopic response at Week 0 had a statistically significant effect when tested on the intercept. None of the pre-specified covariates had a statistically significant interaction with the effect of upadacitinib exposure (slope of the effect).

For clinical remission per patient reported outcomes (PROs), endoscopic response, and endoscopic remission, increasing upadacitinib Cavg was associated with increased percentage of subjects

achieving these endpoints. SES-CD, age, and baseline fecal calprotectin had a statistically significant effect on upadacitinib exposure-response relationship for clinical remission per PROs.
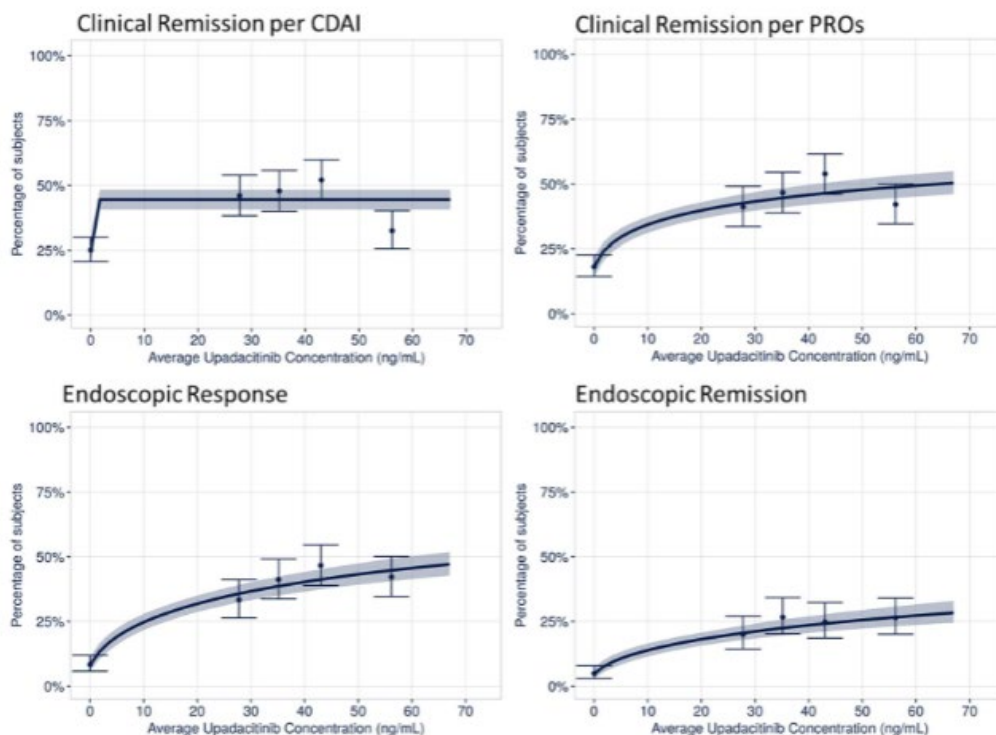
The solid lines represent median predicted response, and the shaded areas represent 95% confidence intervals of the response. The dots and error bars represent median and 95% binomial confidence intervals of binned observed responses within each quartile of upadacitinib C_ave.

Figure 3. Observed and Model-Predicted Percentage of Subjects who Achieved Clinical Remission per CDAI, Clinical Remission per PROs, Endoscopic Response, and Endoscopic Remission During Induction (Non-Responder Imputation [NRI])

Exposure-safety analysis

The relationships between upadacitinib Cavg and different safety endpoints or changes in laboratory parameters at or anytime through Week 12 were explored using data from the Phase 3 UC and CD patient induction studies. No trends were observed between upadacitinib Cavg and percentage of subjects experiencing pneumonia (anytime through Week 12), lymphopenia (Grade 3 or higher) at Week 12 (last observation carried forward [LOCF]), neutropenia (Grade 3 or higher) at Week 12 (LOCF), herpes zoster (anytime through Week 12), serious infections (anytime through Week 12) or hemoglobin < 8 g/dL at Week 12 (LOCF). A statistically significant exposure-response relationship was observed for a > 2 g/dL in hemoglobin from baseline at Week 12 (Figure 4).
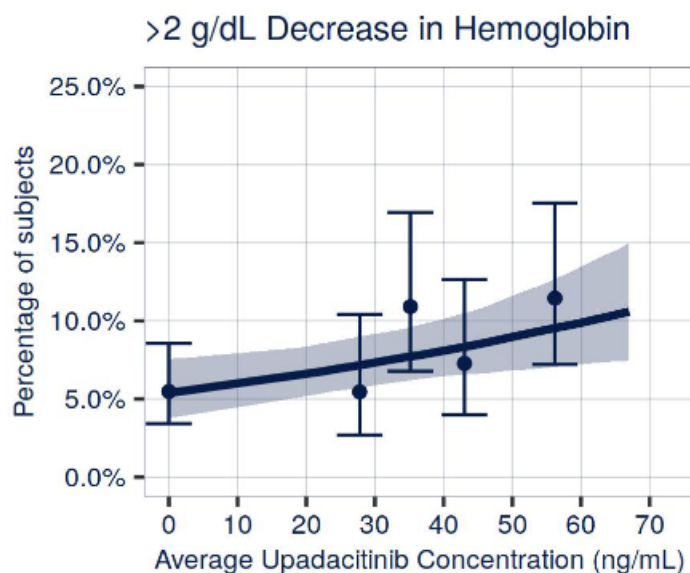
>2 g/dL Decrease in Hemoglobin

Figure 4. Observed and Model-Predicted Percentage of Subjects Experiencing a > 2 g/dL Decrease in Hemoglobin from Baseline (LOCF)

2.3.4. Discussion on clinical pharmacology

Absorption

The design of study M21-561 is appropriate. Upadacitinib does not accumulate significantly, and it has been concluded in previous applications (see initial marketing authorisation application EMEA/H/C/004760/0000 for discussion) that no multiple dose BE-study is necessary. The shapes of the plasma concentration-time curves were further investigated by partial AUCs (AUC_{0-12} and AUC_{12-72}), as recommended in the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) when a multiple-dose study is waived. All primary PK parameters were within conventional acceptance criteria for establishing bioequivalence. The washout period is sufficient, given a terminal elimination half-life of 9-14 hours following administration of the ER formulation. In addition, no pre-dose plasma concentrations above 5% of the C_{max} value for the subject in that period were detected.

Upadacitinib plasma concentrations in one subject were below the LLOQ at all the time points for Regimen D (Period 4), and this subject was therefore excluded from the pharmacokinetic and statistical analysis for Regimen D. The MAH has thoroughly investigated the root cause of the aberrant results, but neither the investigation of study source data (e.g. dispensing protocol, sample collection and storage records), nor the investigation of possible formulation deviations (e.g. via comparison across manufacturing process and release testing records from eleven batches of the 45 mg tablet, including the particular batch used in study M21-561) could explain the outlier observations of zero plasma concentrations observed in this subject.

According to the Guideline on investigation of bioequivalence exclusion of data could, in exceptional cases, be allowed for a subject with lack of any measurable concentrations or only very low plasma concentrations for reference medicinal product. In this study, regimen D represents the reference treatment with the already authorised, commercial formulation ER19 (upatacinib 45 mg). Consequently, the validity of the study should not be jeopardised by the exclusion of regimen D data for subject 308, and no concern is raised.

In a cross-over trial, subjects who do not provide evaluable data for *both* test and reference products should be excluded from the statistical evaluation, i.e. even if there is evaluable subject data for one of the regimens (test *or* reference), any data from the subject should be excluded from the statistical comparison of the regimens. Consequently, the MAH has adequately provided statistical analysis of the pharmacokinetic data, following the exclusion of subject 219 data in the comparison of regimen A *vs.* B, and following exclusion of data from subjects 118 and 308 in the comparison of regimen C *vs.* D.

Plasma concentrations of upadacitinib were determined using an adequately validated liquid chromatography method with tandem mass spectrometric detection. Satisfactory method performance during study sample analysis has been shown.

The statistical analysis results from clinical study M21-561, satisfactorily demonstrate that the administration of three 15 mg upadacitinib tablets (ER17) is bioequivalent to administration of a single 45 mg upadacitinib tablet (ER19) under fasting conditions as well as after a high-fat/high-calorie meal.

Pharmacokinetic analysis

For the population PK analysis, a total 20% of all concentration data were removed from the M14-430 (maintenance study) dataset, of which 15% of data points were removed due to an outlier rule. This is not considered a good data handling practice and limits the use of the remaining data and undermines any conclusions made from analysis of this study. For this reason, only analyses based on the observations from the induction studies are described. In addition to the population PK analysis, the MAH conducted a graphical analysis where the dose-normalised concentration, without data point exclusion, from CD subjects were overlaid concentrations from UC, RA and AD subjects. This analysis indicates that the dose-normalised exposure is similar between the indications. As clinical data are robust with regards to efficacy, and safety is well established with 15 and 30 mg upadacitinib, the issues with the population PK analysis were not pursued by the CHMP.

The MAH used population PK analysis to describe the PK of upadacitinib in CD patients. The model is also used to derive individual Cavg concentrations to be used in the exposure-response analysis. A previously developed model (using phase 2 data) was used. Parameters were re-estimated, including covariates found to be previously significant, and new covariates were tested (no consideration to correlation between covariates was given). The final parameter estimates were estimated with low RSE%. The shrinkage is high on all parameters except CL/F (15%). The condition number of the final model was 43.04. The model could adequately describe the exposure in the induction studies M14-431 and M14-433 and is considered adequate to be used to derive Cavg for exposure-response analysis over the 12-week treatment.

Subjects in the CD studies weighed 36-152 kg. Body weight on CL/F was the only new covariate included in the model; however, as both CrCL (for which body weight is part of the equation) and sex are correlated with body weight, and included in the model, it is not possible to draw a conclusion regarding the actual impact of body weight on CL/F. Correlated covariates should not have been tested and estimated simultaneously, a known relationship could be fixed in the model. Covariates should have been re-evaluated as more information became available. However, this issue was not further pursued by the CHMP.

As 20% of observations respectively were excluded from the maintenance study, many due to an outlier rule, it cannot be assumed that there is not a bias in the model derived Cavg. Therefore, only the results from the 12-week induction study are described. As clinical data are robust with regards to efficacy, and safety is well established with 15 and 30 mg upadacitinib, the issue of exclusion of maintenance data will not be pursued.

As data from studies in UC and CD were combined and safety assessed at different time points (8 and 12 weeks respectively) a conclusion of the relationship between exposure in CD patients given 45 mg over 12 weeks cannot be made for all safety endpoints.

The exposure-response analysis of efficacy is limited as only 45 mg upadacitinib was given to CD patients in the induction studies. There is a small trend towards increased percentage of subjects achieving the efficacy endpoints (PROs, endoscopic response and remission) with increasing upadacitinib C_{avg}. The MAH pooled data from the Phase 2b/3 UC induction studies and phase 3 CD induction studies in the safety analysis. The only trend in safety data identified was relationship between C_{avg} and decrease in haemoglobin at week 12 (UC data not included as induction study ended at week 8). However, anaemia is a known AE for upadacitinib, and recommendations on management are already included in the SmPC. For further discussion, please refer to section 2.5.1. .

2.3.5. Conclusions on clinical pharmacology

Due to the study design and handling of data, the population PK and exposure-response analyses are limited. As clinical data are robust with regards to efficacy, and safety is well established with 15 and 30 mg upadacitinib, the issues with the population PK analysis were not pursued by the CHMP.

The analysis of data indicates that the exposure in Chron's disease is similar to exposures observed in previously approved indications. The information in the SmPC has been updated accordingly.

The clinical pharmacology data was considered acceptable to support the new indication in CD.

2.4. Clinical efficacy

Upadacitinib Crohn's Disease Clinical Development Program comprises a Phase 2 dose ranging study, a Phase 2 long-term extension (LTE) study, and three Phase 3 studies: two induction and one maintenance/LTE study. The Phase 2 dose-ranging Study M13-740 included a double-blind (DB) placebo-controlled 16-week induction treatment that assessed the safety, efficacy, and pharmacokinetics versus placebo followed by a 36-week DB maintenance (extension) period (R&D/16/0677). Subjects who completed Study M13-740 were eligible to enrol in the ongoing LTE Study M14-327.

Table 3   Overview of Upadacitinib Global Phase 3 Studies for Crohn's Disease

	M14-431			M14-433		M14-430	
	Part 1 (Induction)	Part 2 (Induction)	Part 3 (Extended Treatment)	Part 1 (Induction)	Part 2 (Extended Treatment)	Substudy 1 (Maintenance)	Substudy 2 (LTE)
Population	Inadequate response to or are intolerant to biologic therapy			Inadequate response to or are intolerant to conventional and/or biologic therapies		Achieved clinical response after Induction Treatment (at Week 12) or after the blinded Extended Treatment (at Week 24) of Study M14-431 or Study M14-433	Completed Substudy 1 or received OL UPA 30 mg QD Extended Treatment in Study M14-431 (Part 3/Cohort 3) and achieved clinical response at Week 24
Study duration (Weeks)	12	12	12	12	12	52	240
Treatment Groups (N[a])	DB UPA 45 mg QD (324) DB PBO QD (171)	OL UPA 45 mg QD (129)	Cohort 1: DB UPA 45 mg QD (78) Cohort 2: DB UPA 30 mg QD (69) Cohort 3: OL UPA 30 mg QD (14)	DB UPA 45 mg QD (350) DB PBO QD (176)	Cohort 1: DB UPA 45 mg QD (57) Cohort 2: DB UPA 30 mg QD (59)	Cohort 1[b]: DB UPA 15 mg QD (169) DB UPA 30 mg QD (168) DB PBO QD (165) Cohort 2[b]: DB PBO QD (130) Cohort 3[b]: DB UPA 30 mg QD (51)	Cohort 4: OL UPA 30 mg QD (5) Cohort 5: DB UPA 15 mg QD (ongoing) DB UPA 30 mg QD (ongoing) DB PBO QD (ongoing)

a. Number of subjects who received at least 1 dose of study drug.
b. Cohort 1: A total of 673 subjects were re-randomized and received at least one dose of study drug; however, the first 502 subjects randomized on or prior to 29 Mar 2021 were included in the primary efficacy analysis for Study M14-430.
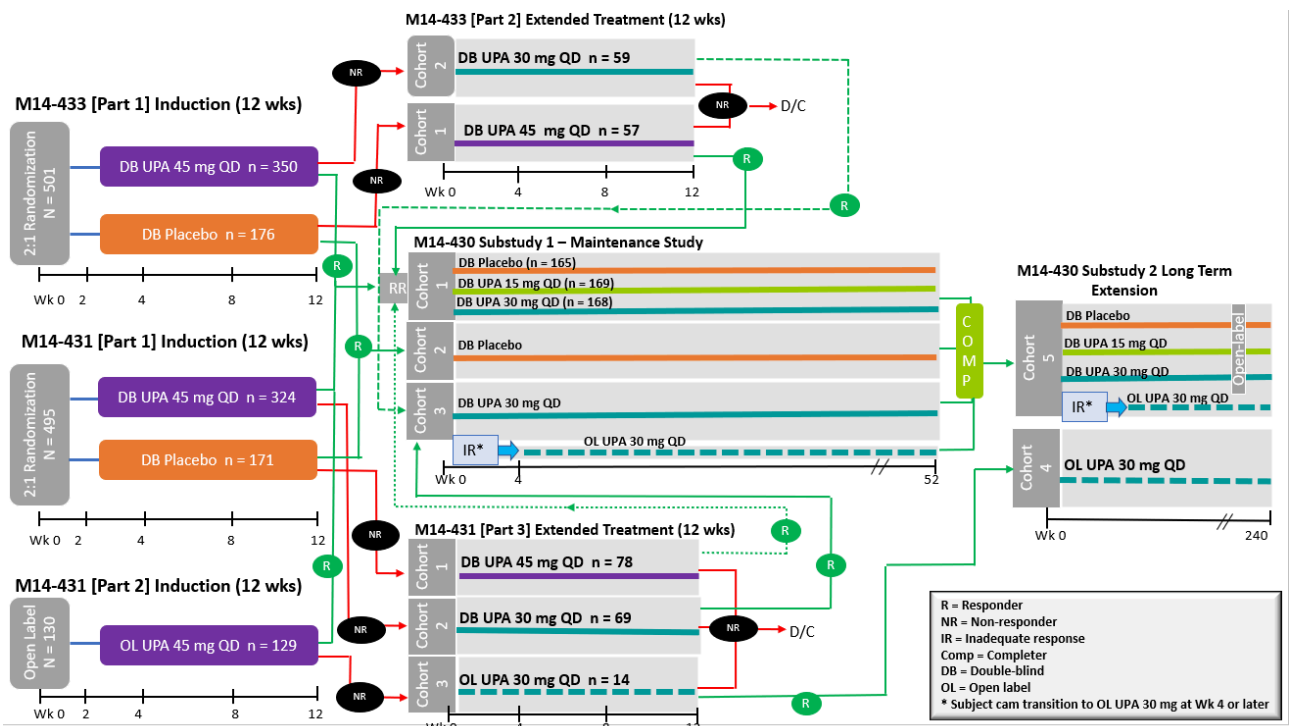
Figure 5   Flow of Subjects Through Upadacitinib Crohn's Disease Phase 3 Studies

2.4.1. Dose response study: Phase 2 Study M13-740

Study M13-740 was a Phase 2, multicenter, randomized, double-blind (DB), placebo- controlled study designed to evaluate the efficacy, safety, and pharmacokinetics of upadacitinib as induction therapy in subjects with moderately to severely active CD and evidence of mucosal inflammation and a history of

inadequate response or intolerance to immunosuppressants or anti-TNF therapy. The study was designed to enroll approximately 210 subjects.

The study duration was to be up to 60 weeks, including a Screening Period of up to 35 days, a 16-week DB Induction Period, a 36-week Extension Phase that had both DB and open-label (OL) components, and a 30-day follow-up period. Subjects who met eligibility criteria were to be randomized in a 1:1:1:1:1:1 ratio to one of the Induction Period dose groups:

- Upadacitinib 3 mg twice daily (BID)

- Upadacitinib 6 mg BID

- Upadacitinib 12 mg BID

- Upadacitinib 24 mg BID

- Upadacitinib 24 mg once daily (QD)

- Placebo

Subjects enrolled in this study were between 18 and 75 years old (inclusive) with a diagnosis of ileal, colonic, or ileocolonic CD for $\geq$ 3 months prior to baseline confirmed by endoscopy during the Screening Period. Eligible study subjects were to have had average daily liquid/very soft stool frequency (SF) $\geq$ 2.5 or average daily abdominal pain (AP) score $\geq$ 2.0, Crohn's Disease Activity Index (CDAI) $\geq$ 220 and $\leq$ 450 and Simplified Endoscopic Score for Crohn's Disease (SES-CD) $\geq$ 6 (or $\geq$ 4 for subjects with disease limited to the ileum) confirmed by a central reader. Subjects were to have inadequately responded to or experienced intolerance to previous treatment with immunosuppressants or an anti-TNF agent (e.g., infliximab, adalimumab, or certolizumab). The clinical measures that defined inadequate response were based on physician/investigator clinical assessment.

A total of 220 subjects were randomized at 93 study sites located in 19 countries/regions (US, Canada, Europe, Australia, and New Zealand). All 220 subjects received study drug, with a majority (180 subjects, 81.8%) completing the 16-week DB Induction Period.

Demographic characteristics were generally balanced across the upadacitinib dose groups and placebo group in the Induction Period. Greater than half (56.8%) of all subjects were female, and the majority of subjects were white, not Hispanic or Latino, and less than 65 years of age. The mean age of all subjects was 40.7 years. These demographic characteristics represent the population at large with CD.

Greater than 90% of subjects across the upadacitinib groups and in the placebo group had previously failed or were intolerant to one or more prior anti-TNF therapies. Greater than 50% of subjects had received 2 or more prior anti-TNF treatments, with a higher number of subjects in the 12 mg BID and 24 mg BID groups receiving more than 2 anti-TNF treatments. Overall, 43.2% of subjects across the upadacitinib groups also received prior non-anti-TNF biologic therapy.

Co-Primary endpoints and definition:

- Clinical remission: Average daily very soft or liquid SF ≤ 1.5 and not worse than baseline AND average daily AP score≤1.0 and not worse than baseline.

- Endoscopic remission: SES-CD ≤4 and at least a 2-point reduction versus baseline and no subscore > 1 in any individual variable.

Results Study M13-740

The co-primary efficacy endpoints, the proportion of mITT subjects who achieved clinical remission at Week 16 and endoscopic remission at Week 12/16, were compared between each of the upadacitinib

groups and placebo using NRI. At Week 12/16, a statistically significantly greater (P ≤ 0.1) proportion of subjects achieved the co-primary endpoint of endoscopic remission in all upadacitinib dose groups compared with the placebo group, with the exception of the 6 mg BID group.

At Week 16, a statistically significantly greater (P ≤ 0.1) proportion of subjects achieved the co-primary endpoint of clinical remission in the 6 mg BID group compared with placebo.

Table 4 Co-Primary Efficacy Endpoint Results at Week 12/16 (mITT Population – NRI)

		Upadacitinib				
	Placebo N = 37	3 mg BID N = 39	6 mg BID N = 37	12 mg BID N = 36	24 mg BID N = 36	24 mg QD N = 35
Endoscopic remission at Week 12/16, n (%)	0	4 (10.3)	3 (8.1)	3 (8.3)	8 (22.2)	5 (14.3)
Adjusted risk difference from placebo (95% confidence interval)	--	9.9 (–0.3, 20.1)	7.4 (–1.6, 16.4)	7.7 (–1.5, 16.8)	21.0 (6.8, 35.2)	13.6 (1.8, 25.5)
P value vs. placebo	--	0.056	0.108	0.099	0.004	0.025
Clinical remission at Week 16, n (%)	4 (10.8)	5 (12.8)	10 (27.0)	4 (11.1)	8 (22.2)	5 (14.3)
Risk difference from placebo (95% confidence interval)	--	2.0 (–12.3, 17.3)	16.2 (–2.0, 34.3)	0.3 (–14.1, 15.0)	11.4 (–6.1, 28.5)	3.5 (–11.5, 19.6)
P value vs. placebo	--	0.740	0.082	0.952	0.205	0.607

		Upadacitinib				
	Placebo N = 37	3 mg BID N = 39	6 mg BID N = 37	12 mg BID N = 36	24 mg BID N = 36	24 mg QD N = 35
Week 12, n (%)						
Clinical remission	4 (10.8)	4 (10.3)	11 (29.7)	5 (13.9)	9 (25.0)	3 (8.6)
P value vs placebo	--	0.896	0.050	0.702	0.117	0.736
Modified clinical remission	3 (9.1) (n = 33)	6 (15.8) (n = 38)	9 (27.3) (n = 33)	10 (29.4) (n = 34)	10 (33.3) (n = 30)	4 (12.5) (n = 32)
P value vs placebo		0.416	0.075	0.045	0.018	0.687
Week 16, n (%)						
Clinical Endpoints						
Modified clinical remission	4 (12.1) (n = 33)	6 (15.8) (n = 38)	10 (30.3) (n = 33)	9 (26.5) (n = 34)	11 (36.7) (n = 30)	6 (18.8) (n = 32)
P value vs placebo		0.647	0.093	0.165	0.023	0.448

Induction Dose Selection

Dose selection was informed by the analysis of the 16-week safety, efficacy, pharmacokinetic, and exposure-response data from Phase 2 CD Study M13-740, which evaluated 5 induction doses of upadacitinib using the immediate-release (IR) formulation (3, 6, 12, or 24 mg twice daily [BID] or 24 mg QD) versus placebo. The results from Study M13-740 demonstrated the clinical and endoscopic efficacy of upadacitinib compared to placebo across several endpoints with doses of 6 mg BID and higher. Pharmacokinetic analyses have shown that the 12 mg BID and 24 mg BID doses of the IR

formulation provided similar daily exposures to the 30 mg QD and 60 mg QD dose of the extended-release (ER) formulation, respectively. Simulations based on the exposure-response analyses showed that doses higher than 45 mg QD (e.g., 60 mg QD) were predicted to provide minimal additional efficacy (2% to 5% increase), while a dose lower than 45 mg QD (e.g., 30 mg QD) predicted 5% to 7% lower efficacy for the endoscopic endpoints compared to the 45 mg QD dose. Exposure-safety analyses demonstrated that there was no observed trend for a relationship between upadacitinib plasma exposures and decreases in hemoglobin ($\geq$ 2g/dL), lymphopenia (Grade 2 or 3), herpes zoster, serious infections, and pneumonia during the 16 weeks of treatment. Therefore, the 45 mg QD dose was predicted to have maximized efficacy without increasing lab abnormalities or infections and therefore offer the optimal benefit-risk profile for an induction dose for Phase 3 in CD

Maintenance Dose Selection

Based on pathophysiology and data from other targeted immunomodulatory therapies, a lower dose for maintenance was expected to be effective once the initial high disease burden is reduced. Therefore, after induction treatment with 45 mg QD, 15 mg and 30 mg QD doses were chosen for maintenance treatment.

Upadacitinib 15 mg QD and 30 mg QD, using the ER formulation, provide equivalent daily area under the plasma concentration-time curve (AUC) and comparable maximum plasma concentration and trough (plasma) concentration measured at the end of a dosing interval (Ctrough) to the IR formulation of upadacitinib 6 mg BID and 12 mg BID, respectively. The upadacitinib 6 mg BID and 12 mg BID doses used in the CD Phase 2 Study M13-740 showed statistically significantly higher endoscopic response at Week 12/16 compared to placebo. Following induction with upadacitinib 45 mg QD, lower doses of upadacitinib 15 mg QD and 30 mg QD were therefore expected to maintain efficacy while minimizing dose dependent risks that may be observed with long-term use of higher doses.

2.4.2. Main studies

- Phase 3 induction Study M14-431 "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Biologic Therapy"

- Phase 3 induction Study M14-433 "A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Conventional and/or Biologic Therapies"

- Phase 3 maintenance/LTE Study M14-430 "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Maintenance and Long-Term Extension Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Crohn's Disease Who Completed the Studies M14-431 or M14-433"

Methods

A total of 1150 subjects were enrolled (1021 subjects randomized into the DB portion and 129 subjects enrolled in the OL portion) in the two global Phase 3 induction studies. At the end of the induction studies, 674 subjects achieved clinical response to 12-week induction treatment with upadacitinib 45 mg QD and were re-randomized into the Study M14-430 Substudy 1 maintenance period (Cohort 1; of whom 673 received at least one dose of study drug). The maintenance primary efficacy analysis was

performed among the first 502 subjects who were re-randomized and dosed in Study M14-430 Substudy 1 Cohort 1 (Study M14-430 Substudy 1 CSR Section 10.2). Out of the 1150 subjects randomized in the two global Phase 3 induction studies, 249 subjects did not achieve clinical response at the end of the induction period (Week 12) and were enrolled in the Extended Treatment Period.

The two Phase 3 induction studies (Study M14-431 and Study M14-433) were multicenter studies conducted in adult subjects $\geq$ 18 and $\leq$ 75 years of age with a confirmed diagnosis of CD for at least 3 months and moderately to severely active CD, with average daily very soft stool frequency (SF) score $\geq$ 4 or average daily abdominal pain score (APS) $\geq$ 2.0, and a centrally-read SES-CD $\geq$ 6 (or $\geq$ 4 for subjects with isolated ileal disease), excluding the narrowing component.
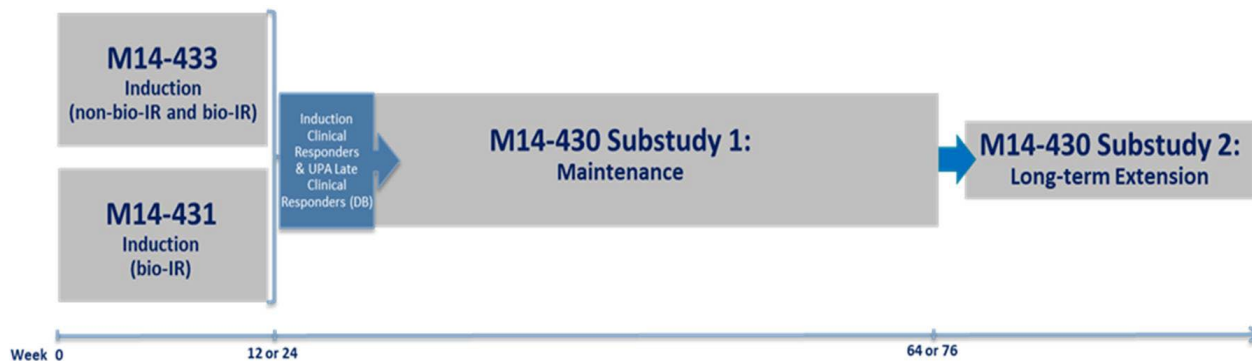
Figure 6   Overview of Upadacitinib Crohn's Disease Phase 3 Program

Study participants

Study M14-431

Subjects with moderately to severely active CD (SF $\geq$ 4 and/or AP score $\geq$ 2) were enrolled, determined by evidence of active intestinal mucosal inflammation assessed by the Simplified Endoscopic Score for CD (SES-CD), confirmed by a central endoscopy reader; and the presence of very soft/liquid stool frequency and abdominal pain. Evidence of intestinal mucosa inflammation with an SES-CD of at least 6 in subjects with ileo-colonic or colonic disease or at least 4 in subjects with isolated ileal disease, excluding the narrowing component was also required to enroll in this study.

Subjects should have had an inadequate response or intolerance to one or more biologic agents (Bio-IR) for CD (adalimumab, certolizumab, infliximab, ustekinumab, vedolizumab, and/or natalizumab). The study allowed for enrollment of up to 35% of subjects who were Bio-IR to 3 or more biologic agents. To be considered Bio-IR, subjects were required to meet criteria for types, doses, and durations of prior CD treatment as defined in the protocol.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, as determined by the investigator, must be available.

2. SES-CD (excluding the presence of narrowing component) $\geq$ 6 (or $\geq$ 4 for subjects with isolated ileal disease), as confirmed by a central reader.

3. Average daily very soft or liquid SF $\geq$ 4.0 **AND/OR** average daily AP score $\geq$ 2.0 at Baseline.

4. Demonstrated an inadequate response or intolerance to one or more of the following biologic agents:

    *   At least one 6-week induction regimen of infliximab (≥ 5 mg/kg intravenous [IV] at Baseline and Weeks 2, and 6),

    *   At least one 4-week induction regimen of adalimumab (one 160 mg subcutaneous [SC] dose at Baseline, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC dose at Baseline, followed by one 40 mg SC dose at Week 2, in countries where this dosing regimen is approved]),

    *   At least one 4-week induction regimen of certolizumab pegol (400 mg SC at Baseline and Weeks 2, and 4),

    *   At least one 6-week induction regimen of vedolizumab (300 mg IV at Baseline and Weeks 2, and 6),

    *   At least one 8-week induction regimen of ustekinumab [260 mg (≤ 55 kg) or 390 mg (> 55 to ≤ 85 kg) or 520 mg (> 85 kg) IV, followed by 90 mg SC at Week 8],

    *   Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics,

    *   Intolerance to a biologic may include, but not limited to infusion-related reaction, rash, serum sickness, anaphylaxis, elevated liver enzymes, demyelination, congestive heart failure, infection. Demonstration of intolerance requires no minimum dose or duration of use.

Main Exclusion:

1. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.

Concomitant Medications and Treatments

2. Subject on CD related antibiotics who:

    *   has not been on stable doses of these medications for at least 14 days prior to Baseline, or

    *   has discontinued these medications within 14 days of Baseline.

3. Subject on oral aminosalicylates who:

    *   has not been on stable doses of these medications for at least 14 days prior to Baseline, or

    *   has discontinued these medications within 14 days of Baseline.

4. Subject on corticosteroids who meet the following:

    *   prednisone or equivalent dose > 30 mg/day; or

    *   budesonide > 9 mg/day; or

    *   has not been on the current course for at least 14 days prior to Baseline and on a stable dose for at least 7 days prior to Baseline.

5. Subject on MTX who:

    *   has not been on the current course for ≥ 42 days prior to Baseline, and

    *   has not been on a stable dose for ≥ 28 days prior to Baseline

<u>CD Related</u>

6. Subject with the following ongoing known complications of CD:

   - abscess (abdominal or peri-anal),

   - symptomatic bowel strictures,

   - \> 2 entire missing segments of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum,

   - fulminant colitis,

   - toxic megacolon,

   - or any other manifestation that might require surgery while enrolled in the study.

7. Subject with ostomy or ileoanal pouch

8. Subject diagnosed with conditions that could interfere with drug absorption including but not limited to short gut or short bowel syndrome.

9. Subject with surgical bowel resection within the past 3 months prior to Baseline, or a history of \> 3 bowel resections

Study M14-433

Subjects should have had an inadequate response or intolerance to conventional therapies but had not failed biologic therapy (Non-Bio-IR population) and/or one or more biologic agents for CD (Bio-IR population). Within the Non-Bio-IR subjects enrolled, the study allowed for enrollment of approximately 20% of subjects who could also have had previous use of biologic therapies for up to 1 year but discontinued based on reasons other than inadequate response or intolerance. Within the Bio-IR subjects, the study allowed for enrolment of approximately 30% of subjects who had failed 3 or more biologics. To be considered inadequate responders, subjects were required to meet criteria for types, doses, and durations of prior CD treatment as defined in the protocols.

Severity of CD was defined using the CDAI scoring system components of very soft or liquid SF and APS for signs and symptoms called patient-reported outcomes (PROs or SF/APS) and confirmed intestinal mucosa inflammation evaluated by central readers using the SES-CD as described above for Study M14-431.

Diagnosis and Main Criteria for Inclusion/Exclusion:

<u>Main Inclusion:</u>

1. Confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the investigator, must be available.

2. SES-CD (excluding the presence of narrowing component) ≥ 6 (or ≥ 4 for subjects with isolated ileal disease), as confirmed by a central reader.

3. Average daily very soft or liquid SF ≥ 4.0 AND/OR average daily AP score ≥ 2.0 at Baseline.

4. Demonstrated an inadequate response or intolerance to one or more conventional and/or biologic therapies, in the opinion of the investigator, as defined below:

   - Oral locally acting steroids

- Signs and symptoms of persistently active disease during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone, OR

- Inability to taper oral budesonide at or below 6 mg/day without recurrent active disease, OR

- Intravenous or oral corticosteroids

  - Signs and symptoms of persistently active disease despite a history of at least one induction regimen consisting of a dose equivalent to prednisone (or equivalent) ≥ 40 mg/day orally for at least 3 weeks or intravenously for 1 week, OR

  - Inability to taper corticosteroids at or below a dose equivalent to prednisone 10 mg/day without recurrent active disease, OR

- Immunosuppressants

  - Signs and symptoms of persistently active disease despite a history of at least one 12-week regimen of the following:

  - AZA: ≥ 2.0 mg/kg/day (≥ 1 mg/kg/day for subjects in Japan, Korea, Taiwan, Singapore, Hong Kong, or China), rounded to the nearest available tablet or half tablet formulation, OR a documented 6-thioguanine nucleotide (6-TGN) level of > 235 pmol/8 × 10^8 RBC at a dose < 2 mg/kg/day OR documentation that a dose reduction was required due to elevated 6-MP levels (> 5700 pmol/8 ×10^8 erythrocytes) OR

  - 6-MP: ≥ 1 mg/kg/day (≥ 0.6 mg/kg/day for subjects in Japan, Korea, Taiwan, Singapore, Hong Kong, or China), rounded to the nearest available tablet or half tablet formulation, (or a 6-TGN level of > 235 pmol/8 × 10^8 RBC) OR

  - MTX (≥ 25 mg/week subcutaneous [SC] or intramuscular [IM]), OR

  - Tacrolimus (for subjects in Australia, China, Japan or Taiwan only): documented trough level of ≥ 5 ng/mL.

Note: Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study.

- Biologic therapies for CD

  - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg intravenous [IV] at Baseline and Weeks 2, and 6), OR

  - At least one 4-week induction regimen of adalimumab (one 160 mg subcutaneous [SC] dose at Baseline, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC dose at Baseline, followed by one 40 mg SC dose at Week 2, in countries where this dosing regimen is approved]), OR

  - At least one 4-week induction regimen of certolizumab pegol (400 mg SC at Baseline and Weeks 2, and 4), OR

  - At least one 6-week induction regimen of vedolizumab (300 mg IV at Baseline and Weeks 2, and 6), OR

- At least one 8-week induction regimen of ustekinumab [260 mg (≤ 55 kg) or 390 mg (> 55 to ≤ 85 kg) or 520 mg (> 85 kg) IV, followed by 90 mg SC at Week 8], OR

- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics.

- Intolerance to corticosteroids may include depression, severe insomnia, osteopenia, cushingoid features, etc. Intolerance to AZA/6-MP should include elevations of liver enzymes, pancreatitis, etc., and may include subjects with known thiopurine methyltransferase (TPMT) genetic mutation or low activity or genetic polymorphism of NUDT-15. Intolerance to a biologic may include, but not be limited to infusion-related reaction, rash, serum sickness, anaphylaxis, elevated liver enzymes, demyelination, congestive heart failure, infection, etc. Demonstration of intolerance requires no minimum dose or duration of use.

Note: Non-bio-IR subjects who have received prior biologic for up to 1 year but have not failed may be enrolled; however, subjects must have discontinued the biologic for reasons other than inadequate response or intolerance (e.g., change of insurance, well controlled disease), and must meet the criteria for intolerance or inadequate response to oral locally acting steroids, systemic steroids and/or immunosuppressants as defined above.

Main Exclusion:

1. Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.

2. Subject on CD related antibiotics who:

    - has not been on stable doses of these medications for at least 14 days prior to Baseline; or

    - has discontinued these medications within 14 days of Baseline.

3. Subject on oral aminosalicylates who:

    - has not been on stable doses of these medications for at least 14 days prior to Baseline; or

    - has discontinued these medications within 14 days of Baseline.

4. Subject on corticosteroids who meet the following:

    - prednisone or equivalent dose > 30 mg/day; or

    - budesonide > 9 mg/day; or

    - has not been on the current course for at least 14 days prior to Baseline and on a stable dose for at least 7 days prior to Baseline.

5. Subject on MTX who:

    - has not been on the current course for ≥ 42 days prior to Baseline, and

    - has not been on a stable dose for ≥ 28 days prior to Baseline CD Related

6. Subject with the following ongoing known complications of CD:

    - abscess (abdominal or peri-anal),

    - symptomatic bowel strictures,

- > 2 entire missing segments of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum,

- fulminant colitis,

- colon,

- or any other manifestation that might require surgery while enrolled in the study.

7. Subject with ostomy or ileoanal pouch

8. Subject diagnosed with conditions that could interfere with drug absorption including but not, although the CHMP limited to short gut or short bowel syndrome

9. Subject with surgical bowel resection within the past 3 months prior to Baseline, or a history of > 3 bowel resections

Study M14-430

Study M14-430 consisted of two substudies: Substudy 1 and Substudy 2. Substudy 1 enrolled subjects who achieved clinical response to induction treatment with upadacitinib 45 mg (Cohort 1) or placebo (Cohort 2), or Extended Treatment with upadacitinib 30 mg (Cohort 3) in Studies M14-431 or M14-433. Substudy 2 is an ongoing LTE for subjects who complete Substudy 1 (Cohort 5) and those with clinical response to OL upadacitinib 30 mg QD during the Extended Treatment Period in Study M14-431 (Cohort 4).

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

Substudy 1

1. Subject achieved clinical response in Study M14-431 or Study M14-433.

2. Subject completed Week 12 (in subjects who achieve response at Week 12) or Week 24 (in subjects who achieve response at Week 24) visit and procedures in Study M14-431 or Study M14-433. The final endoscopy for Studies M14-431 or M14-433 may be missing, if the endoscopy cannot be performed during the COVID-19 pandemic.

Note: Subjects completing Part 3/Cohort 3 of Study M14-431, who received open-label Extended Treatment, should enroll in Substudy 2.

Substudy 2

1. Subject completed Week 52 of the maintenance period of Study M14-430 (Substudy 1). Completion includes the Week 52 endoscopy of Substudy 1. The Week 52 endoscopy may be missing, if the endoscopy cannot be performed during the COVID-19 pandemic.

2. Subject achieved clinical response at Week 24 and completed Week 24 visit and procedures in Part 3/Cohort 3 of Study M14-431.

Main Exclusion:

Substudy 1 and 2

1. Subject is considered by the investigator, for any reason, to be an unsuitable candidate for the study.

2. Subject who has a known hypersensitivity to upadacitinib or its excipients, or had an AE during Study M14-431, M14-433, or Substudy 1 of Study M14-430 that in the investigator's judgment makes the subject unsuitable for this study.

3. Subject with any active or chronic recurring infections based on the investigator's assessment that makes the subject an unsuitable candidate for the study. Subjects with serious infections undergoing treatment may be enrolled BUT NOT dosed until the infection treatment has been completed, and the infection is resolved, based on the investigator's assessment.

4. Subjects with high grade colonic dysplasia or malignancy diagnosed at the endoscopy performed at the final visit of Study M14-431, M14-433, or Substudy 1 of Study M14-430 (Week 52).

Treatments

Induction

Induction periods from Part 1 of both studies were DB, 12-week, placebo-controlled periods in which subjects were randomized 2:1 to upadacitinib 45 mg QD or matching placebo QD. To ensure enough clinical responders would be eligible for re-randomization into the Study M14-430 Substudy 1 (maintenance period) while minimizing unnecessary exposure to placebo, a second 12-week open-label, single-arm, induction treatment group was included in Study M14-431 (Part 2). Subjects who did not achieve clinical response at Week 12 in both induction studies continued into an Extended Treatment Period (Part 3 in Study M14-431 and Part 2 in Study M14-433) with upadacitinib 45 mg for subjects who were placebo non-responders and with upadacitinib 30 mg for subjects who were upadacitinib 45 mg non-responders.

Subjects who were enrolled on oral steroids initiated a protocol-required taper at Week 4 to assess corticosteroid-free endpoints at Week 12.
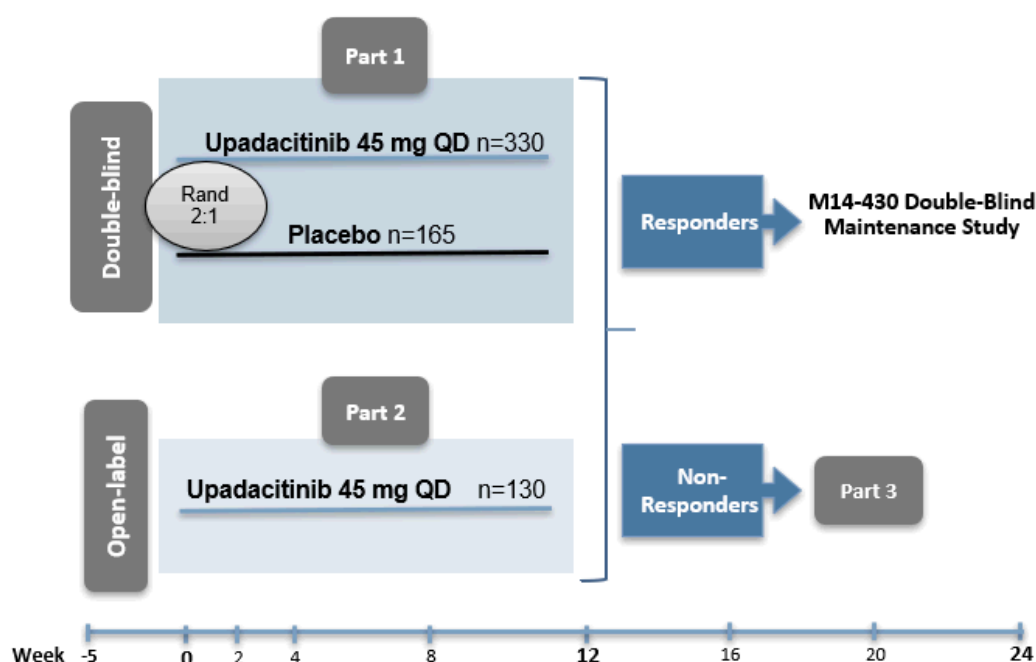
Figure 7   Induction phase study M14-431
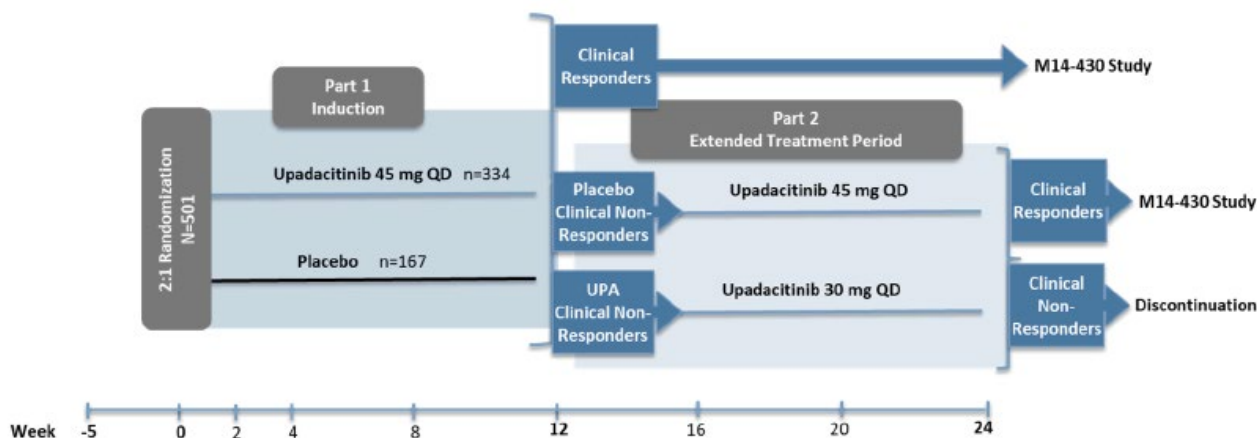
Figure 8   Induction phase study M14-433

Maintenance

Substudy 1 (52-Week, re-randomized, DB, maintenance) included 3 cohorts (Figure 9).

Cohort 1: Included subjects who received upadacitinib 45 mg induction treatment for 12 weeks in Study M14-431 (from Part 1 or Part 2) or Study M14-433 (Part 1), and subjects who received upadacitinib 45 mg QD induction treatment for 12 weeks during the Extended Treatment Period of Study M14-431 (Cohort 1 of Part 3) or Study M14-433 (Cohort 1 of Part 2) and achieved clinical response. Subjects were re-randomized in a 1:1:1 ratio to one of the following 3 treatment groups:

- Group 1: upadacitinib 15 mg QD

- Group 2: upadacitinib 30 mg QD

- Group 3: placebo

Cohort 2: Included subjects who received DB placebo for 12 weeks during Part 1 of Study M14-431 or Study M14-433 and achieved clinical response and continued to receive blinded placebo.

Cohort 3: Included subjects who entered the Extended Treatment Period of Study M14-431 or Study M14-433 and received DB upadacitinib 30 mg QD for 12 weeks and achieved clinical response at Week 24 and continued to receive blinded upadacitinib 30 mg QD.

During Substudy 1, at or after Week 4, subjects who met the criteria for inadequate response and required medical treatment were eligible to receive rescue treatment with OL upadacitinib 30 mg QD and protocol allowed CD-related medications (Figure 9).

Note: Baseline was defined as the Baseline Visit of Study M14-431 or Study M14-433 (induction) and Week 0 is defined as the first study visit in Study M14-430 (maintenance).
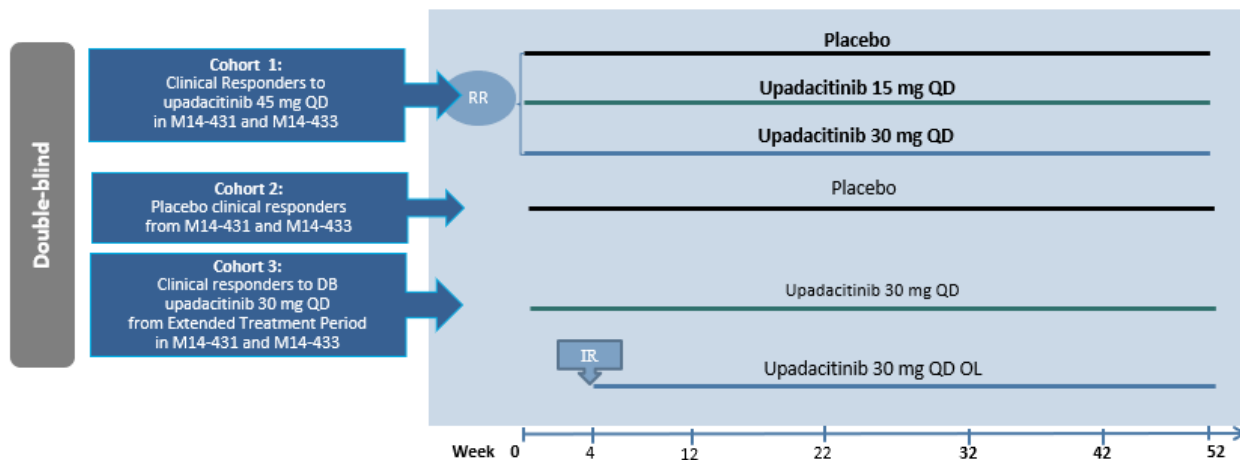
Figure 9   Study Design Schematic – M14-430 Substudy 1 (Maintenance)

All subjects who completed Week 52 visit in Substudy 1 (all cohorts) were eligible to enrol into Substudy 2 (LTE).

Substudy 2 (240-week LTE) included subjects from 2 separate cohorts (Cohort 4 and Cohort 5) (Figure 10).

Cohort 4: Included subjects who achieved clinical response in the OL Extended Treatment Period (Part 3/Cohort 3 of Study M14-431) at Week 24 and continued to receive OL upadacitinib 30 mg QD for 240 weeks.

Cohort 5: All subjects who completed Substudy 1 were eligible to enroll in this cohort. At Week 0, all subjects continued to receive their originally assigned DB treatment (placebo, 15 or 30 mg QD upadacitinib). During Substudy 2, subjects who met the criteria for inadequate response may receive rescue treatment with upadacitinib 30 mg.
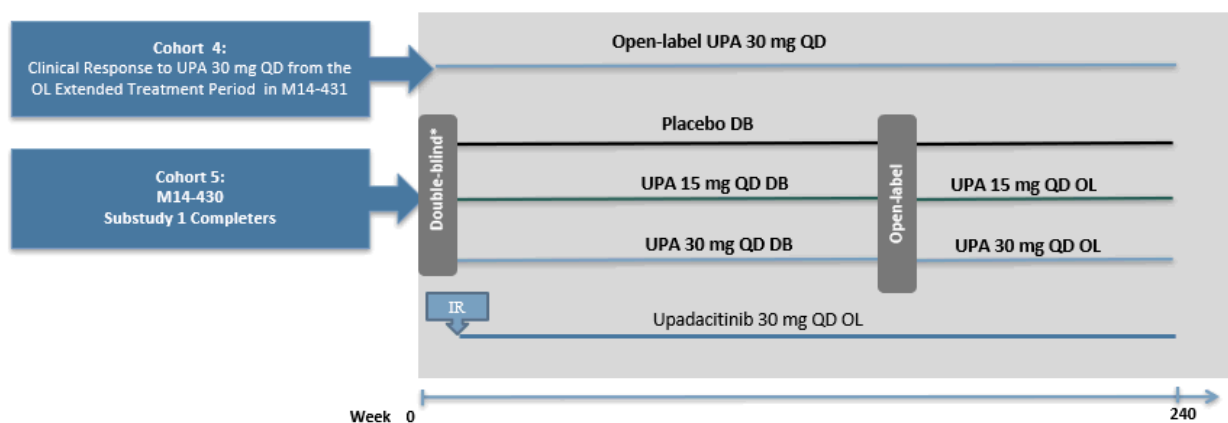
*The three treatment arms in Cohort 5 remain blinded until the last subject completes Substudy 1. After all sites and subjects are unblinded, subjects receiving placebo only receive the concomitant CD-related medications, if any.

Figure 10   Study Design Schematic – M14-430 Substudy 2 (Long-term Extension)

Objectives

The objective of Study M14-431 and Study M14-433 was to evaluate the efficacy and safety of upadacitinib compared to placebo as induction therapy in subjects with moderately and severely active CD.

The primary objective of maintenance/LTE Study M14-430 Substudy 1 (randomized, double-blind, placebo-controlled maintenance) was to evaluate the efficacy and safety of two doses of upadacitinib 15 mg and 30 mg QD versus placebo as maintenance therapy in subjects with moderately to severely active CD who responded to upadacitinib induction treatment in Studies M14-431 or M14-433 and enrolled in Cohort 1.

Outcomes/endpoints

<u>Induction (identical for both induction studies M14-431 and M14-433)</u>

The co-primary and key secondary endpoints were analyzed separately for EU/EMA and United States (US)/Food and Drug Administration (FDA) regulatory purposes for both studies. The endpoints were specified separately for each set of analyses.

Co-primary endpoints for US/FDA regulatory purposes:

- Proportion of subjects with clinical remission per CDAI at Week 12, and
- Proportion of subjects with endoscopic response at Week 12.

Co-primary endpoints for EU/EMA regulatory purposes:

- Proportion of subjects with clinical remission per SF/APS at Week 12, and
- Proportion of subjects with endoscopic response at Week 12.

EU/EMA Ranked Secondary Endpoints:

1. Proportion of subjects with clinical remission per CDAI (CDAI < 150) at Week 12
2. Proportion of subjects with clinical remission per PROs at Week 4
3. Proportion of subjects with endoscopic remission at Week 12
4. Proportion of subjects who discontinue corticosteroid use for CD and achieve clinical remission at Week 12, in subjects taking corticosteroids for CD at Baseline
5. Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue at Week 12
6. Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) at Week 12
7. Proportion of subjects achieving CR-100 at Week 2
8. Proportion of subjects achieving CR-100 at Week 12
9. Proportion of subjects with hospitalizations due to CD during the 12-week double-blind induction period
10. Proportion of subjects with resolution of extra-intestinal manifestation (EIM) at Week 12, in subjects with EIM at Baseline

Maintenance

As with the induction studies, the primary analyses were conducted separately for EU/EMA and US/FDA regulatory purposes; the primary endpoint was specified separately for each set of analyses.

Co-primary endpoints for US/FDA regulatory purposes:

- Proportion of subjects with clinical remission per CDAI at Week 52, AND

- Proportion of subjects with endoscopic response at Week 52.

Co-primary endpoints for EU/EMA regulatory purposes:

- Proportion of subjects with clinical remission per SF/APS at Week 52, and

- Proportion of subjects with endoscopic response at Week 52.

EU/EMA Ranked secondary endpoints:

1. Proportion of subjects with clinical remission per CDAI at Week 52

2. Proportion of subjects with endoscopic remission at Week 52

3. Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) at Week 52

4. Proportion of subjects achieving CR-100 at Week 52

5. Proportion of subjects without corticosteroid use for CD at least 90 days prior to Week 52 and achieved clinical remission per PROs at Week 52 (among all subjects)

6. Proportion of subjects who discontinued corticosteroid use for CD for at least 90 days prior to Week 52 and achieved clinical remission per PROs at Week 52 in subjects taking corticosteroids for CD at Baseline of induction

7. Proportion of subjects with clinical remission per PROs at Week 0 and Week 52

8. Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT- F) at Week 52

9. Proportion of subjects with clinical remission per PROs and endoscopic remission at Week 52

10. Proportion of subjects with CD-related hospitalizations during the 52-Week double-blind maintenance period

11. Proportion of subjects with resolution of extra-intestinal manifestations (EIMs) at Week 52, in subjects with EIMs at Baseline.

Efficacy Measurements

The treatment targets for CD are to rapidly obtain a clinical response with induction treatment and then to maintain clinical response or remission, along with normalization of inflammatory markers (C-reactive protein [CRP] and FCP) and endoscopic mucosal healing.

Criteria for Evaluation:

Efficacy Endpoint Definitions: (identical for induction studies M14-431 and M14-433 and maintenance study M14-430)

- Clinical remission per patient reported outcomes (PROs): average daily very soft or liquid SF ≤ 2.8 AND average daily AP score ≤ 1.0 and both not greater than baseline

- Clinical remission per CDAI: CDAI < 150

- Enhanced Clinical Response: ≥ 60% decrease in average daily very soft of liquid SF and/or≥ 35% decrease in average daily AP score and both not greater than baseline, or clinical remission

- Clinical response 100 (CR-100): Decrease of at least 100 points in CDAI from Baseline

- Clinical response: ≥ 30% decrease in average daily very soft or liquid SF and/or ≥ 30% decrease in average daily AP score and both not greater than baseline

- Endoscopic remission: SES-CD ≤ 4 and at least 2-point reduction from Baseline and no subscore > 1 in any individual variable, as scored by central reviewer

- Endoscopic response: decrease in SES-CD > 50% from Baseline of the induction study (or for subjects with an SES-CD of 4 at Baseline, at least a 2-point reduction from Baseline), as scored by central reviewer

CDAI Clinical Remission and Clinical Response

The CDAI is a composite instrument that includes patient symptoms evaluated over 7 days (abdominal pain [AP], very soft or liquid SF, and general wellbeing), as well as physical and laboratory findings.

Historically, CDAI has been the primary scoring system to measure clinical remission and clinical response, and CDAI clinical remission has been used as the primary endpoint for all previously approved biologics for moderately to severely active CD. Higher CDAI scores indicate more severe disease; CDAI clinical remission is defined as a total score < 150 and CDAI clinical response is defined as a drop in total score from Baseline of either in 70 (CR-70) or 100 points (CR-100).

The upadacitinib Phase 3 trials measured clinical remission and clinical response using CDAI < 150 and CR-100, respectively.

SF/APS Clinical Remission and Enhanced SF/APS Clinical Response

Although the CDAI has been used historically, it has limitations. For these reasons, consideration has been given to replacing CDAI with a different PRO instrument. At the time of initiation of the upadacitinib Phase 2 program, there was not another prospectively evaluated and validated PRO instrument available for use in clinical trials of subjects with CD. Therefore, for the upadacitinib Phase 3 program, the PRO instruments selected (SF and APS components of the CDAI) were based on clinical relevance to subjects with CD, a high concordance with the historic CDAI definitions of remission and response, responsiveness to change (Khanna 2015), and their initial prospective evaluation in the upadacitinib Phase 2 Study M13-740.

The cut-offs for clinical response per SF/APS (≥ 30% decrease in average daily very soft or liquid SF and/or ≥ 30% decrease in average daily APS and both not worse than baseline), clinical remission per SF/APS (average daily very soft or liquid SF ≤ 2.8 and not worse than baseline and average daily APS ≤ 1 and not worse than baseline) and enhanced SF/APS clinical response (≥ 60% decrease in average daily very soft or liquid SF and/or ≥ 35% decrease in average daily APS and both not worse than baseline, and/or clinical remission) were established based on analyses of historical adalimumab studies in CD and further validated in the upadacitinib Phase 2 and Phase 3 program.

Based on internal calculations by the MAH, the SF/APS clinical response, clinical remission and enhanced SF/APS clinical response had a correlation with CR-70, over 90% with CDAI clinical remission and CR-100, respectively.

<u>Corticosteroid-Free (or Steroid-Free) Clinical Remission</u>

During the upadacitinib Phase 3 induction studies, beginning at Week 4, all subjects taking corticosteroids for CD at Baseline were required to undergo a mandatory taper schedule as outlined in the protocols. Subjects who were on corticosteroids at Baseline, discontinued their use and achieved clinical remission (per CDAI and per SF/APS) at Week 12 were considered to be in steroid-free clinical remission.

For the upadacitinib Phase 3 maintenance study, steroid-free clinical remission was defined in two ways:

- Subjects without corticosteroid use for CD at least 90 days prior to Week 52 and who achieved clinical remission (per CDAI and per SF/APS) at Week 52, among all subjects

- Subjects who discontinued corticosteroid use for CD at least 90 days prior to Week 52 and achievement of clinical remission (per CDAI and per SF/APS) at Week 52 among subjects taking corticosteroids for CD at Induction Baseline.

<u>Endoscopic Assessments</u>

The upadacitinib CD Phase 3 studies utilized the Simple Endoscopic Score for CD (SES-CD) to measure improvements in mucosal inflammation, including endoscopic response, endoscopic remission, SES-CD 0-2, and absence of ulcers by endoscopy/mucosal healing. SES-CD is calculated based on the sum of individual segment values for four endoscopic variables (presence and size of ulcers, ulcerated surface, affected surface and presence of narrowing). The five segments of the bowel evaluated on endoscopy for SES-CD were: ileum, right colon, transverse colon, sigmoid and left colon and rectum. Each variable in each segment is scored 0 to 3 resulting in SES-CD values ranging from 0 to 56 with higher scores indicating more severe disease. Endoscopic assessments were centrally read by blinded external expert physicians who were not study investigators. While the SES-CD is a validated scoring system, the thresholds to define endoscopic remission or endoscopic response have not been validated (Daperno 2004). Therefore, upadacitinib CD Phase 3 studies included the recommended endoscopic efficacy definitions (Abreu 2020) that both align with recent consensus and are associated with clinically meaningful endpoints (e.g., corticosteroid-free clinical remission), based on analyses of ROC curves and positive and negative likelihood ratios.

<u>Markers of Inflammation</u>

Hs-CRP and Fecal Calprotectin are markers of systemic and intestinal inflammation, respectively, used in routine clinical practice

<u>Quality of Life</u>

Fatigue

One common and validated instrument to measure patient experience of fatigue is the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) scale, which assesses concepts related to the severity and impacts of fatigue over the past seven days, using 13 items rated on a five-point scale ranging from 0 ("not at all") to 4 ("very much"). The FACIT-Fatigue total score ranges from 0 to 52, where a higher score represents less fatigue. AbbVie completed the validation of FACIT-Fatigue in CD subjects and results demonstrate that the instrument has adequate psychometric properties to be an outcome measure and assesses the burden for subjects over time.

IBDQ – Inflammatory Bowel Disease Questionnaire

The 32-item questionnaire is divided into 4 domains: bowel symptoms (e.g., loose stools, AP), systemic symptoms (e.g., weight loss, altered sleep pattern), social function (e.g., work attendance,

need to cancel social events), and emotional function (e.g., anger, depression, irritability). Each individual item has graded responses from 1 (poorest) to 7 (best). The total score ranges from 32 to 224 with a higher score indicating better outcome.

SF-36

The SF-36 questionnaire assesses the general health-related QoL over 8 domains of a patient's functional health and well-being including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. These domains are summarized into a physical component summary score and a mental component summary score with higher scores representing better outcomes.

CD-Related Hospitalizations

Quality of life is negatively impacted by CD-related hospitalizations, due to complications such as disease exacerbation, bowel obstruction, fistulizing disease, infections, need of surgical procedures, etc. In the upadacitinib Phase 3 clinical program, hospitalizations were categorized as CD-related, based on the investigator assessment of the hospitalization and documented in the case report form. These hospitalizations were defined as overnight hospital admissions or prolongation of an existing hospitalization due to adverse event (AE) or complications that are related to CD including hospitalizations for surgical procedures related to CD or nonsurgical CD-related events, such as CD-related flares or related to the complications of CD.

Sample size

Induction Studies M14-431 and M14-433

For EU/EMA regulatory purposes M14-431: Assuming a rate of 12% for clinical remission per PROs in the placebo group and 29% in the upadacitinib group at Week 12, a total sample size of 495 subjects randomized in a 2:1 ratio (330 subjects in the upadacitinib group and 165 subjects in the placebo group) will be adequate to detect at least a 17% treatment difference in clinical remission rates at Week 12 between the treatment groups using Fisher's exact test with at least 95% power at a 0.05 two-sided significant level.

Assuming an endoscopic response rate of 10% in the placebo group and 25% in the upadacitinib group at Week 12, this sample size will be adequate to detect at least a 15% treatment difference in endoscopic response rates at Week 12 between the treatment groups using Fisher's exact test with at least 95% power at a 0.05 two-sided significant level.

The objective of Part 2 is to have a sufficient number of subjects with clinical response to be re-randomized in the double-blind maintenance portion of Study M14-430. A total of 130 subjects enrolled in Part 2 would provide adequate number of subjects achieving clinical response to be re-randomized to the maintenance portion of Study M14-430.

For EU/EMA regulatory purposes M14-433: Assuming a clinical remission rate of 15% in the placebo group and 33% in the upadacitinib group at Week 12, a total sample size of 501 subjects randomized in a 2:1 ratio (334 subjects in the upadacitinib group and 167 subjects in the placebo group) will be adequate to detect at least a 18% treatment difference in clinical remission rates at Week 12 between the treatment groups using Fisher's exact test with at least 95% power at a 0.05 two-sided significant level.

Assuming an endoscopic response rate of 11.5% in the placebo group and 28.5% in the upadacitinib group at Week 12, this sample size will be adequate to detect at least a 17% treatment difference in

endoscopic response rates at Week 12 between the treatment groups using Fisher's exact test with at least 95% power at a 0.05 two-sided significant level.

A total of 495 and 526 subjects were randomized in Study M14-431 (Bio-IR population) and Study M14-433 (Non-Bio-IR and Bio-IR populations), respectively. These studies evaluated the efficacy and safety of upadacitinib 45 mg compared to placebo as induction therapy for 12 weeks in subjects with moderately to severely active CD (

Figure **7**). In Study M14-433, 45.4% of enrolled subjects were Bio-IR and 54.6% were Non-Bio-IR. Study M14-431, by design, only enrolled subjects with prior inadequate response and intolerance to biologics, with 60.8% of subjects having failed at least 2 biologics representing a patient population that is usually more refractory to existing treatments.

Maintenance (Study M14-430 Substudy 1)

For EU/EMA regulatory purposes: Assuming a Week 52 clinical remission (per PROs) rate of 42% for one of the upadacitinib dose groups and 17% for the placebo group, a total sample size of 501 subjects randomized in a 1:1:1 ratio (167 subjects each in upadacitinib 30 mg QD, upadacitinib 15 mg QD, placebo groups) will have approximately 99% power to detect at least a 25% treatment difference in clinical remission rates at Week 52 between the treatment groups and placebo using Fisher's exact test at a 0.025 two-sided significant level.

Assuming an endoscopic response rate of 35% for one of the upadacitinib dose groups and 17% for the placebo group, this sample size will have approximately 94% power to detect at least a 18% treatment difference in endoscopic response rates at Week 52 between the treatment groups and placebo using Fisher's exact test at a 0.025 two-sided significant level.

To ensure at least 90% power for simultaneous achievement of these endpoints, this sample size of 501 subjects (167 subjects each in upadacitinib 30 mg QD, upadacitinib 15 mg QD, placebo groups) is planned for the Primary Analysis in Cohort 1.

The first 502 subjects who were randomized and received at least one dose of study drug in Study M14-430 Substudy 1 Cohort 1 were included in the ITT1 Population for the primary efficacy analysis. Among these subjects, 75.9% completed study treatment Overall, a similar proportion of subjects from the ITT1 Population completed study drug across the treatment arms.

Randomisation and Blinding (masking)

M14-431: A total of 495 subjects were randomized in Part 1 of the study in a 2:1 ratio to upadacitinib 45 mg QD or matching placebo (330 subjects for upadacitinib 45 mg dose group and 165 for placebo group). Randomization was stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD < 15 and $\geq$ 15), and number of prior biologic treatments (> 1 and $\leq$ 1).

Subjects enroll into Part 3 from Part 2 of the study in an open-label manner. Subjects enrolling in Part 3 from Part 1 are assigned either upadacitinib 45 mg QD or upadacitinib 30 mg QD depending on the randomized treatment received in Part 1 (placebo or upadacitinib 45 mg) in a blinded fashion.

M14-433: Approximately 501 subjects were randomized in Part 1 in a 2:1 ratio into upadacitinib 45 mg group or matching placebo (334 subjects for upadacitinib 45 mg QD dose group and 167 subjects for placebo group). Randomization was stratified by baseline corticosteroid use (yes or no), endoscopic disease severity (SES-CD < 15 and $\geq$ 15) and number of prior biologics with prior inadequate response or intolerance (0, 1, > 1). Subjects enrolling in Part 2 from Part 1 are assigned either upadacitinib 45

mg QD or upadacitinib 30 mg QD depending on the randomized treatment received in Part 1 (placebo or upadacitinib 45 mg) in a blinded fashion.

M14-430: Approximately 427 subjects who received upadacitinib 45 mg QD induction treatment for 12 weeks in Study M14-431 (from Part 1 or Part 2) or Study M14-433 (Part 1), and approximately 110 subjects who received upadacitinib 45 mg QD induction treatment for 12 weeks during the Extended Treatment Period of Study M14-431 (Cohort 1 of Part 3) or Study M14-433 (Cohort 1 of Part 2) and achieve clinical response will be re-randomized in a 1:1:1 ratio to one of the following three treatment groups:

1. Group 1: Upadacitinib 15 mg

2. Group 2: Upadacitinib 30 mg

3. Group 3: Placebo

The randomization was stratified by prior induction study population (1)

Study M14-433 non-bio-IR, 2) Study M14-433 bio-IR or Study M14-431 Part 1/Part 3, 3) Study M14-431 Part 2), clinical remission per PROs status (yes or no), and endoscopic response status (yes or no; based on the local read) at Week 12 or 24 of Study M14-431 or Study M14-433.

Subjects enrolling in Cohorts 2 and 3 of this study are assigned placebo and upadacitinib 30 mg QD, respectively, in a blinded fashion. Subjects enrolled into Cohort 4 in an open-label manner. Subjects enrolling into Cohort 5 are assigned placebo or upadacitinib 30 mg QD or upadacitinib 15 mg QD in a blinded fashion, according to the randomized treatment received in Substudy 1.

Statistical methods

Within each study, different sets of primary and key secondary endpoints were defined for US/FDA and EU/EMA regulatory purposes.

Analysis populations

Induction studies; M14-431 and M14-433

The ITT populations (one for each study part) includes all subjects who received at least one dose of double-blind study drug during that study Part. For ITT1 population, subjects were included in the analysis according to the treatment groups that they were randomized to.

The Per-Protocol (PP) population represents a subset of the ITT1 population, consisting of subjects that did not have a major protocol deviation. Major protocol deviations leading to exclusion from the PP population were identified prior to database lock. For PP population, subjects were included in the analysis according to the treatment groups that they were randomized to.

Maintenance study; M14-430

Population	Definition
ITT1 Population	The first approximately 501 subjects[a] randomized in Cohort 1 who received at least 1 dose of study drug in Substudy 1.
ITT2 Population	Subjects who were enrolled in Cohort 2 and received at least 1 dose of study drug in Substudy 1, and either a) completed 52 weeks of study treatment or b) were enrolled at least 52 weeks prior but have prematurely withdrawn from the study.
ITT3 Population	Subjects who were enrolled in Cohort 3 and received at least 1 dose of study drug in Substudy 1, and either a) completed 52 weeks of study treatment or b) were enrolled at least 52 weeks prior but have prematurely withdrawn from the study.

a. The last two subjects randomized on the same date of 29 March 2021; therefore, an actual N = 502 subjects were included.

The Per-Protocol (PP) population represents a subset of the ITT1 population, consisting of subjects that did not have a major protocol deviation. Major protocol deviations leading to exclusion from the PP population were identified prior to database lock. For PP population, subjects were included in the analysis according to the treatment groups that they were randomized to.

Estimands

Induction studies; M14-431 and M14-433

The estimands corresponding to the primary efficacy objectives were defined as follows:

- The difference in the proportion of subjects achieving clinical remission per PROs at Week 12 regardless of premature discontinuation of study drug but before initiation of CD-related confounding medications, and without initiation or dose escalation of CD-related corticosteroids in the upadacitinib 45 mg QD and placebo groups in the ITT population.

- The difference in the proportion of subjects achieving endoscopic response at Week 12 regardless of premature discontinuation of study drug but before initiation of CD-related confounding medications, and without initiation or dose escalation of CD-related corticosteroids in the upadacitinib 45 mg QD and placebo groups in the ITT population.

The estimands corresponding to the secondary efficacy objectives were defined as follows:

- For each of the binary ranked secondary endpoints except occurrence of hospitalizations due to CD during Part 1: The difference in the proportion of subjects achieving binary endpoints regardless of premature discontinuation of study drug but before initiation of CD-related confounding medications, and without initiation or dose escalation of CD-related corticosteroids in the upadacitinib 45 mg QD and placebo groups in the ITT population.

- For occurrence of hospitalizations due to CD during Part 1: The difference in the proportion of subjects with at least one occurrence of hospitalization due to CD during Part 1 regardless of premature discontinuation of study drug, and regardless of initiation or dose escalation of CD-related corticosteroids in the upadacitinib 45 mg QD and placebo groups in the ITT population.

- For each of the continuous ranked secondary endpoints: The difference in the mean change from baseline regardless of premature discontinuation of study drug but before initiation of CD-related confounding medications, and if subjects would not initiate or escalate dose of CD-related corticosteroids in the upadacitinib 45 mg QD and placebo groups in the ITT population.

Maintenance study; M14-430

The estimands corresponding to the primary efficacy objectives were defined as follows:

- The difference in the proportion of subjects achieving clinical remission per PROs at Week 52 regardless of premature discontinuation of study drug but before initiation of CD-related confounding medications, and without initiation or dose escalation of CD-related rescue medications (See Section 8.0) in each of the upadacitinib 15 mg QD, upadacitinib 30 mg QD groups in comparison with the placebo group in the ITT1 population.

- The difference in the proportion of subjects achieving endoscopic response at Week 52 regardless of premature discontinuation of study drug but before initiation of CD-related confounding medications, and without initiation or dose escalation of CD-related rescue medications (See Section 8.0) in the upadacitinib 15 mg QD, upadacitinib 30 mg QD groups in comparison with the placebo group in the ITT1 population.

The estimands corresponding to the secondary efficacy objectives were defined as follows:

- For each of the binary ranked secondary endpoints except occurrence of hospitalizations due to CD through Week 52: The difference in the proportion of subjects achieving binary endpoints regardless of premature discontinuation of study drug but before initiation of CD-related confounding medications, and without initiation or dose escalation of CD-related rescue medications in the upadacitinib 15 mg QD or upadacitinib 30 mg QD and placebo groups in the ITT1 population.

- For occurrence of hospitalizations due to CD through Week 52: The difference in the exposure-adjusted incidence rate of hospitalization due to CD regardless of premature discontinuation of study drug, and regardless of initiation or dose escalation of CD-related rescue medications but without initiating open-label upadacitinib 30 mg QD in the upadacitinib 15 mg QD or upadacitinib 30 mg QD and placebo groups in the ITT1 population.

- For each of the continuous ranked secondary endpoints: The difference in the mean change from baseline regardless of premature discontinuation of study drug, and without initiation or dose escalation of CD-related rescue medications in the upadacitinib 15 mg QD or upadacitinib 30 mg QD and placebo groups in the ITT1 population.

Missing Data

Induction studies; M14-431 and M14-433 and Maintenance study; M14-430

The primary approach for handling missing data in the analysis of binary endpoints were Non-Responder Imputation (NRI) while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 (NRI-C). A sensitivity analysis for binary endpoints were NRI with No special data handling for missing due to COVID-19 (NRI-NC).

For continuous efficacy endpoints where Mixed-Effect Model Repeat Measurement (MMRM) analysis or Analysis of Covariance (ANCOVA) were performed, missing data were not explicitly imputed.

In addition, As Observed (AO) and tipping point analysis were performed as supplementary and sensitivity analyses.

Efficacy Analyses

Induction studies; M14-431 and M14-433

The primary and secondary efficacy endpoints were analyzed based on ITT1 for Part 1. No statistical comparisons were performed for Part 2 and Part 3. The Primary Analysis were performed after all

enrolled subjects had completed Part 1, Part 2 and Part 3, and the database had been locked. This were the only and final efficacy analysis.

The co-primary endpoints were analyzed between upadacitinib group and placebo group at Week 12 using the CMH test, stratified by the randomization stratification factors (baseline steroid use [Yes, No], endoscopic disease severity [SES-CD < 15, ≥ 15] and number of prior biologics [0, 1, > 1] based on Intent-to-Treat population in Part 1 [ITT1]). The non-responder imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 (NRI-C) was the primary approach for missing data handling in the analyses of the co-primary efficacy endpoints. The NRI-C categorized any subjects who did not have an evaluation during a pre-specified visit window (either due to missing assessment or due to early withdrawal from the study) as a non-responder for the visit. The only exception was that subjects with missing data due to COVID-19 infection or logistical restriction were handled by MI and the subjects were characterized as responders or non-responders based on MI imputed values. In addition, at and after the CD-related corticosteroids intercurrent event and on/after the date of initiation of CD-related confounding medications after premature discontinuation of study drug, subjects were considered as non-responders.

Continuous variables collected longitudinally were analyzed using a Mixed-Effect Model Repeated Measurement (MMRM) model. Continuous efficacy variables which were collected at only one post-baseline visit (such as SES-CD) were analyzed using an Analysis of Covariance (ANCOVA) model. Point estimates and 95% CIs of mean change from baseline within each treatment group, and the difference between upadacitinib group and placebo group were provided.

Maintenance study; M14-430

The primary and final analysis for the 52-week efficacy analyses included subjects who have either completed Substudy 1 or have been enrolled least 52 weeks prior but have prematurely withdrawn from Substudy 1, and safety analyses of all subjects enrolled in Substudy 1 with the data cut-off as of 30 March 2022.

The co-primary and key secondary efficacy endpoints were analyzed based on ITT1 for Cohort 1. No statistical comparisons were performed for Cohort 2 and Cohort 3. For all efficacy endpoints, the descriptive statistics were provided for each cohort, and by treatment group for Cohort 1. Unless otherwise specified, any subject who was randomized based on a wrong stratum was analyzed according to the actual stratum the subject belonged to. For categorical variables, frequencies, and percentages were reported for each cohort and by treatment group for Cohort 1. Within the ITT1 population, pairwise comparison between each upadacitinib group and placebo group was performed using the CMH test adjusting for stratification factors. For continuous variables, the model based mean and standard error was provided; pairwise comparison between each upadacitinib group and placebo group was performed using MMRM.

Type-I Error Control

The overall type I error rate of the co-primary and ranked secondary endpoints were strongly controlled at two-sided 0.05 level of significance using a fixed sequence multiple-testing procedure as well as Holm procedure as described below. Analyses of other efficacy endpoints were performed at significance level alpha = 0.05 (2-sided) without multiplicity adjustment.
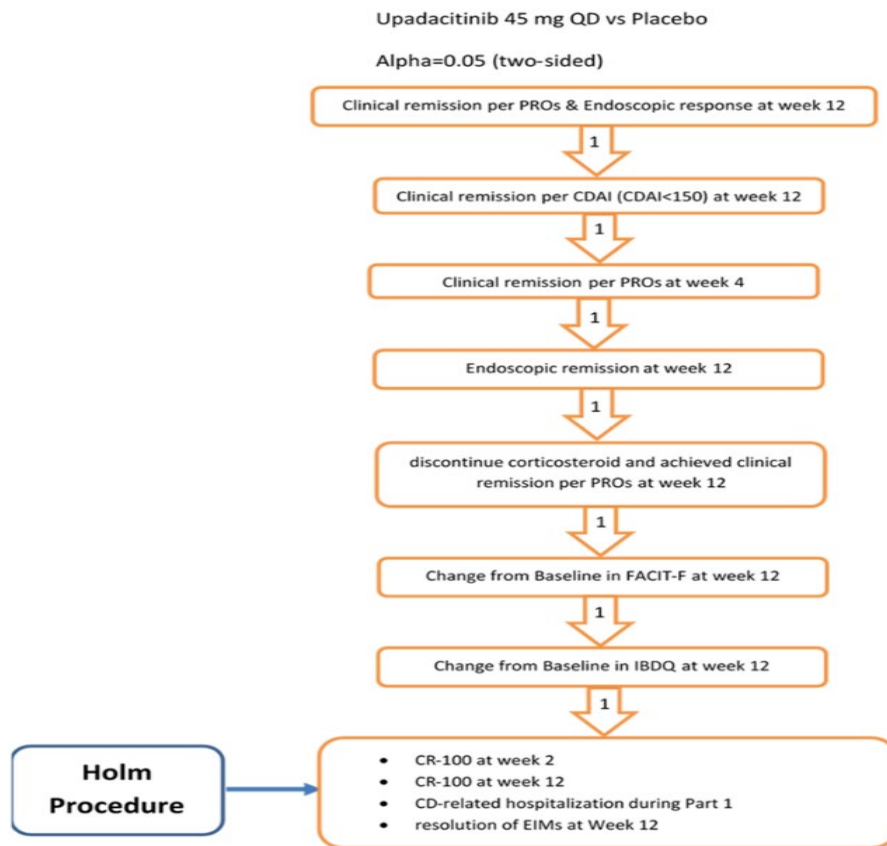
Figure 11   Graphical Multiple Testing Procedure for Co-Primary and Ranked Secondary Endpoints; Induction studies; M14-431 and M14-433
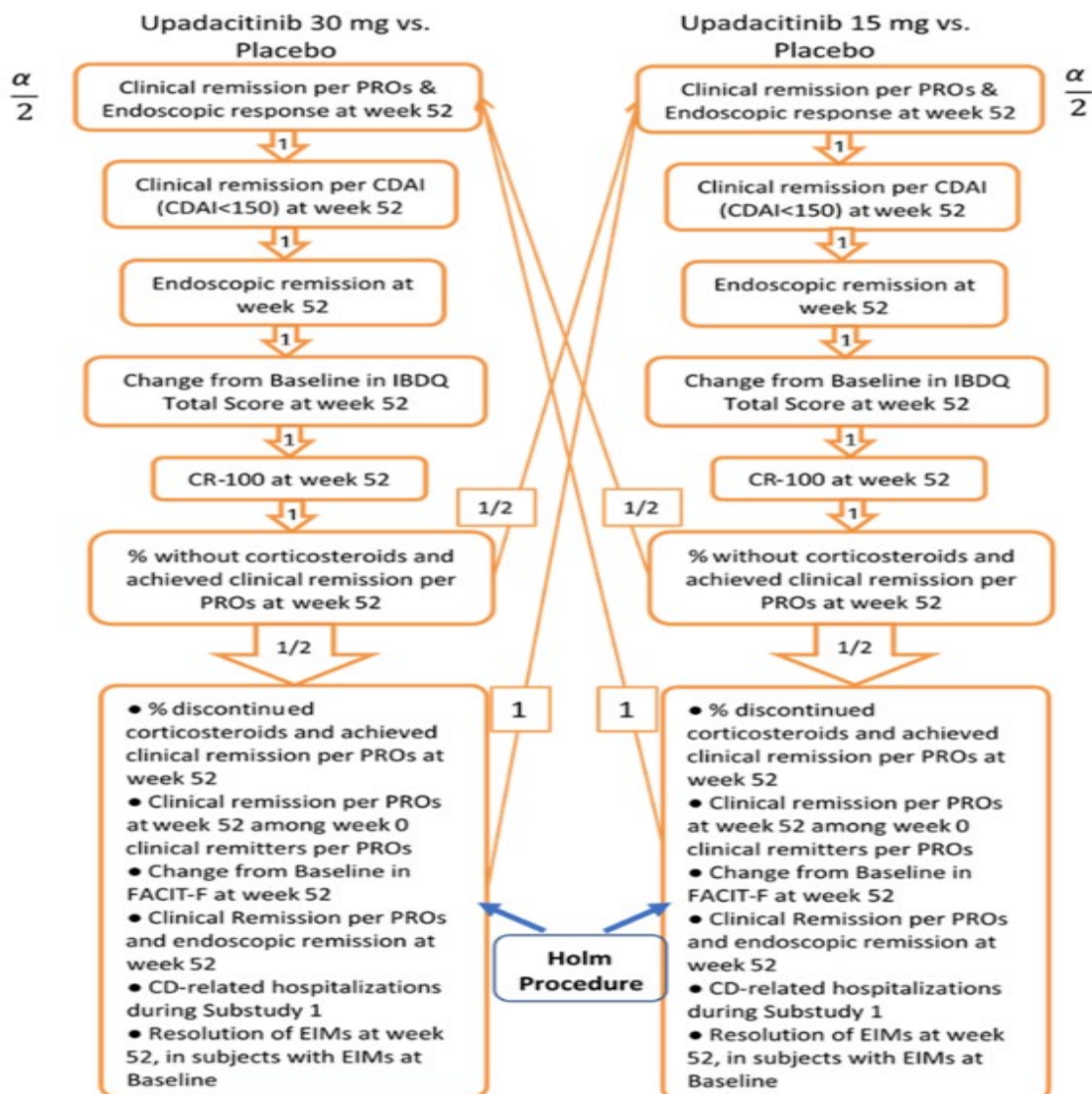
Figure 12   Graphical Multiple Testing Procedure for Co-Primary and Ranked Secondary Endpoints, Maintenance study; M14-430

Results

Participant flow

Induction studies

M14-431: A total of 624 (planned 625) subjects were enrolled at 229 sites in the following countries: Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Canada, Chile, China, Croatia, Czech Republic, Denmark, Egypt, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Japan, Korea (Republic of), Malaysia, Mexico, Netherlands, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, Slovenia, South Africa, Spain, Switzerland, Taiwan (Province of China), Turkey, United Kingdom, and United States, including Puerto Rico.

Table 5   Subject Accountability (All Enrolled Subjects M14-431:)

Sites Treatment	Randomized n	Treated n	Study Drug Discontinued n	Completed n	Study Discontinued n
All sites					
Part 1 (Double-Blind)					
Placebo	171	171	22	149	22
UPA 45 mg	324	324	33	291	33
Total	495	495	55	440	55
Part 2 (Open-Label)					
UPA 45 mg	--	129	7	122	6
Part 3 (Double-Blind)					
Placebo/UPA 45 mg	--	78	11	67	11
UPA 45 mg/UPA 30 mg	--	69	18	51	18
Total	--	147	29	118	29
Part 3 (Open-Label)					
UPA 45 mg/UPA 30 mg	--	14	6	8	6

UPA = upadacitinib

Table 6   Subject Disposition M14-431 (12-Week Induction Period, ITT1 and ITT2 Populations

	Part 1 (Double-Blind)		Part 2 (Open-Label)
	Placebo (N = 171) n (%)	UPA 45 mg (N = 324) n (%)	UPA 45 mg (N = 129) n (%)
Discontinuation of study drug due to			
Primary Reason	22 (12.9)	33 (10.2)	7 (5.4)
Adverse event	5 (2.9)	16 (4.9)	2 (1.6)
Withdrew consent	8 (4.7)	7 (2.2)	3 (2.3)
Lost to follow-up	0	1 (0.3)	0
Lack of efficacy	8 (4.7)	5 (1.5)	1 (0.8)
COVID-19 infection	0	0	0
COVID-19 logistical restrictions	0	0	0
Other	1 (0.6)	4 (1.2)	1 (0.8)
Discontinuation of study due to			
Primary Reason	22 (12.9)	33 (10.2)	6 (4.7)
Adverse event	5 (2.9)	17 (5.2)	2 (1.6)
Withdrew consent	8 (4.7)	8 (2.5)	3 (2.3)
Lost to follow-up	0	1 (0.3)	0
Lack of efficacy	8 (4.7)	4 (1.2)	0
COVID-19 infection	0	0	0
COVID-19 logistical restrictions	0	0	0
Other	1 (0.6)	3 (0.9)	1 (0.8)

COVID-19 = coronavirus disease 2019; ITT1 = intent-to-treat population in Part 1; ITT2 = intent to treat population in Part 2; UPA = upadacitinib

Table 7   Subject Disposition M14-431 (12-Week Induction Period, ITT3 population)

	Part 3 (Double-Blind)		Part 3 (Open-Label)
	PBO/UPA 45 mg (N = 78) n (%)	UPA 45 mg/UPA 30 mg (N = 69) n (%)	UPA 45 mg/UPA 30 mg (N = 14) n (%)
Discontinuation of study drug due to			
Primary Reason	11 (14.1)	18 (26.1)	6 (42.9)
Adverse event	7 (9.0)	5 (7.2)	0
Withdrew consent	0	5 (7.2)	0
Lost to follow-up	0	0	1 (7.1)
Lack of efficacy	3 (3.8)	6 (8.7)	4 (28.6)
COVID-19 infection	0	0	0
COVID-19 logistical restrictions	0	1 (1.4)	0
Other	1 (1.3)	1 (1.4)	1 (7.1)
Discontinuation of study due to			
Primary Reason	11 (14.1)	18 (26.1)	6 (42.9)
Adverse event	8 (10.3)	5 (7.2)	0
Withdrew consent	0	5 (7.2)	1 (7.1)
Lost to follow-up	0	0	1 (7.1)
Lack of efficacy	2 (2.6)	6 (8.7)	3 (21.4)
COVID-19 infection	0	0	0
COVID-19 logistical restrictions	0	1 (1.4)	0
Other	1 (1.3)	1 (1.4)	1 (7.1)

COVID-19 = coronavirus disease 2019; ITT3 = intent to treat population in Part 3; PBO = placebo; UPA = upadacitinib

M14-433 A total of 526 (planned 501) subjects were randomized at 209 sites in the following countries: Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Croatia, Czechia, Denmark, Egypt, France, Germany, Greece, Hungary, Israel, Italy, Japan, South Korea, Latvia, Lithuania, Malaysia, Mexico, Netherlands, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan (Province of China), Turkey, Ukraine, United Kingdom, and United States, including Puerto Rico.

Table 8 Subject Accountability M14-433 (All Enrolled Subjects)

Sites Treatment	Randomized n	Treated n	Study Drug		Study Discontinued n
			Discontinued n	Completed n	
All sites					
Part 1 (Double-Blind)					
Placebo	176	176	21	155	22
UPA 45 mg	350	350	22	328	20
Total	526	526	43	483	42
Part 2 (Extended Treatment)					
Placebo/UPA 45 mg	--	57	8	49	8
UPA 45 mg/UPA 30 mg	--	59	10	49	10
Total	--	116	18	98	18

Table 9 Subject Disposition M14-433 (12-Week Induction Period, ITT1 Population)

	Part 1 (Double-Blind)	
	Placebo (N = 176) n (%)	UPA 45 mg (N = 350) n (%)
Discontinuation of study drug due to		
Primary Reason[a]	21 (11.9)	22 (6.3)
Adverse event	7 (4.0)	13 (3.7)
Withdrew consent	5 (2.8)	3 (0.9)
Lost to follow-up	0	1 (0.3)
Lack of efficacy	9 (5.1)	4 (1.1)
COVID-19 infection	0	0
COVID-19 logistical restrictions	0	0
Other	0	1 (0.3)
Discontinuation of study due to		
Primary Reason[b]	22 (12.5)	20 (5.7)
Adverse event	8 (4.5)	12 (3.4)
Withdrew consent	6 (3.4)	3 (0.9)
Lost to follow-up	0	1 (0.3)
Lack of efficacy	8 (4.5)	3 (0.9)
COVID-19 infection	0	0
COVID-19 logistical restrictions	0	0
Other	0	1 (0.3)

COVID-19 = coronavirus disease 2019; ITT1 = intent-to-treat population in Part 1; UPA = upadacitinib

a. Subjects who discontinued study drug are counted under each reason given for discontinuation, therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.

b. Subjects who discontinued study are counted under each reason given for discontinuation, therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.

Table 10   Subject Disposition M14-433 (12-Week Extended Treatment Period, ITT2 Population)

	Part 2	
	Placebo/UPA 45 mg (N = 57) n (%)	UPA 45 mg/UPA 30 mg (N = 59) n (%)
Discontinuation of study drug due to		
Primary Reason[a]	8 (14.0)	10 (16.9)
Adverse event	1 (1.8)	2 (3.4)
Withdrew consent	3 (5.3)	1 (1.7)
Lost to follow-up	0	0
Lack of efficacy	2 (3.5)	5 (8.5)
COVID-19 infection	0	1 (1.7)
COVID-19 logistical restrictions	1 (1.8)	0
Other	1 (1.8)	1 (1.7)
Discontinuation of study due to		
Primary Reason[b]	8 (14.0)	10 (16.9)
Adverse event	2 (3.5)	2 (3.4)
Withdrew consent	3 (5.3)	1 (1.7)
Lost to follow-up	0	0
Lack of efficacy	1 (1.8)	5 (8.5)
COVID-19 infection	0	1 (1.7)
COVID-19 logistical restrictions	1 (1.8)	0
Other	1 (1.8)	1 (1.7)

COVID-19 = coronavirus disease 2019; ITT2 = intent to treat population in Part 2; UPA = upadacitinib

Maintenance study M14-430

A total of 502 subjects were randomized in Cohort 1 on or prior to 29 Mar 2021 and were included in the ITT1 analysis set.

Among subjects in the ITT1 population, a similar percentage of subjects in the placebo group (10.9%), upadacitinib 15 mg (13.6%), and upadacitinib 30 mg (11.9%) discontinued the blinded study drug prematurely; the primary reason for study drug discontinuation in upadacitinib groups was adverse event (AE), and lack of efficacy in the placebo group (Table 11).

In addition, a higher proportion of subjects from the placebo group received rescue treatment of open-label upadacitinib 30 mg, compared to the upadacitinib 15 mg and 30 mg groups.

Table 11   Summary of Study Drug Discontinuation (ITT1 Population) M14-430

Discontinuation due to	PBO (N = 165) n (%)	UPA 15 mg (N = 169) n (%)	UPA 30 mg (N = 168) n (%)	Total (N = 502) n (%)
Without Receiving OL Rescue UPA 30 mg QD	18 (10.9)	23 (13.6)	20 (11.9)	61 (12.2)
All Reasons[a]				
Adverse event	6 (3.6)	11 (6.5)	11 (6.5)	28 (5.6)
Withdrew consent	5 (3.0)	5 (3.0)	7 (4.2)	17 (3.4)
Lost to follow-up	1 (0.6)	2 (1.2)	1 (0.6)	4 (0.8)
Lack of efficacy	7 (4.2)	6 (3.6)	4 (2.4)	17 (3.4)
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	0	0	0
Other	3 (1.8)	4 (2.4)	3 (1.8)	10 (2.0)
Primary Reason				
Adverse event	6 (3.6)	10 (5.9)	10 (6.0)	26 (5.2)
Withdrew consent	4 (2.4)	4 (2.4)	7 (4.2)	15 (3.0)
Lost to follow-up	1 (0.6)	2 (1.2)	1 (0.6)	4 (0.8)
Lack of efficacy	6 (3.6)	5 (3.0)	1 (0.6)	12 (2.4)
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	0	0	0
Other	1 (0.6)	2 (1.2)	1 (0.6)	4 (0.8)
After Receiving OL Rescue, UPA 30 mg QD	25 (15.2)	21 (12.4)	14 (8.3)	60 (12.0)
All Reasons[a]				
Adverse event	8 (4.8)	11 (6.5)	3 (1.8)	22 (4.4)
Withdrew consent	1 (0.6)	3 (1.8)	2 (1.2)	6 (1.2)
Lost to follow-up	1 (0.6)	1 (0.6)	0	2 (0.4)
Lack of efficacy	17 (10.3)	11 (6.5)	10 (6.0)	38 (7.6)
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	0	0	0
Other	2 (1.2)	2 (1.2)	1 (0.6)	5 (1.0)

Discontinuation due to	PBO (N = 165) n (%)	UPA 15 mg (N = 169) n (%)	UPA 30 mg (N = 168) n (%)	Total (N = 502) n (%)
Primary Reason				
Adverse event	4 (2.4)	6 (3.6)	3 (1.8)	13 (2.6)
Withdrew consent	1 (0.6)	3 (1.8)	2 (1.2)	6 (1.2)
Lost to follow-up	1 (0.6)	1 (0.6)	0	2 (0.4)
Lack of efficacy	17 (10.3)	9 (5.3)	9 (5.4)	35 (7.0)
Primary Reason				
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	0	0	0
Other	2 (1.2)	2 (1.2)	0	4 (0.8)

Recruitment

M13-740 (Phase 2)

Studied Period (Years):
First Subject First Visit: 17 March 2015
Last Subject Last Visit: 03 August 2017

M14-431

Studied Period (Years):
First Subject First Visit: 29 November 2017
Last Subject Last Visit: 11 August 2021

M14-433

Studied Period (Years):
First Subject First Visit: 07 December 2017
Last Subject Last Visit: 13 January 2022

M14-430

Studied Period (Years):
First Subject First Visit: 21 March 2018
Last Subject Last Visit: 30 March 2022

Conduct of the study

The original protocol (01 June 2017, 0 subjects) had 7 global amendments, 16 country-specific amendments and 2 administrative changes.

Global amendments listed below for Induction studies M14-431 and M14-433

Global Amendment 1 (02 October 2017, 13 subjects M14-431 and 2 subjects M14-433).

- Updated eligibility criteria.

- Updated the duration of the maintenance part of Substudy 1 from 48 to 52 weeks.

- Revised ranked secondary and additional secondary efficacy endpoints.

Global Amendment 2 (24 January 2018, 156 subjects M14-431 and 47 subjects M14-433).

- Added vedolizumab as a prohibited biologic therapy during the study.

- Clarified that the primary variables would be analyzed for subjects enrolled in Part 1.

- Clarified that the secondary variables would be analyzed for subjects enrolled in Part 1.

- Added SES-CD ≤ 2 at Week 12 to be consistent with pre-specified endpoint analysis for descriptive statistics. **Only M14-431**

- Clarification on the pre-specified endpoint analysis for descriptive statistics for subjects enrolled in Part 2. **Only M14-431**

- Added pre-specified endpoints for descriptive statistics for subjects enrolled in Part 3. **Only M14-431**

- Clarification on the analysis methods considered for continuous secondary endpoints.

Global Amendment 3 (24 August 2018, 139 subjects M14-431)

- Updated the Introduction to add 52-week data from AbbVie Study M13-740 and to clarify that the once-daily modified release formulation is being used in this study.

- Updated Overall Study Design and Plan to note that the minimum Screening period duration was corrected to reflect the minimum number of days for abdominal pain and stool frequency, accounting for the exclusion of non-usable days due to endoscopy-related procedures.

- Updated eligibility criteria.

- Clarified and provided additional guidance on the use of corticosteroids during the study.

- Corrected the cutoff age for females in defining postmenopausal and updated contraception language.

- Added the Montreal classification for Crohn's disease at screening for the assessment of disease severity.

Global Amendment 3 (24 August 2018, 50 subjects) M14-433

- Minimum screening period duration was corrected and rescreening process was clarified.

- Updated eligibility criteria.

- Clarified and provided additional guidance on the use of concomitant corticosteroids.

- Updated and clarified prohibited therapies.

- Corrected and updated contraception recommendations.

- Added the Montreal classification for CD at Screening.

- Revised ranked secondary and additional secondary efficacy endpoints.

- Updated the list of adverse events of special interest (AESIs).

- Removed Section 6.1.3.1.

- Reduced the number of data point collections of the Crohn's SymptomSeverity (CSS) during the study.

Global Amendment 4 (08 April 2019, 139 subjects M14-431).

- Updated overall study design and plan.

- Updated exclusion criteria to ensure more appropriate selection of subjects into the study to avoid interference with efficacy assessments, to minimize or better manage the potential risks to the participants, and/or to provide further clarifications.

- Removed mention of Japan and China from text describing conditions under which a chest x-ray will not be required, as a prior CT scan can apply to subjects from any country.

- Updated Toxicity Management to align with the entire upadacitinib clinical programs, based on cumulative data with the compound.

- Updated Secondary Efficacy Variables to ensure accurate descriptions of statistical methods.

Global Amendment 4 (08 April 2019, 190 subjects M14-433)

- Revised study title.

- Updated Section 5.1 and Section 5.3.1.1 for alignment with induction Study M14-431 to include enrollment of Bio-IR subjects which increased the subject population.

- Updated eligibility criteria.

- Corrected and updated contraception recommendations.

- Revised ranked secondary and additional secondary efficacy endpoints.

Global Amendment 5 (29 April 2020, 63 subjects M14-431).

- Updated Introduction to include results of recent long-term integrated data from the Phase 3 Rheumatoid Arthritis program and the recent risk updates to the JAK inhibitor class.

- Updated overall study design.

- Updated eligibility criteria.

- Updated efficacy variables: Changed co-primary efficacy endpoint to clinical remission based on CDAI for the US/FDA. The EU/EMA co-primary efficacy endpoint for clinical remission remained based on PROs. Ranked secondary variables now include change from baseline in IBDQ at Week 12, proportion of subjects achieving CR-100 at Week 2 and Week 12, and assessment of extraintestinal manifestations. Four variables (proportion of subjects with enhanced clinical response, $\geq$ 50% reduction in draining fistulas, response in IBDQ bowel domain at Week 12 and change from baseline in CSS) will not be ranked but included under additional efficacy variables

- Updated Toxicity Management section.

- Added management of missing date due to COVID-19.

Global Amendment 5 (29 April 2020, 49 subjects M14-433)

- Removed the number of subjects and the maximum enrollment in the subpopulations.

- Included COVID-19 pandemic provisions for post-baseline endoscopy.

- Updated eligibility criteria.

- Revised prohibited therapy.

- Removed eGFR at Week 12 and Week 24.

- Increased the number of intestinal biopsy samples to be collected.

- Changed co-primary efficacy endpoint to clinical remission based on CDAI for the US/FDA.

- Revised ranked secondary and additional secondary efficacy endpoints.

- Updated the AESIs.

Global Amendment 6 (24 September 2020, 37 subjects M14-431and 81 subjects M14-433).

- Updated information on the re-evaluation of the benefit and risk to subjects participating in the study, updated wording to allow for changes in visits and procedures affected by COVID-19 pandemic and asocial changes in global/local regulations.

Global Amendment 7 (05 March 2021, 0 subjects).

- Updated protocol to decrease the sample size of Part 2 from approximately 150 subjects to approximately 130 subjects, and consequently the total sample size from 645 to 625 subjects.

- Increased the maximum percentage of subjects enrolled who have had inadequate response or intolerance to 3 or more biologics from 30% to 35%.

Baseline data

Induction studies M14-431 Demographics

Characteristics were generally balanced between treatment groups (**Table 12**). No subjects less than 18 years of age were enrolled. Overall, the majority of subjects were white, not Hispanic or Latino, were between the ages of 18 and < 40 years of age, were of normal weight according to body mass index (BMI).

Table 12   Key Demographic Characteristics (ITT1 Population and ITT2 Population)

	Part 1 Double-Blind			Part 2 Open-Label
Variable	PBO (N = 171)	UPA 45 mg (N = 324)	Total (N = 495)	UPA 45 mg (N = 129)
Sex - n (%)				
Female	75 (43.9)	155 (47.8)	230 (46.5)	60 (46.5)
Male	96 (56.1)	169 (52.2)	265 (53.5)	69 (53.5)
Age (years)				
n	171	324	495	129
Mean (SD)	37.5 (12.12)	38.4 (13.71)	38.1 (13.18)	39.1 (12.05)
Median	37.0	36.0	36.0	37.0
Min, Max	18, 74	18, 73	18, 74	18, 68
Age - n (%)				
18 years - < 40 years	96 (56.1)	187 (57.7)	283 (57.2)	69 (53.5)
40 years - < 65 years	71 (41.5)	122 (37.7)	193 (39.0)	57 (44.2)
≥ 65 years	4 (2.3)	15 (4.6)	19 (3.8)	3 (2.3)
Ethnicity - n (%)				
Hispanic or Latino	8 (4.7)	24 (7.4)	32 (6.5)	8 (6.2)
not Hispanic or Latino	163 (95.3)	300 (92.6)	463 (93.5)	121 (93.8)
Race - n (%)				
White	126 (73.7)	230 (71.0)	356 (71.9)	113 (87.6)
Black or African American	6 (3.5)	19 (5.9)	25 (5.1)	5 (3.9)
Asian	38 (22.2)	69 (21.3)	107 (21.6)	11 (8.5)
American Indian or Alaska Native	1 (0.6)	1 (0.3)	2 (0.4)	0
Native Hawaiian or other Pacific Islander	0	0	0	0
Multiple	0	5 (1.5)	5 (1.0)	0

Variable	Part 1 Double-Blind			Part 2 Open-Label
	PBO (N = 171)	UPA 45 mg (N = 324)	Total (N = 495)	UPA 45 mg (N = 129)
Body Mass Index (kg/m^2)				
n	171	324	495	129
Mean (SD)	23.901 (6.1894)	24.164 (5.9763)	24.073 (6.0458)	25.263 (5.9620)
Median	22.611	23.142	23.001	24.075
Min, Max	14.61, 46.40	13.92, 50.52	13.92, 50.52	14.79, 52.85
Body Mass Index (kg/m^2) – n (%)				
< 18.5 kg/m^2	34 (19.9)	48 (14.8)	82 (16.6)	13 (10.1)
≥ 18.5 - < 25 kg/m^2	81 (47.4)	160 (49.4)	241 (48.7)	60 (46.5)
≥ 25 - < 30 kg/m^2	28 (16.4)	68 (21.0)	96 (19.4)	28 (21.7)
≥ 30 kg/m^2	28 (16.4)	48 (14.8)	76 (15.4)	28 (21.7)

Table 13　　Key Demographic Characteristics (ITT3 Population)

Variable	Part 3 Double-Blind		Part 3 Open-Label
	PBO/UPA 45 mg (N = 78)	UPA 45 mg/UPA 30 mg (N = 69)	UPA 45 mg/UPA 30 mg (N = 14)
Sex - n (%)			
Female	34 (43.6)	34 (49.3)	6 (42.9)
Male	44 (56.4)	35 (50.7)	8 (57.1)
Age (years)			
n	78	69	14
Mean (SD)	35.5 (11.20)	38.6 (11.15)	43.4 (11.38)
Median	33.5	38.0	43.0
Min, Max	18, 74	19, 65	24, 67
Age - n (%)			
18 years - < 40 years	52 (66.7)	39 (56.5)	4 (28.6)
40 years - < 65 years	24 (30.8)	29 (42.0)	9 (64.3)
≥ 65 years	2 (2.6)	1 (1.4)	1 (7.1)
Ethnicity - n (%)			
Hispanic or Latino	2 (2.6)	9 (13.0)	1 (7.1)
not Hispanic or Latino	76 (97.4)	60 (87.0)	13 (92.9)
Race - n (%)			
White	55 (70.5)	54 (78.3)	12 (85.7)
Black or African American	1 (1.3)	4 (5.8)	1 (7.1)
Asian	22 (28.2)	10 (14.5)	1 (7.1)
American Indian or Alaska Native	0	1 (1.4)	0
Native Hawaiian or other Pacific Islander	0	0	0
Multiple	0	0	0
Body Mass Index (kg/m^2)			
n	78	69	14
Mean (SD)	23.558 (6.6883)	23.870 (5.4340)	23.831 (4.0534)
Median	21.406	23.815	23.104
Min, Max	14.61, 46.40	15.41, 49.83	17.59, 32.59

| Variable | Part 3 Double-Blind | | Part 3 Open-Label |
	PBO/UPA 45 mg (N = 78)	UPA 45 mg/UPA 30 mg (N = 69)	UPA 45 mg/UPA 30 mg (N = 14)
Body Mass Index (kg/m^2) – n (%)			
< 18.5 kg/m^2	17 (21.8)	10 (14.5)	1 (7.1)
≥ 18.5 - < 25 kg/m^2	39 (50.0)	36 (52.2)	8 (57.1)
≥ 25 - < 30 kg/m^2	8 (10.3)	17 (24.6)	4 (28.6)
≥ 30 kg/m^2	14 (17.9)	6 (8.7)	1 (7.1)

Induction study M14-433 Demographics

Table 14　　Key Demographic Characteristics (12-Week Induction Period, ITT1 Population)

| Variable | Part 1 Double-Blind | | |
	PBO (N = 176)	UPA 45 mg (N = 350)	Total (N = 526)
Sex - n (%)			
Female	82 (46.6)	161 (46.0)	243 (46.2)
Male	94 (53.4)	189 (54.0)	283 (53.8)
Age (years)			
n	176	350	526
Mean (SD)	39.3 (13.63)	39.7 (13.71)	39.6 (13.67)
Median	38.0	37.0	38.0
Min, Max	18, 71	18, 74	18, 74
Age - n (%)			
18 years - < 40 years	91 (51.7)	193 (55.1)	284 (54.0)
40 years - < 65 years	80 (45.5)	142 (40.6)	222 (42.2)
≥ 65 years	5 (2.8)	15 (4.3)	20 (3.8)
Ethnicity - n (%)			
Hispanic or Latino	8 (4.5)	27 (7.7)	35 (6.7)
not Hispanic or Latino	168 (95.5)	323 (92.3)	491 (93.3)
Race - n (%)			
White	130 (73.9)	258 (73.7)	388 (73.8)
Black or African American	4 (2.3)	17 (4.9)	21 (4.0)
Asian	36 (20.5)	73 (20.9)	109 (20.7)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Multiple	6 (3.4)	2 (0.6)	8 (1.5)
Body Mass Index (kg/m^2)			
n	176	350	526
Mean (SD)	25.610 (6.9691)	24.471 (5.9575)	24.852 (6.3303)
Median	24.529	23.143	23.734
Min, Max	14.64, 51.16	14.36, 49.93	14.36, 51.16
< 18.5 kg/m^2	22 (12.5)	53 (15.1)	75 (14.3)

Variable	Part 1 Double-Blind		
	PBO (N = 176)	UPA 45 mg (N = 350)	Total (N = 526)
≥ 18.5 - < 25 kg/m^2	69 (39.2)	158 (45.1)	227 (43.2)
≥ 25 - < 30 kg/m^2	53 (30.1)	76 (21.7)	129 (24.5)
≥ 30 kg/m^2	32 (18.2)	63 (18.0)	95 (18.1)

Table 15   Key Demographic Characteristics (12-Week Extended Treatment Period, ITT2 Population)

Variable	Part 2 Extended Treatment	
	Placebo/UPA 45 mg (N = 57) n (%)	UPA 45 mg/UPA 30 mg (N = 59) n (%)
Sex - n (%)		
Female	25 (43.9)	29 (49.2)
Male	32 (56.1)	30 (50.8)
Age (years)		
n	57	59
Mean (SD)	39.3 (14.00)	43.6 (12.05)
Median	36.0	43.0
Min, Max	19, 70	21, 67
Age - n (%)		
18 years - < 40 years	31 (54.4)	25 (42.4)
40 years - < 65 years	23 (40.4)	31 (52.5)
≥ 65 years	3 (5.3)	3 (5.1)
Ethnicity - n (%)		
Hispanic or Latino	5 (8.8)	6 (10.2)
not Hispanic or Latino	52 (91.2)	53 (89.8)

Variable	Part 2 Extended Treatment	
	Placebo/UPA 45 mg (N = 57) n (%)	UPA 45 mg/UPA 30 mg (N = 59) n (%)
Race - n (%)		
White	39 (68.4)	45 (76.3)
Black or African American	1 (1.8)	2 (3.4)
Asian	15 (26.3)	12 (20.3)
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Multiple	2 (3.5)	0
Body Mass Index (kg/m^2)		
n	57	59
Mean (SD)	24.922 (6.8885)	25.418 (6.6926)
Median	23.789	24.950
Min, Max	14.64, 47.26	15.02, 49.93
< 18.5 kg/m^2	9 (15.8)	9 (15.3)
≥ 18.5 - < 25 kg/m^2	22 (38.6)	21 (35.6)
≥ 25 - < 30 kg/m^2	16 (28.1)	19 (32.2)
≥ 30 kg/m^2	10 (17.5)	10 (16.9)

Induction study M14-431 Baseline characteristics

Baseline disease characteristics were generally well balanced between treatment groups. In the ITT1 population 31.1% of subjects failed ≥ 3 biologics; 95.4% of subjects had prior failure to at least one an anti-TNF agent. The most common CD location per SES-CD was in the ileal-colonic location at 49.3%. Overall, 33.9% and 7.5% of subjects were on concomitant corticosteroids and/or immunosuppressants at baseline, respectively. Mean Crohn's disease duration was approximately 11.7 years with a median value of 9.4 years.

The most commonly (>10%) reported medical conditions in subjects' medical history for those enrolled in the DB 12-week Induction Period (Part 1) were arthralgia (22.0%), anemia (22.0%), anal fistulas (21.8%), gastroesophageal reflux disease (16.6%), anxiety (13.5%), depression (12.5%), abdominal pain (11.9%), drug hypersensitivity (11.7%), arthropathy (11.7%), and hypertension (10.7%).

12-Week Induction Period, Open-Label (Part 2)

In the ITT2 population 42.6% of subjects failed ≥ 3 biologics. The most common CD location per SES-CD was in the ileal-colonic location at 47.3%. Overall, 35.7% and approximately 2.3% of subjects were on concomitant corticosteroids and/or immunosuppressants at baseline, respectively. Mean Crohn's disease duration was approximately 11.4 years with a median value of 10.2 years.

The most commonly reported medical conditions in subjects' medical history for those enrolled in the OL 12-week Induction Period (Part 2) were anemia (24.8%), anal fistulas (21.7%), arthralgia (19.4%), headache (12.4%), hypertension (12.4%), gastroesophageal reflux disease (12.4%), anxiety (10.9%), arthropathy (10.1%), iron deficiency anemia (10.1%), and asthma (10.1%)).

Extended Treatment Period (Part 3)

The disease characteristics of subjects in the ITT3 population were consistent with those observed in Part 1 and Part 2, with the exception of subjects in Cohort 3 where the sample size is limited (N = 14),

the OL portion (upadacitinib 45 mg/upadacitinib 30 mg) with 64.3% of subjects having failed ≥ 3 biologics and a longer mean disease duration of 17.5 years with a median value of 14.9 years.

Table 16   Baseline Disease Characteristics M14-431 (ITT1 and ITT2) populations)

Variable	Part 1 (Double-Blind)			Part 2 (Open-Label)
	PBO (N = 171) n (%)	UPA 45 mg (N = 324) n (%)	Total (N = 495) n (%)	UPA 45 mg (N = 129) n (%)
Crohn's disease duration (years)				
N	171	324	495	129
Mean (SD)	10.9361 (7.9930)	12.0521 (9.5409)	11.6666 (9.0436)	11.4030 (8.2380)
Median	9.8261	9.2512	9.3908	10.2094
Min, Max	0.6352, 46.0726	0.4901, 55.1677	0.4901, 55.1677	0.9829, 48.6242
Biologics failure history – n (%)				
≤ 1	68 (39.8)	126 (38.9)	194 (39.2)	44 (34.1)
2	55 (32.2)	92 (28.4)	147 (29.7)	30 (23.3)
≥ 3	48 (28.1)	106 (32.7)	154 (31.1)	55 (42.6)
Prior Failure to anti-TNF Agent – n (%)				
Yes	164 (95.9)	308 (95.1)	472 (95.4)	114 (88.4)
No	7 (4.1)	16 (4.9)	23 (4.6)	15 (11.6)
Prior Vedolizumab/Natalizumab Failure – n (%)				
Yes	47 (27.5)	99 (30.6)	146 (29.5)	53 (41.1)
No	124 (72.5)	225 (69.4)	349 (70.5)	76 (58.9)
Prior Ustekinumab Failure – n (%)				
Yes	57 (33.3)	118 (36.4)	175 (35.4)	70 (54.3)
No	114 (66.7)	206 (63.6)	320 (64.6)	59 (45.7)
Baseline CDAI				
N	171	322	493	129
Mean (SD)	308.08 (84.267)	306.64 (89.423)	307.14 (87.586)	313.50 (99.237)
Median	303.00	298.80	299.80	312.00
Min, Max	112.0, 545.0	102.0, 627.0	102.0, 627.0	80.0, 657.0

| Variable | Part 1 (Double-Blind) | | | Part 2 (Open-Label) |
	PBO (N = 171) n (%)	UPA 45 mg (N = 324) n (%)	Total (N = 495) n (%)	UPA 45 mg (N = 129) n (%)
Baseline SES-CD				
N	171	324	495	129
Mean (SD)	14.9 (7.75)	15.2 (7.82)	15.1 (7.79)	14.9 (6.78)
Median	13.0	13.0	13.0	14.0
Min, Max	4, 41	4, 40	4, 41	4, 34
CD location per SES-CD – n (%)				
Ileal only	23 (13.5)	48 (14.8)	71 (14.3)	13 (10.1)
Colonic only	68 (39.8)	112 (34.6)	180 (36.4)	55 (42.6)
Ileal-colonic	80 (46.8)	164 (50.6)	244 (49.3)	61 (47.3)
Average daily very soft or liquid stool frequency				
N	171	323	494	129
Mean (SD)	6.0929 (3.3355)	5.7299 (3.3603)	5.8555 (3.3528)	5.9103 (3.4082)
Median	5.7143	5.1429	5.2857	5.2857
Min, Max	0.1429, 19.1429	0.0000, 20.1429	0.0000, 20.1429	0.1429, 23.1429
Average daily abdominal pain score[a]				
N	171	323	494	129
Mean (SD)	1.7955 (0.6849)	1.8508 (0.6913)	1.8317 (0.6889)	1.9181 (0.7218)
Median	2.0000	2.0000	2.0000	2.0000
Min, Max	0.0000, 3.0000	0.0000, 3.0000	0.0000, 3.0000	0.0000, 3.0000
Baseline hs-CRP (mg/L)				
N	163	319	482	125
Mean (SD)	18.983 (24.0176)	20.860 (25.9725)	20.225 (25.3189)	17.994 (20.2435)
Median	9.470	10.500	10.400	12.600
Min, Max	0.41, 126.00	0.20, 144.00	0.20, 144.00	0.21, 122.00
Baseline FCP (µg/g)				
N	159	298	457	117
Mean (SD)	2184.7 (3148.34)	2286.6 (3880.36)	2251.1 (3639.20)	2406.4 (3351.27)
Median	1115.0	1041.0	1090.0	1486.0
Min, Max	30, 19104	30, 28800	30, 28800	30, 28800

Variable	Part 1 (Double-Blind)			Part 2 (Open-Label)
	PBO (N = 171) n (%)	UPA 45 mg (N = 324) n (%)	Total (N = 495) n (%)	UPA 45 mg (N = 129) n (%)
Draining fistulas (yes, no) – n (%)				
Yes	16 (9.4)	27 (8.4)	43 (8.7)	8 (6.2)
No	155 (90.6)	296 (91.6)	451 (91.3)	121 (93.8)
Missing	0	1	1	0
Non-draining fistulas (yes, no) – n (%)				
Yes	16 (9.4)	31 (9.6)	47 (9.5)	12 (9.3)
No	155 (90.6)	292 (90.4)	447 (90.5)	117 (90.7)
Missing	0	1	1	0
Baseline corticosteroid use (yes, no) – n (%)				
Yes	60 (35.1)	108 (33.3)	168 (33.9)	46 (35.7)
No	111 (64.9)	216 (66.7)	327 (66.1)	83 (64.3)
Baseline immunosuppressant use (yes, no) – n (%)				
Yes	13 (7.6)	24 (7.4)	37 (7.5)	3 (2.3)
No	158 (92.4)	300 (92.6)	458 (92.5)	126 (97.7)

Table 17   Baseline Disease Characteristics, M14-431 (ITT3Population)

	Part 3 (Double-Blind)			Part 3 (Open-Label)
Variable	PBO/UPA 45mg (N = 78) n (%)	UPA 45 mg/UPA 30 mg (N = 69) n (%)	Total (N = 147) n (%)	UPA 45 mg/UPA 30 mg (N = 14) n (%)
Crohn's disease duration (years)				
N	78	69	147	14
Mean (SD)	10.6288 (6.6003)	12.8077 (9.5876)	11.6515 (8.1840)	17.5025 (11.5032)
Median	10.3354	9.8535	10.0589	14.8802
Min, Max	1.0513, 29.0130	0.4901, 43.5264	0.4901, 43.5264	5.2512, 48.6242
Biologics failure history (≤ 1, >1) – n (%)				
≤ 1	25 (32.1)	23 (33.3)	48 (32.7)	2 (14.3)
2	24 (30.8)	16 (23.2)	40 (27.2)	3 (21.4)
≥ 3	29 (37.2)	30 (43.5)	59 (40.1)	9 (64.3)
Prior Failure to anti-TNF Agent – n (%)				
Yes	76 (97.4)	66 (95.7)	142 (96.6)	14 (100)
No	2 (2.6)	3 (4.3)	5 (3.4)	0
Prior Vedolizumab/Natalizumab Failure – n (%)				
Yes	26 (33.3)	23 (33.3)	49 (33.3)	7 (50.0)
No	52 (66.7)	46 (66.7)	98 (66.7)	7 (50.0)
Prior Ustekinumab Failure – n (%)				
Yes	27 (34.6)	37 (53.6)	64 (43.5)	10 (71.4)
No	51 (65.4)	32 (46.4)	83 (56.5)	4 (28.6)
Baseline CDAI				
N	78	69	147	14
Mean (SD)	297.99 (88.909)	293.57 (80.079)	295.91 (84.620)	267.42 (125.789)
Median	284.95	284.00	284.00	288.50
Min, Max	124.0, 523.0	116.0, 516.0	116.0, 523.0	97.6, 546.3
Baseline SES-CD				
N	78	69	147	14
Mean (SD)	16.6 (8.06)	14.6 (7.88)	15.6 (8.01)	13.5 (5.96)

| | Part 3 (Double-Blind) | | Part 3 (Open-Label) | |
	PBO/UPA 45mg (N = 78) n (%)	UPA 45 mg/UPA 30 mg (N = 69) n (%)	PBO/UPA 45mg (N = 78) n (%)	UPA 45 mg/UPA 30 mg (N = 69) n (%)
Median	16.0	12.0	13.0	13.0
Min, Max	4, 41	5, 36	4, 41	4, 26
CD location per SES-CD – n (%)				
Ileal only	6 (7.7)	14 (20.3)	20 (13.6)	2 (14.3)
Colonic only	35 (44.9)	21 (30.4)	56 (38.1)	5 (35.7)
Ileal-colonic	37 (47.4)	34 (49.3)	71 (48.3)	7 (50.0)
Average daily very soft or liquid stool frequency				
N	78	69	147	14
Mean (SD)	6.0304 (3.7436)	5.7277 (3.2015)	5.8884 (3.4911)	6.5408 (2.6556)
Median	5.5857	5.1429	5.4286	5.5000
Min, Max	0.1429, 19.1429	0.0000, 18.0000	0.0000, 19.1429	4.1429, 14.2857
Average daily abdominal pain score				
N	78	69	147	14
Mean (SD)	1.6357 (0.7168)	1.6504 (0.7988)	1.6426 (0.7538)	1.2653 (0.9256)
Median	1.7143	1.8571	1.8571	1.5000
Min, Max	0.0000, 3.0000	0.0000, 3.0000	0.0000, 3.0000	0.0000, 2.5714
Baseline hs-CRP (mg/L)				
N	73	68	141	13
Mean (SD)	20.306 (23.6639)	16.355 (21.8104)	18.401 (22.7940)	14.696 (25.2041)
Median	12.400	9.040	10.900	5.970
Min, Max	0.63, 109.00	0.35, 144.00	0.35, 144.00	0.77, 94.20
Baseline FCP (µg/g)				
N	73	63	136	13
Mean (SD)	2677.5 (3611.65)	1758.2 (2852.37)	2251.6 (3302.27)	1449.8 (1793.98)
Median	1650.0	484.0	994.5	517.0
Min, Max	122, 19104	30, 17694	30, 19104	100, 4735

	Part 3 (Double-Blind)		Part 3 (Open-Label)	
	PBO/UPA 45mg (N = 78) n (%)	UPA 45 mg/UPA 30 mg (N = 69) n (%)	PBO/UPA 45mg (N = 78) n (%)	UPA 45 mg/UPA 30 mg (N = 69) n (%)
Draining fistulas (yes, no) – n (%)				
Yes	9 (11.5)	5 (7.2)	14 (9.5)	1 (7.1)
No	69 (88.5)	64 (92.8)	133 (90.5)	13 (92.9)
Missing	--	--	--	--
Non-draining fistulas (yes, no) – n (%)				
Yes	9 (11.5)	4 (5.8)	13 (8.8)	0
No	69 (88.5)	65 (94.2)	134 (91.2)	14 (100)
Missing	--	--	--	--
Baseline corticosteroid use (yes, no) – n (%)				
Yes	22 (28.2)	23 (33.3)	45 (30.6)	2 (14.3)
No	56 (71.8)	46 (66.7)	102 (69.4)	12 (85.7)
Baseline immunosuppressant use (yes, no) – n (%)				
Yes	8 (10.3)	8 (11.6)	16 (10.9)	2 (14.3)
No	70 (89.7)	61 (88.4)	131 (89.1)	12 (85.7)

Prior Use of CD-Related Medications M14-431:

12-Week Induction Period, Double-Blind (Part 1)

Use of any prior CD related medication was reported by 100% of subjects in the DB 12-week Induction Period (Part 1) The most frequently reported prior CD-related medications used in the DB 12-week Induction Period (Part 1) were adalimumab (70.2% of subjects from the placebo group) and infliximab (69.4% of subjects from the upadacitinib 45 mg QD group)

12-Week Induction Period, Open-Label (Part 2)

Use of any prior CD related medication was reported by 99.2% of subjects in the OL 12-week Induction Period (Part 2) (**Table 18**). The most frequently reported prior CD-related medications used in the OL 12-week Induction Period (Part 2) were infliximab (69.8%) and adalimumab (65.1%)

Table 18 Crohn's Disease-Related Biologic Medications Taken Prior to Baseline M14-431 (ITT1 and ITT2 Populations)

Generic Name (WHO 2021 Q1)	Part 1 (Double-Blind)			Part 2 (Open-Label)
	PBO (N = 171) n (%)	UPA 45 mg (N = 324) n (%)	Total (N = 495) n (%)	UPA 45 mg (N = 129) n (%)
CD-related medication	171 (100)	324 (100)	495 (100)	128 (99.2)
Biologics				
Adalimumab	120 (70.2)	216 (66.7)	336 (67.9)	84 (65.1)
Certolizumab	5 (2.9)	7 (2.2)	12 (2.4)	1 (0.8)
Certolizumab pegol	16 (9.4)	33 (10.2)	49 (9.9)	6 (4.7)
Infliximab	117 (68.4)	225 (69.4)	342 (69.1)	90 (69.8)
Ustekinumab	58 (33.9)	122 (37.7)	180 (36.4)	72 (55.8)
Vedolizumab	48 (28.1)	104 (32.1)	152 (30.7)	55 (42.6)

Induction study M14-433 Baseline characteristics

Baseline disease characteristics were generally well balanced between treatment groups. A total of 54.6% of subjects have failed conventional therapies and had not failed a biologic therapy (non-bio-IR) and 45.4% of subjects had failed at least one biologic therapy (bio-IR). Among the bio-IR subjects, 97.1% of subjects had prior failure to at least one an anti-TNF agent. The most common CD location per SES-CD was in the ileal-colonic location at 50.0%. Overall, 36.1% and 3.0% of subjects were on concomitant corticosteroids and/or immunomodulators at Baseline, respectively. Mean Crohn's disease duration was approximately 8.9 years with a median value of approximately 6.1 years.

Table 19   Baseline Disease Characteristics, M14-433 (12-Week Induction Period, ITT1 Population)

| | Part 1 (Double-Blind) | | |
Variable	PBO (N = 176) n (%)	UPA 45 mg (N = 350) n (%)	Total (N = 526) n (%)
Crohn's disease duration (years)			
Mean (SD)	8.1005 (7.9901)	9.2993 (9.4684)	8.8982 (9.0110)
Median	5.6810	6.6516	6.0794
Min, Max	0.2765, 46.2752	0.0575, 52.1123	0.0575, 52.1123
Biologics use/failure history – Bio-IR status n (%)			
Bio-IR	78 (44.3)	161 (46.0)	239 (45.4)
Non-Bio-IR	98 (55.7)	189 (54.0)	287 (54.6)
Prior exposure to biologic therapy among Non-Bio-IR subjects – n(%)			
N (Non-Bio-IR)	98	189	287
Yes	9 (9.2)	16 (8.5)	25 (8.7)
No	89 (90.8)	173 (91.5)	262 (91.3)
Biologics failure history– n (%)			
N (Bio-IR)	78	161	239
1	28 (35.9)	58 (36.0)	86 (36.0)
2	24 (30.8)	52 (32.3)	76 (31.8)
≥ 3	26 (33.3)	51 (31.7)	77 (32.2)

| Variable | Part 1 (Double-Blind) | | |
	PBO (N = 176) n (%)	UPA 45 mg (N = 350) n (%)	Total (N = 526) n (%)
Prior Failure to anti-TNF Agent– n (%)			
N (Bio-IR)	78	161	239
Yes	75 (96.2)	157 (97.5)	232 (97.1)
No	3 (3.8)	4 (2.5)	7 (2.9)
Prior Vedolizumab/Natalizumab Failure – n (%)			
N (Bio-IR)	78	161	239
Yes	25 (32.1)	49 (30.4)	74 (31.0)
No	53 (67.9)	112 (69.6)	165 (69.0)
Prior Ustekinumab Failure– n (%)			
N (Bio-IR)	78	161	239
Yes	33 (42.3)	64 (39.8)	97 (40.6)
No	45 (57.7)	97 (60.2)	142 (59.4)
Baseline CDAI			
N[a]	176	349	525
Mean (SD)	293.85 (85.378)	292.42 (81.250)	292.90 (82.578)
Median	290.50	284.00	285.00
Min, Max	89.5, 530.0	62.0, 543.8	62.0, 543.8
Baseline SES-CD			
Mean (SD)	13.6 (6.95)	13.7 (7.29)	13.7 (7.17)
Median	12.0	12.0	12.0
Min, Max	4, 35	4, 38	4, 38
CD location per SES-CD – n (%)			
Ileal only	27 (15.3)	58 (16.6)	85 (16.2)
Colonic only	57 (32.4)	121 (34.6)	178 (33.8)
Ileal-colonic	92 (52.3)	171 (48.9)	263 (50.0)
Average daily very soft or liquid stool frequency			
Mean (SD)	5.0857 (2.8366)	5.1864 (2.6130)	5.1527 (2.6876)
Median	4.8571	4.8571	4.8571
Min, Max	0.0000, 16.0000	0.0000, 16.0000	0.0000, 16.0000

Variable	Part 1 (Double-Blind)		
	PBO (N = 176) n (%)	UPA 45 mg (N = 350) n (%)	Total (N = 526) n (%)
Average daily abdominal pain score			
Mean (SD)	1.9064 (0.6942)	1.8917 (0.6795)	1.8966 (0.6839)
Median	2.0000	2.0000	2.0000
Min, Max	0.0000, 3.0000	0.0000, 3.0000	0.0000, 3.0000
Baseline hs-CRP (mg/L)			
N^a	176	341	517
Mean (SD)	16.192 (22.0788)	15.974 (20.4710)	16.048 (21.0110)
Median	7.035	8.210	7.560
Min, Max	0.20, 113.00	0.20, 120.00	0.20, 120.00
Baseline FCP (µg/g)			
N^a	161	319	480
Mean (SD)	1792.1 (2773.81)	2170.2 (3991.69)	2043.4 (3630.43)
Median	949.0	904.0	906.0
Min, Max	30, 24234	30, 28800	30, 28800
Draining fistulas (yes, no) – n (%)			
Yes	6 (3.4)	17 (4.9)	23 (4.4)
No	170 (96.6)	333 (95.1)	503 (95.6)
Non-draining fistulas (yes, no) – n (%)			
Yes	13 (7.4)	25 (7.1)	38 (7.2)
No	163 (92.6)	325 (92.9)	488 (92.8)
Baseline corticosteroid use (yes, no) – n (%)			
Yes	64 (36.4)	126 (36.0)	190 (36.1)
No	112 (63.6)	224 (64.0)	336 (63.9)
Baseline immunosuppressant use (yes, no) – n (%)			
Yes	3 (1.7)	13 (3.7)	16 (3.0)
No	173 (98.3)	337 (96.3)	510 (97.0)

Table 20   Baseline Disease Characteristics, M14-433 (12-Week Extended Treatment Period, ITT2 Population)

Variable	Part 2 Extended Treatment	
	Placebo/UPA 45 mg (N = 57) n (%)	UPA 45 mg/UPA 30 mg (N = 59) n (%)
Crohn's disease duration (years)		
Mean (SD)	9.3403 (7.9992)	11.3666 (10.9985)
Median	7.2526	9.1828
Min, Max	0.2765, 34.5982	0.0575, 41.4127
Biologics use/failure history – Bio-IR status n (%)		
Bio-IR	29 (50.9)	31 (52.5)
Non-Bio-IR	28 (49.1)	28 (47.5)
Prior exposure to biologic therapy among Non-Bio-IR subjects – n (%)		
N (Non-Bio-IR)	28	28
Yes	1 (3.6)	2 (7.1)
No	27 (96.4)	26 (92.9)
Biologics failure history – n (%)		
N (Bio-IR)	29	31
1	12 (41.4)	8 (25.8)
2	6 (20.7)	11 (35.5)
≥ 3	11 (37.9)	12 (38.7)
Prior Failure to anti-TNF Agent – n (%)		
N (Bio-IR)	29	31
Yes	28 (96.6)	31 (100)
No	1 (3.4)	0
Prior Vedolizumab/Natalizumab Failure – n (%)		
N (Bio-IR)	29	31
Yes	7 (24.1)	6 (19.4)
No	22 (75.9)	25 (80.6)
Prior Ustekinumab Failure – n (%)		
N (Bio-IR)	29	31
Yes	13 (44.8)	15 (48.4)
No	16 (55.2)	16 (51.6)

Variable	Part 2 Extended Treatment	
	Placebo/UPA 45 mg (N = 57) n (%)	UPA 45 mg/UPA 30 mg (N = 59) n (%)
Baseline CDAI		
Mean (SD)	286.34 (82.846)	258.50 (81.233)
Median	288.00	250.00
Min, Max	89.5, 479.0	62.0, 455.6
Baseline SES-CD		
Mean (SD)	14.3 (7.38)	10.9 (5.85)
Median	12.0	9.0
Min, Max	4, 34	4, 33
CD location per SES-CD – n (%)		
Ileal only	6 (10.5)	16 (27.1)
Colonic only	18 (31.6)	9 (15.3)
Ileal-colonic	33 (57.9)	34 (57.6)
Average daily very soft or liquid stool frequency		
Mean (SD)	5.2206 (2.6870)	5.2476 (2.8447)
Median	5.4286	4.7143
Min, Max	0.0000, 16.0000	0.0000, 16.0000
Average daily abdominal pain score		
Mean (SD)	1.6842 (0.7582)	1.5676 (0.7182)
Median	1.8571	1.7143
Min, Max	0.0000, 3.0000	0.0000, 3.0000
Baseline hs-CRP (mg/L)		
N[a]	57	58
Mean (SD)	15.764 (23.7509)	12.339 (18.5910)
Median	7.000	4.525
Min, Max	0.20, 113.00	0.20, 99.40
Baseline FCP (µg/g)		
N[a]	51	56
Mean (SD)	2147.4 (3767.12)	1345.9 (3907.23)
Median	1025.0	543.0
Min, Max	30, 24234	30, 28800

	Part 2 Extended Treatment	
Variable	Placebo/UPA 45 mg (N = 57) n (%)	UPA 45 mg/UPA 30 mg (N = 59) n (%)
Draining fistulas (yes, no) – n (%)		
Yes	2 (3.5)	2 (3.4)
No	55 (96.5)	57 (96.6)
Non-draining fistulas (yes, no) – n (%)		
Yes	3 (5.3)	6 (10.2)
No	54 (94.7)	53 (89.8)
Baseline corticosteroid use (yes, no) – n (%)		
Yes	24 (42.1)	18 (30.5)
No	33 (57.9)	41 (69.5)
Baseline immunosuppressant use (yes, no) – n (%)		
Yes	2 (3.5)	2 (3.4)
No	55 (96.5)	57 (96.6)

Prior Use of CD-Related Medications M14-433:

12-Week Induction Period, Double-Blind (Part 1)

Use of any prior CD related medication was reported by 100% of subjects in the DB 12-week Induction Period (Part 1). The most frequently reported prior CD-related biologics were adalimumab and infliximab (each had 33.0% of subjects) in the placebo group and infliximab and adalimumab (38.0% and 30.6% of subjects, respectively) in the upadacitinib 45 mg QD group (Table 21).

Table 21   Crohn's Disease-Related Biologic Medications, M14-433, Taken Prior to Baseline (12-Week Induction Period, ITT1 Population)

	Part 1 (Double-Blind)		
Generic Name (WHO 2021 Q1)	PBO (N = 176) n (%)	UPA 45 mg (N = 350) n (%)	Total (N = 526) n (%)
Adalimumab	58 (33.0)	107 (30.6)	165 (31.4)
Certolizumab	3 (1.7)	1 (0.3)	4 (0.8)
Certolizumab pegol	5 (2.8)	10 (2.9)	15 (2.9)
Infliximab	58 (33.0)	133 (38.0)	191 (36.3)
Risankizumab	1 (0.6)	0	1 (0.2)
Ustekinumab	36 (20.5)	72 (20.6)	108 (20.5)
Vedolizumab	26 (14.8)	52 (14.9)	78 (14.8)

Numbers analysed

A total of 1,021 subjects were randomized and received at least one dose of blinded study drug in the induction studies. Approximately 90% of subjects completed the induction period; the most common reason for discontinuation of treatment was AE for subjects on upadacitinib and withdrew consent or lack of efficacy for subjects on placebo.

Outcomes and estimation

Induction study M14-431

The study met the co-primary endpoints of clinical remission and endoscopic response for upadacitinib 45 mg compared to placebo for both the US/FDA and EU/EMA regulatory purposes. At Week 12, a statistically significantly greater (p-value < 0.0001) proportion of subjects in the upadacitinib 45 mg group achieved the co-primary endpoint of clinical remission (defined by CDAI for the US/FDA and by PROs in the EU/EMA) compared to placebo group. At Week 12, a statistically significantly greater (p-value < 0.0001) proportion of subjects in the upadacitinib 45 mg group achieved endoscopic response, for both US/FDA and EU/EMA regulatory purposes, compared to the placebo group.

Consistency of results across key sub-groups were demonstrated for the co-primary endpoints of clinical remission per CDAI and PROs respectively, and endoscopic response. The majority of the 95% confidence intervals for the treatment difference between upadacitinib 45 mg compared to placebo in each subgroup excluded zero in favour of the upadacitinib 45 mg dose group.

Table 22   Co-primary efficacy variables for US and EU at week 12 (ITT1 population)

		Responder (NRI-C)			Response Rate Diff Compared to Placebo		
Treatment	N	n (%)	[95% CI][a]	Missing Due to COVID-19	Adjusted Diff (%)[b]	[95% CI][c]	P-value[c]
Clinical Remission per CDAI							
Placebo	171	36 (21.1)	[14.9, 27.2]	0			
UPA 45 mg	324	126 (38.9)	[33.6, 44.2]	1	17.9	[10.0, 25.8]	< 0.0001
Clinical Remission per PROs							
Placebo	171	24 (14.0)	[8.8, 19.2]	0			
UPA 45 mg	324	129 (39.8)	[34.5, 45.1]	0	25.9	[18.7, 33.1]	< 0.0001
Endoscopic Response							
Placebo	171	6 (3.5)	[0.8, 6.3]	1			
UPA 45 mg	324	112 (34.6)	[29.4, 39.8]	4	31.2	[25.5, 37.0]	< 0.0001
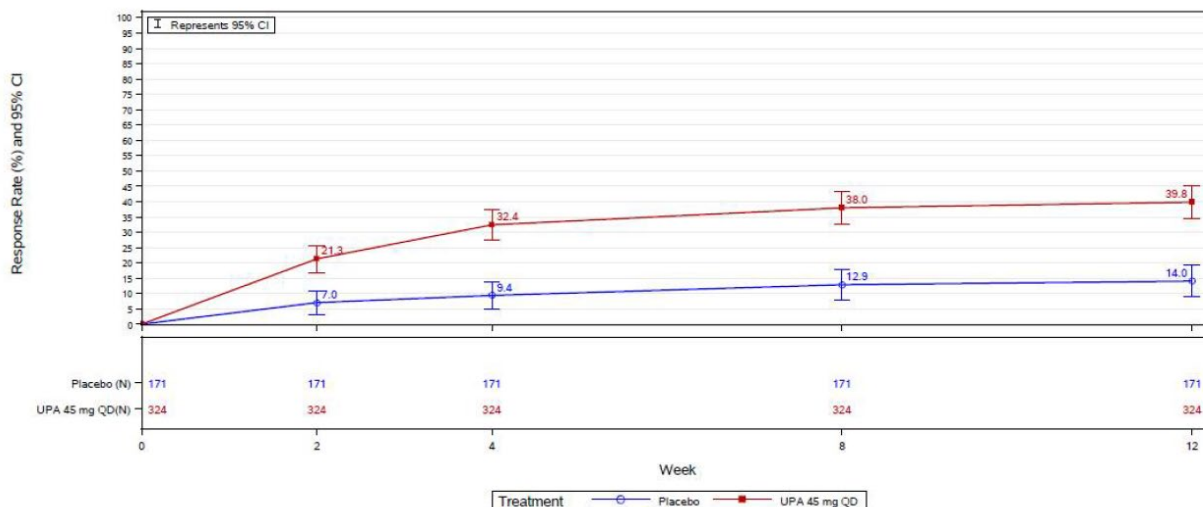
Figure 13 **Summary of Achievement of SF/APS Clinical Remission During Induction Study M14-431 (NRI-C, ITT1)**

The key secondary endpoints (i.e., endpoints under the overall type I error control) for the US/FDA and EU/EMA regulatory purposes are summarized in **Table 23** and **Table 24**, respectively. Overall, upadacitinib 45 mg has clear treatment effect over placebo for resolution of clinical symptoms, improvements in quality of life (QoL), and reduction in mucosal inflammation as measured by endoscopy. A majority of endpoints were statistically significant for upadacitinib 45 mg versus placebo for both US/FDA and EU/EMA regulatory purposes.

Clinical response 100 (CR-100) (defined as decrease of at least 100 points in CDAI from Baseline) was achieved as early as Week 2, with statistically significant differences observed for upadacitinib 45 mg QD versus placebo. Additionally, clinical remission per CDAI was achieved as early as Week 4, with statistically significant differences observed for upadacitinib 45 mg QD versus placebo. The treatment effect increased over time, with greater treatment differences between upadacitinib 45 mg QD and placebo observed at Week 12. Moreover, endoscopic remission and steroid-free clinical remission were also achieved at Week 12, with statistically significant differences observed for upadacitinib 45 mg QD versus placebo. Patient reported outcome (PRO) questionnaires that summarize QoL (by Inflammatory Bowel Disease Questionnaire [IBDQ]) and fatigue (by Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue) also showed overall statistically significantly higher improvement in upadacitinib 45 mg versus placebo. CD-related hospitalizations were numerically lower in the upadacitinib 45 mg group versus placebo. Additionally, while the total number of subjects analyzed was small, there was a trend for reduction in extra-intestinal manifestations (EIMs) for subjects who received upadacitinib 45 mg versus placebo.

Table 23   Summary of Key Secondary Efficacy Endpoints Under the Overall Type I Error Control, US/FDA (ITT1 Population)

	Endpoints	PBO (N = 171) % (n)[a] or LS MEAN (SE)	UPA 45 mg (N = 324) % (n)[a] or LS MEAN (SE)	Adjusted Treatment Difference 95% CI[b] UPA 45 mg – PBO	p-Value[b] UPA 45 mg vs. PBO
1	Clinical remission per PROs at Week 12 (NRI-C)	14.0 (24)	39.8 (129)	25.9 (18.7, 33.1)	< 0.0001
2	Endoscopic remission at Week 12 (NRI-C)	2.3 (4)	19.1 (62)	16.8 (12.0, 21.6)	< 0.0001
3	Steroid-free and clinical remission per CDAI at Week 12 (NRI-C)	11.7 (7)	34.3 (37)	22.5 (11.1, 34.0)	0.0001
4	Change from baseline in FACIT-Fatigue at Week 12 (MMRM)	3.9 (0.97)	11.4 (0.69)	7.5 (5.2, 9.8)	< 0.0001
5	Change from baseline in IBDQ at Week 12 (MMRM)	21.6 (3.02)	46.0 (2.14)	24.3 (17.2, 31.5)	< 0.0001
Holm Procedure	CR-100 at Week 2 (NRI-C)	12.4 (21)	33.2 (107)	20.7 (13.7, 27.8)	< 0.0001
	CR-100 at Week 12 (NRI-C)	27.5 (47)	50.5 (164)	22.8 (14.4, 31.2)	< 0.0001
	Clinical remission per CDAI at Week 4 (NRI-C)	17.7 (30)	29.6 (96)	12.1 (4.7, 19.5)	0.0013
	CD-related hospitalization through Week 12 (AO)	8.8 (15)	6.2 (20)	-2.6 (-7.6, 2.4)	0.2834
	Resolution of EIMs at Week 12, in subjects with any EIMs at baseline (NRI-C)	21.7 (13)	32.8 (43)	11.5 (-1.5, 24.4)	0.0833

AO = as observed; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CR-100 = Decrease of at least 100 points in CDAI from Baseline; EIM = extra-intestinal manifestation; FACIT = Functional Assessment of Chronic Illness Therapy; FDA = Food and Drug Administration; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT = intent-to-treat; LS = least squares; MMRM = mixed effect model repeat measurement; NRI-C = Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO = placebo; PROs = patient-reported outcomes of average daily very soft or liquid stool frequency and abdominal pain score; SE = standard error; UPA = upadacitinib; US = United States
a.   The % (n) represents the synthesized results from multiple imputation. b Adjusted treatment difference, 95% CI and p-values for comparison of binary endpoints between upadacitinib and placebo were calculated using CMH test adjusted for randomization stratification factors; 95% CI and p-values for comparison of continuous endpoints between upadacitinib and placebo were calculated using MMRM with baseline, treatment, visit, treatment by visit interaction and stratification factors in the model.

Table 24   Summary of Key Secondary Efficacy Endpoints Under the Overall Type I Error Control, EU/EMA (NRI-C) (ITT1 Population)

	Endpoints	PBO (N = 171) % (n)[a] or LS MEAN (SE)	UPA 45 mg (N = 324) % (n)[a] or LS MEAN (SE)	Adjusted Treatment Difference 95% CI[b] UPA 45 mg – PBO	p-Value[b] UPA 45 mg vs. PBO
1	Clinical remission per CDAI at Week 12 (NRI-C)	21.1 (36)	38.9 (126)	17.9 (10.0, 25.8)	< 0.0001
2	Clinical remission per PROs at Week 4 (NRI-C)	9.4 (16)	32.4 (105)	23.3 (16.6, 29.9)	< 0.0001
3	Endoscopic remission at Week 12 (NRI-C)	2.3 (4)	19.1 (62)	16.8 (12.0, 21.6)	< 0.0001
4	Steroid-free and clinical remission per PROs at Week 12 (NRI-C)	6.7 (4)	37.0 (40)	30.2 (19.4, 41.0)	< 0.0001
5	Change from baseline in FACIT-Fatigue at Week 12 (MMRM)	3.9 (0.97)	11.4 (0.69)	7.5 (5.2, 9.8)	< 0.0001
6	Change from baseline in IBDQ at Week 12 (MMRM)	21.6 (3.02)	46.0 (2.14)	24.3 (17.2, 31.5)	< 0.0001
Holm Procedure	CR-100 at Week 2 (NRI-C)	12.4 (21)	33.2 (107)	20.7 (13.7, 27.8)	< 0.0001
	CR-100 at Week 12 (NRI-C)	27.5 (47)	50.5 (164)	22.8 (14.4, 31.2)	< 0.0001
	CD-related hospitalization through Week 12 (AO)	8.8 (15)	6.2 (20)	-2.6 (-7.6, 2.4)	0.2834
	Resolution of EIMs at Week 12, in subjects with any EIMs at baseline (NRI-C)	21.7 (13)	32.8 (43)	11.5 (-1.5, 24.4)	0.0833

Footnote see Table 23

Other endpoints

More stringent endoscopic measures, including SES-CD 0-2 and absence of ulcers (SES-CD ulcerated surface subscore of 0 among subjects with ulcers at Baseline), endoscopic remission and steroid-free, clinical and endoscopic remission were also observed at Week 12 with upadacitinib. For example, SES-

CD 0-2 UPA n= 46 (14.2%) compared with placebo n=0, P<0.0001***, SES-CD ulcerated surface subscore of 0 among subjects with ulcers at Baseline UPA n= 55 (17.1%) compared with placebo n=0, P<0.0001***. Steroid-free, endoscopic remission in subjects taking Corticosteroids for CD at baseline UPA n= 18 (16.7%) placebo n=0, P<0.0001***.

Additionally, decreases in the biomarkers of fecal calprotectin (FCP) and high sensitivity C-reactive protein (hs-CRP) were observed as early as Week 4 or Week 2, respectively, for upadacitinib versus placebo.

12-Week Open-Label Induction Period, ITT2 Population

In this group of subjects who received OL induction treatment with upadacitinib 45 mg daily for 12 weeks (Part 2), clinical improvements were generally similar or greater relative to the group of subjects receiving DB upadacitinib in Part 1. Improvements in endoscopic, QoL, FCP and hs-CRP measures with OL upadacitinib were similar to the group of subjects receiving DB upadacitinib in Part 1.

Induction study M14-433

Table 25   Co-primary efficacy variables for US and EU at week 12 (ITT1 population)

| Treatment	N	Responder (NRI-C)		Missing due to COVID-19	Response Rate Diff Compared to Placebo		
		n (%)	[95% CI][a]		Adjusted Diff (%)[b]	[95% CI][c]	P-value[c]
Clinical Remission per CDAI							
Placebo	176	51 (29.1)	[22.4, 35.8]	2			
UPA 45 mg	350	173 (49.5)	[44.2, 54.8]	4	20.8	[12.7, 28.8]	< 0.0001***
Clinical Remission per PROs							
Placebo	176	39 (22.2)	[16.0, 28.3]	0			
UPA 45 mg	350	178 (50.7)	[45.5, 56.0]	2	28.7	[20.9, 36.4]	< 0.0001***
Endoscopic Response							
Placebo	176	23 (13.1)	[8.1, 18.0]	5			
UPA 45 mg	350	159 (45.5)	[40.3, 50.8]	7	33.0	[26.2, 39.9]	< 0.0001***
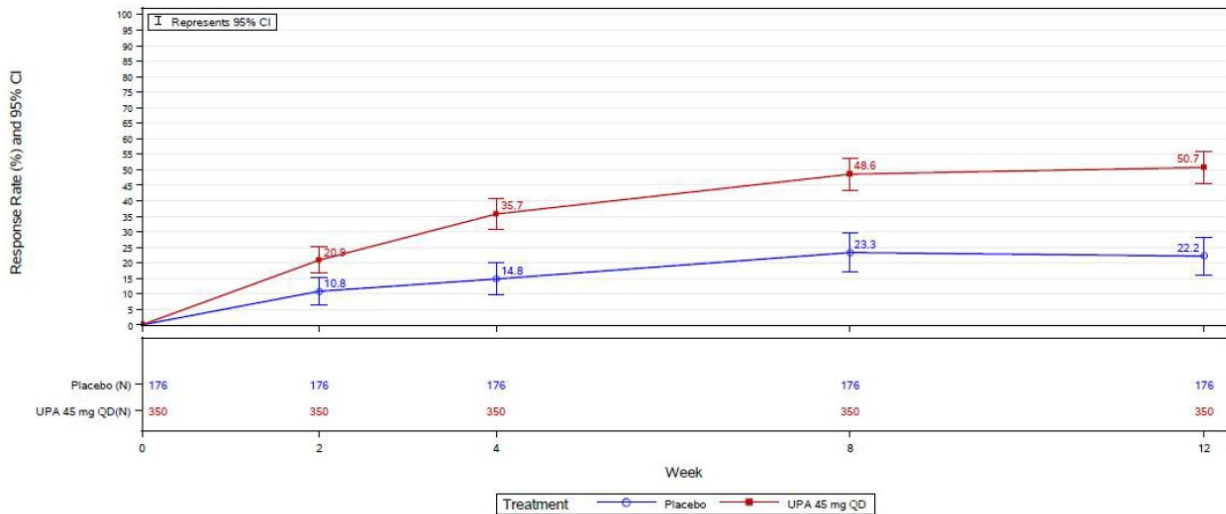
Figure 14 Summary of Achievement of CDAI Clinical Remission During Induction Study M14-433 (NRI-C, ITT1)

Table 26   Summary of Key Secondary Efficacy Endpoints Under the Overall Type I Error Control, US/FDA (12-Week Induction Period, ITT1 Population

	Endpoints	PBO (N = 176) % (n)[a] or LS MEAN (SE)	UPA 45 mg (N = 350) % (n)[a] or LS MEAN (SE)	Adjusted Treatment Difference 95% CI[b] UPA 45 mg – PBO	p-Value[b] UPA 45 mg vs. PBO
1	Clinical remission per PROs at Week 12 (NRI-C)	22.2 (39)	50.7 (178)	28.7 [20.9, 36.4]	< 0.0001***
2	Endoscopic remission at Week 12 (NRI-C)	7.4 (13)	28.9 (101)	21.8 [15.8, 27.8]	< 0.0001***
3	Steroid-free and clinical remission per CDAI at Week 12 (NRI-C)	15.7 (10)	42.9 (54)	27.7 [15.7, 39.8]	< 0.0001***
4	Change from baseline in FACIT-Fatigue at Week 12 (MMRM)	5.0 (0.90)	11.3 (0.63)	6.3 [4.2, 8.3]	< 0.0001***
5	Change from baseline in IBDQ at Week 12 (MMRM)	24.423 (2.7562)	46.265 (1.9185)	21.842 [15.566, 28.118]	< 0.0001***
Holm Procedure	CR-100 at Week 2 (NRI-C)	20.4 (36)	32.2 (113)	11.7 [4.2, 19.2]	0.0022**
	CR-100 at Week 12 (NRI-C)	37.3 (66)	56.6 (198)	19.8 [11.3, 28.4]	< 0.0001***
	Clinical remission per CDAI at Week 4 (NRI-C)	26.7 (47)	37.1 (130)	10.8 [2.9, 18.6]	0.0071**
	CD-related hospitalization through Week 12 (AO)	5.1 (9)	3.7 (13)	-1.4 [-5.2, 2.4]	0.4494
	Resolution of EIMs at Week 12, in subjects with any EIMs at baseline (NRI-C)	20.9 (16)	28.5 (43)	9.0 [-1.9, 19.9]	0.1044

Table 27   Summary of Key Secondary Efficacy Endpoints Under the Overall Type I Error Control, EU/EMA (12-Week Induction Period, ITT1 Population)

	Endpoints	PBO (N = 176) % (n)[a] or LS MEAN (SE)	UPA 45 mg (N = 350) % (n)[a] or LS MEAN (SE)	Adjusted Treatment Difference 95% CI[b] UPA 45 mg – PBO	p-Value[b] UPA 45 mg vs. PBO
1	Clinical remission per CDAI at Week 12 (NRI-C)	29.1 (51)	49.5 (173)	20.8 [12.7, 28.8]	< 0.0001***
2	Clinical remission per PROs at Week 4 (NRI-C)	14.8 (26)	35.7 (125)	21.2 [14.3, 28.2]	< 0.0001***
3	Endoscopic remission at Week 12 (NRI-C)	7.4 (13)	28.9 (101)	21.8 [15.8, 27.8]	< 0.0001***
4	Steroid-free and clinical remission per PROs at Week 12 (NRI-C)	12.5 (8)	44.4 (56)	32.6 [21.5, 43.7]	< 0.0001***
5	Change from baseline in FACIT-Fatigue at Week 12 (MMRM)	5.0 (0.90)	11.3 (0.63)	6.3 [4.2, 8.3]	< 0.0001***
6	Change from baseline in IBDQ at Week 12 (MMRM)	24.423 (2.7562)	46.265 (1.9185)	21.842 [15.566, 28.118]	< 0.0001***
Holm Procedure	CR-100 at Week 2 (NRI-C)	20.4 (36)	32.2 (113)	11.7 [4.2, 19.2]	0.0022**
	CR-100 at Week 12 (NRI-C)	37.3 (66)	56.6 (198)	19.8 [11.3, 28.4]	< 0.0001***
	CD-related hospitalization through Week 12 (AO)	5.1 (9)	3.7 (13)	-1.4 [-5.2, 2.4]	0.4494
	Resolution of EIMs at Week 12, in subjects with any EIMs at baseline (NRI-C)	20.9 (16)	28.5 (43)	9.0 [-1.9, 19.9]	0.1044

Integrated analyses Induction

Please see section Analysis performed across trials

Maintenance study M14-430

Study Design and Subject Population

Study M14-430 is a Phase 3, multicenter study to evaluate the safety and efficacy of maintenance and long-term treatment with upadacitinib in adult subjects with moderately to severely active CD who have achieved clinical response and completed the induction Studies M14-431 or M14-433. The study population includes subjects who have had an inadequate response or have been intolerant to at least one biologic (Bio-IR) and subjects who have had an inadequate response or have been intolerant to conventional therapies but no biologics (Non-Bio-IR).

At Week 0, all eligible subjects were to enroll in Substudy 1 to receive study drug in a blinded fashion in one of 3 cohorts.

Cohort 1: Subjects who received the 12-week induction treatment with upadacitinib 45 mg (including those who did not achieve clinical response with placebo and then received upadacitinib 45 mg for 12 weeks) and achieved clinical response in Studies M14-431 or M14-433 were re-randomized to either upadacitinib 30 mg QD, upadacitinib 15 mg QD, or matching placebo in a 1:1:1 ratio. The randomization was stratified by Bio-IR and Non-Bio-IR status in the induction studies, as well as the clinical remission (per PROs) and endoscopic response status at the entry of Study M14-430 Substudy 1. According to the protocol, all primary and secondary efficacy endpoints were to be analyzed among the ITT1 population, planned to include the first approximately 501 subjects who were randomized and received at least one dose of study drug. The actual number of subjects included in the ITT1 population is 502, since the last 2 subjects were randomized on the same date of 29 March 2021.

Cohort 2: Subjects who received the 12-week induction treatment with placebo and achieved clinical response in Studies M14-431 or M14-433 continued to receive placebo. Cohort 3: Subjects who did not achieve clinical response after the 12-week induction treatment with upadacitinib 45 mg, received the 12-week extended treatment with upadacitinib 30 mg and achieved clinical response in Studies M14-431 or M14-433, continued to receive upadacitinib 30 mg QD. Baseline is defined as the Baseline Visit of Study M14-431 or Study M14-433 (induction study) and Week 0 is defined as the first study visit in Study M14-430 (maintenance study).

Conduct of the study

The original protocol (05 June 2017, 0 subjects) had 7 global amendments, 16 country-specific amendments, and 6 administrative changes. The protocol changes described in the amendments and administrative changes did not affect the interpretation of the study results.

Global Amendment 1 (02 October 2017, 3 subjects).

- Updated the duration of the maintenance part of Substudy 1 from 48 to 52 weeks.

- The duration of Substudy 1 was increased to 56 weeks based on the extension of the maintenance phase of Substudy 1 to 52 weeks (including a 30 day follow up period).

- Updated eligibility criteria for clarification.

- Revised secondary endpoints, based on regulatory scientific advice, and for clarification.

- Updated list of AESIs to include embolic and thrombotic events (non-cardiac, non-central nervous system [CNS]), and to collect additional information in a supplemental electronic case report form (eCRF).

- Clarified ranking of secondary variables in Substudy 1.

Global Amendment 2 (24 January 2018, 66 subjects).

- Updated study design to allow for subjects to continue upadacitinib if it is still not available beyond the 240-week duration of the study.

- Added vedolizumab as a prohibited biologic therapy during the study.

- Clarified the analysis methods considered for continuous secondary endpoints.

- Updated discontinuation criteria for subjects who did not respond to rescue therapy, to enable patients to receive standard of care treatment.

Global Amendment 3 (24 August 2018, 127 subjects).

- Updated the Introduction to add 52-week data from AbbVie Study M13-740 and to clarify that the once-daily modified release formulation is being used in this study.

- Substudy 2 was edited to reflect the dose escalation from upadacitinib 15 mg QD to 30 mg QD for subjects who are not in clinical response at Week 0, and/or meet the criteria for inadequate response during Substudy 2.

- Removed the reference to placebo administration as no placebo will be administered in Substudy 2.

- Removed Inclusion Criterion 6 due to removal of the male contraception requirement across studies in the upadacitinib program.

- Removed Exclusion Criterion 5 due to removal of the male contraception requirement.

- Exclusion Criterion 12 was updated to lower estimated glomerular filtration (eGFR) rate.

- Clarified and provided additional guidance on the use of corticosteroids during the study.

- Update prohibited therapies.

- Corrected the cutoff age for females in defining postmenopausal and updated contraception language.

- Added the Montreal classification for Crohn's disease at Week 0 for the assessment of disease severity.

- Updated Substudy 1 Efficacy Variables.

- Updated the Adverse Events of Special Interest (AESI) list for consistency across programs.

- Reduced number of Crohn's Symptoms Severity (CSS) Questionnaire data collection points. Global Amendment 4 (04 April 2019, 265 subjects).

- The number of subjects to be enrolled in the study was updated to reflect the updates in the parent Studies M14-431 and M14-433.

- Updated the stratification factors to align with the updates in the study population in Study M14-433.

- Added rescue treatment with open-label upadacitinib for inadequate response for subjects.

- Exclusion criterion #6 clarified that subjects with serious infections (as opposed to ongoing infections) may be enrolled but not dosed until treatment is completed and the infection is resolved.

- Removed mention of Japan and China from text describing conditions under which a chest x-ray will not be required, as a prior CT scan can apply to subjects from any country.

- Updated discontinuation criteria.

- Updated Toxicity Management to align with the entire upadacitinib clinical programs, based on cumulative data with the compound.

Global Amendment 5 (29 April 2020, 92 subjects).

- Updated Introduction to include results of recent long-term integrated data from the Phase 3 Rheumatoid Arthritis program and the recent risk updates to the JAK inhibitor class.

- Updated overall study design.

- Updated eligibility criteria.

- Updated efficacy variables: Changed co-primary efficacy endpoint to clinical remission based on CDAI for the US/FDA. The EU/EMA co-primary efficacy endpoint for clinical remission remained based on PROs. Ranked secondary variables now include change from baseline in IBDQ at Week 52, proportion of subjects achieving CR-100 at Week 52, and assessment of extraintestinal manifestations. Four variables (proportion of subjects with enhanced clinical response, $\geq 50\%$ reduction in draining fistulas, response in IBDQ bowel domain at Week 52 and change from baseline in CSS) will not be ranked but included under additional efficacy variables.

- Updated Toxicity Management section.

- Added management of missing date due to COVID-19.

Global Amendment 6 (25 October 2020, 173 subjects).

- Updated information on the re-evaluation of the benefit and risk to subjects participating in the study, updated wording to allow for changes in visits and procedures affected by COVID-19 pandemic and asocial changes in global/local regulations.

- Revised order of ranked secondary endpoints.

- Revised sample size determination.

Global Amendment 7 (16 November 2021, 3 subjects).

- Added a ranked secondary efficacy endpoint of steroid-free and clinical remission among the entire ITT patient population.

- Added an additional efficacy endpoint of steroid-free and clinical remission per CDAI over time.

Participant flow

A total of 901 subjects entered Substudy 1 at 277 sites in the following countries: Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Croatia, Czech Republic, Denmark, Egypt, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Japan, Korea (Republic of), Latvia, Lithuania, Malaysia, Mexico, Netherlands, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan (Province of China), Turkey, Ukraine, United Kingdom, and United States, including Puerto Rico. A total of 502 subjects were randomized in Cohort 1 on or prior to 29 Mar 2021 and were included in the ITT1 analysis set.

Table 28   Subject Accountability (All Enrolled Subjects) Study M14-430

Cohort Treatment	Rando-mized n	Treated n	Study Drug			Study		
			DC n	Completed n	Ongoing n	DC n	Completed n	Ongoing n
Cohort 1 (ITT1)								
PBO	165	165	43	122	0	43	121	1
UPA 15 mg	169	169	44	125	0	43	126	0
UPA 30 mg	168	168	34	134	0	34	134	0
Total	502	502	121	381	0	120	381	1
Cohort 1 (All subjects)								
PBO	223	223	51	129	43	51	121	51
UPA 15 mg	221	221	48	134	39	47	130	44
UPA 30 mg	230	229	41	139	49	41	137	51
Total	674	673	140	402	131	139	388	146
Cohort 2 (ITT2)								
PBO	130	130	36	94	0	36	94	0
Cohort 2 (All subjects)								
PBO	161	161	41	95	25	40	94	27
Cohort 3 (ITT3)								
UPA 30 mg	51	51	13	38	0	13	38	0
Cohort 3 (All subjects)								
UPA 30 mg	66	66	15	39	12	14	38	14

Table 29   Summary of Study Drug Discontinuation (ITT1 Population) Study M14–430

Discontinuation due to	PBO (N = 165) n (%)	UPA 15 mg (N = 169) n (%)	UPA 30 mg (N = 168) n (%)	Total (N = 502) n (%)
Without Receiving OL Rescue UPA 30 mg QD	18 (10.9)	23 (13.6)	20 (11.9)	61 (12.2)
All Reasons[a]				
Adverse event	6 (3.6)	11 (6.5)	11 (6.5)	28 (5.6)
Withdrew consent	5 (3.0)	5 (3.0)	7 (4.2)	17 (3.4)
Lost to follow-up	1 (0.6)	2 (1.2)	1 (0.6)	4 (0.8)
Lack of efficacy	7 (4.2)	6 (3.6)	4 (2.4)	17 (3.4)
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	0	0	0
Other	3 (1.8)	4 (2.4)	3 (1.8)	10 (2.0)
Primary Reason				
Adverse event	6 (3.6)	10 (5.9)	10 (6.0)	26 (5.2)
Withdrew consent	4 (2.4)	4 (2.4)	7 (4.2)	15 (3.0)
Lost to follow-up	1 (0.6)	2 (1.2)	1 (0.6)	4 (0.8)
Lack of efficacy	6 (3.6)	5 (3.0)	1 (0.6)	12 (2.4)
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	0	0	0
Other	1 (0.6)	2 (1.2)	1 (0.6)	4 (0.8)
After Receiving OL Rescue, UPA 30 mg QD	25 (15.2)	21 (12.4)	14 (8.3)	60 (12.0)
All Reasons[a]				
Adverse event	8 (4.8)	11 (6.5)	3 (1.8)	22 (4.4)
Withdrew consent	1 (0.6)	3 (1.8)	2 (1.2)	6 (1.2)
Lost to follow-up	1 (0.6)	1 (0.6)	0	2 (0.4)
Lack of efficacy	17 (10.3)	11 (6.5)	10 (6.0)	38 (7.6)
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	0	0	0
Other	2 (1.2)	2 (1.2)	1 (0.6)	5 (1.0)

Discontinuation due to	PBO (N = 165) n (%)	UPA 15 mg (N = 169) n (%)	UPA 30 mg (N = 168) n (%)	Total (N = 502) n (%)
Primary Reason				
Adverse event	4 (2.4)	6 (3.6)	3 (1.8)	13 (2.6)
Withdrew consent	1 (0.6)	3 (1.8)	2 (1.2)	6 (1.2)
Lost to follow-up	1 (0.6)	1 (0.6)	0	2 (0.4)
Lack of efficacy	17 (10.3)	9 (5.3)	9 (5.4)	35 (7.0)
Primary Reason				
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	0	0	0
Other	2 (1.2)	2 (1.2)	0	4 (0.8)

Intent-to-Treat (ITT) Populations

- ITT population: All subjects who received at least 1 dose of study drug in Substudy 1.

- ITT1 population: The subset of ITT population who were the first 502 subjects randomized in Cohort 1. The ITT1 population is the primary analysis population in Cohort 1 for efficacy and baseline analyses.

- ITT1-ALL population: The subset of ITT population who were randomized and received at least one dose of study drug in Cohort 1.

- ITT2 population: The subset of ITT population who have been enrolled in Cohort 2 including subjects who a) completed 52 weeks of study treatment or b) were enrolled at least 52 weeks prior but have prematurely withdrawn from the study. The ITT2 population was used for the efficacy and baseline analyses for Cohort 2.

- ITT2-ALL population: The subset of ITT population who enrolled in Cohort 2.

- ITT3 population: The subset of ITT population who were enrolled in Cohort 3 including subjects who a) completed 52 weeks of study treatment or b) were enrolled at least 52 weeks prior but have prematurely withdrawn from the study. The ITT3 population was used for efficacy and baseline analyses for Cohort 3.

- ITT3-ALL population: The subset of ITT population who enrolled in Cohort 3.

Demographics

Table 30   Key Demographic Characteristics (ITT1, ITT2, and ITT3 Populations) Study M14-430

Variable	Cohort 1				Cohort 2	Cohort 3
	PBO (N = 165)	UPA 15 mg (N = 169)	UPA 30 mg (N = 168)	Total (N = 502)	PBO (N = 130)	UPA 30 mg (N = 51)
Sex - n (%)						
Female	77 (46.7)	67 (39.6)	75 (44.6)	219 (43.6)	64 (49.2)	30 (58.8)
Male	88 (53.3)	102 (60.4)	93 (55.4)	283 (56.4)	66 (50.8)	21 (41.2)
Age (years)						
n	165	169	168	502	130	51
Mean (SD)	38.1 (13.03)	38.1 (13.46)	37.0 (13.27)	37.7 (13.24)	39.2 (12.36)	40.2 (12.18)
Median	36.0	34.0	33.0	35.0	39.5	38.0
Min, Max	18, 72	18, 71	18, 68	18, 72	19, 70	19, 66
Age - n (%)						
≥ 18 years - < 40 years	97 (58.8)	102 (60.4)	101 (60.1)	300 (59.8)	65 (50.0)	27 (52.9)
≥ 40 years - < 65 years	62 (37.6)	62 (36.7)	60 (35.7)	184 (36.7)	63 (48.5)	23 (45.1)
≥ 65 years	6 (3.6)	5 (3.0)	7 (4.2)	18 (3.6)	2 (1.5)	1 (2.0)
Ethnicity - n (%)						
Hispanic or Latino	9 (5.5)	11 (6.5)	13 (7.7)	33 (6.6)	6 (4.6)	3 (5.9)
not Hispanic or Latino	156 (94.5)	158 (93.5)	155 (92.3)	469 (93.4)	124 (95.4)	48 (94.1)
Race - n (%)						
White	119 (72.1)	118 (69.8)	114 (67.9)	351 (69.9)	98 (75.4)	38 (74.5)
Black or African American	11 (6.7)	6 (3.6)	7 (4.2)	24 (4.8)	7 (5.4)	1 (2.0)
Asian	35 (21.2)	43 (25.4)	45 (26.8)	123 (24.5)	22 (16.9)	12 (23.5)
American Indian or Alaska Native	0	0	0	0	1 (0.8)	0

| Variable | Cohort 1 | | | | Cohort 2 | Cohort 3 |
	PBO (N = 165)	UPA 15 mg (N = 169)	UPA 30 mg (N = 168)	Total (N = 502)	PBO (N = 130)	UPA 30 mg (N = 51)
Race - n (%)						
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0
Multiple	0	2 (1.2)	2 (1.2)	4 (0.8)	2 (1.5)	0
Body Mass Index (kg/m^2)						
n	165	169	168	502	130	51
Mean (SD)	24.640 (6.6469)	24.096 (6.0353)	24.172 (6.5571)	24.300 (6.4083)	24.490 (5.3633)	24.891 (7.5343)
Median	23.459	22.600	22.578	22.829	23.729	23.896
Min, Max	14.36, 52.85	14.64, 47.26	13.92, 49.55	13.92, 52.85	14.96, 41.02	16.23, 49.93
Body Mass Index - n (%)						
< 18.5 kg/m^2	26 (15.8)	32 (18.9)	28 (16.7)	86 (17.1)	16 (12.3)	11 (21.6)
$\geq 18.5 - < 25$ kg/m^2	76 (46.1)	74 (43.8)	85 (50.6)	235 (46.8)	62 (47.7)	20 (39.2)
$\geq 25 - < 30$ kg/m^2	31 (18.8)	26 (15.4)	24 (14.3)	81 (16.1)	34 (26.2)	12 (23.5)
≥ 30 kg/m^2	32 (19.4)	37 (21.9)	31 (18.5)	100 (19.9)	18 (13.8)	8 (15.7)

Baseline Characteristics

Baseline characteristics were generally balanced across treatment groups in the ITT1 population. In the ITT1 population approximately 75% of subjects failed 1 or more biologics with 35.0% of subjects failed $\geq$ 3 biologics among the Bio-IR study population. A total of 95.0% of Bio-IR subjects had prior failure to at least 1 anti-TNF agent. The most common CD location per SES-CD was ileal-colonic at 47.2%. Overall, 37.3% and 5.0% of subjects were on concomitant corticosteroids and/or immunosuppressants at baseline, respectively. Mean Crohn's disease duration was approximately 10 years with a median value of 7.4606 years. The most commonly (>10%) reported medical conditions in subjects' medical history in the ITT1 population were anemia (26.7%), anal fistula (23.1%); arthralgia (20.5%), gastroesophageal reflux disease (15.5%), hypertension (12.2%), haemorrhoids (12.2%), depression (11.4%), abdominal pain (11.2%), anxiety (11.2%), drug hypersensitivity (11.0%), seasonal allergy (10.8%), and headache (10.4%) (**Table 31**). The Baseline characteristics of subjects in Cohort 2 (ITT2) and Cohort 3 (ITT3) were generally consistent with moderate to severe active CD. More subjects in the ITT2 population were Non-Bio-IR or had failed 1 biologic compared to the other cohorts. Subjects in the ITT3 population had longer disease duration, had a high proportion of subjects with prior failure to 3 or more biologics and more frequently had failed ustekinumab, had isolated ileal disease or extra-intestinal manifestations. At Week 0, more than half of subjects in the ITT1 population were in clinical remission, 75.1% achieved CR-100 response and 46.4% achieved endoscopic response

Table 31   Baseline Disease Characteristics, Selective Variables (ITT1, ITT2, and ITT3 Populations) Study M14-430

| | Cohort 1 | | | | Cohort 2 | Cohort 3 |
| | PBO (N = 165) n (%) | UPA 15 mg (N = 169) n (%) | UPA 30 mg (N = 168) n (%) | Total (N = 502) n (%) | PBO (N = 130) n (%) | UPA 30 mg (N = 51) n (%) |
Variable						
Crohn's disease duration (years)						
N	165	169	168	502	130	51
Mean (SD)	10.3390 (8.9523)	10.5902 (8.9129)	9.2965 (8.4237)	10.0747 (8.7659)	9.4144 (8.1905)	12.0643 (8.7659)
Median	7.6030	7.8713	7.2197	7.4606	7.3703	9.8535
Min, Max	0.3258, 48.7283	0.2765, 40.0767	0.3422, 44.9281	0.2765, 48.7283	0.2875, 46.2752	1.4401, 36.7118
Biologics use/failure history – Bio – IR status n (%)						
Bio-IR	126 (76.4)	124 (73.4)	127 (75.6)	377 (75.1)	91 (70.0)	39 (76.5)
Failure to conventional therapy (non-bio-IR) n (%)	39 (23.6)	45 (26.6)	41 (24.4)	125 (24.9)	39 (30.0)	12 (23.5)
Biologics failure history – n (%), among Bio-IR subjects						
N (bio-IR)	126	124	127	377	91	39
1	52 (41.3)	52 (41.9)	43 (33.9)	147 (39.0)	40 (44.0)	12 (30.8)
2	32 (25.4)	31 (25.0)	35 (27.6)	98 (26.0)	27 (29.7)	9 (23.1)
≥ 3	42 (33.3)	41 (33.1)	49 (38.6)	132 (35.0)	24 (26.4)	18 (46.2)
Prior Failure to anti-TNF Agent – n (%), among Bio-IR subjects						
N (Bio-IR)	126	124	127	377	91	39
Yes	118 (93.7)	117 (94.4)	123 (96.9)	358 (95.0)	85 (93.4)	39 (100)
No	8 (6.3)	7 (5.6)	4 (3.1)	19 (5.0)	6 (6.6)	0

Variable	Cohort 1				Cohort 2	Cohort 3
	PBO (N = 165) n (%)	UPA 15 mg (N = 169) n (%)	UPA 30 mg (N = 168) n (%)	Total (N = 502) n (%)	PBO (N = 130) n (%)	UPA 30 mg (N = 51) n (%)
Prior Vedolizumab/Natalizumab Failure – n (%), among Bio-IR subjects						
N (bio-IR)	126	124	127	377	91	39
Yes	38 (30.2)	39 (31.5)	43 (33.9)	120 (31.8)	29 (31.9)	12 (30.8)
No	88 (69.8)	85 (68.5)	84 (66.1)	257 (68.2)	62 (68.1)	27 (69.2)
Prior Ustekinumab Failure – n (%), among Bio-IR subjects						
N (bio-IR)	126	124	127	377	91	39
Yes	48 (38.1)	41 (33.1)	49 (38.6)	138 (36.6)	32 (35.2)	20 (51.3)
No	78 (61.9)	83 (66.9)	78 (61.4)	239 (63.4)	59 (64.8)	19 (48.7)
Baseline CDAI						
N	164	168	168	500	130	51
Mean (SD)	308.42 (82.291)	300.78 (90.769)	312.13 (75.376)	307.10 (83.026)	304.48 (84.960)	283.85 (75.833)
Median	305.90	283.50	300.50	299.50	302.50	281.20
Min, Max	114.4, 509.0	102.0, 657.0	153.8, 543.8	102.0, 657.0	96.1, 545.0	116.0, 473.0
Average daily very soft or liquid stool frequency						
N	165	168	168	501	130	51
Mean (SD)	5.6003 (2.8025)	5.3755 (3.2652)	5.5355 (2.7927)	5.5032 (2.9582)	5.7503 (3.0243)	5.5582 (3.0710)
Median	5.2857	4.7143	5.4286	5.1429	5.1429	4.8571
Min, Max	0.0000, 16.0000	0.1429, 23.1429	0.0000, 17.1429	0.0000, 23.1429	0.1429, 16.0000	0.0000, 16.0000

Variable	Cohort 1				Cohort 2	Cohort 3
	PBO (N = 165) n (%)	UPA 15 mg (N = 169) n (%)	UPA 30 mg (N = 168) n (%)	Total (N = 502) n (%)	PBO (N = 130) n (%)	UPA 30 mg (N = 51) n (%)
Average daily abdominal pain score[a]						
N	165	168	168	501	130	51
Mean (SD)	1.9492 (0.6586)	1.8485 (0.7005)	1.9419 (0.6026)	1.9130 (0.6554)	1.9700 (0.6239)	1.6398 (0.7683)
Median	2.0000	2.0000	2.0000	2.0000	2.0000	2.0000
Min, Max	0.0000, 3.0000	0.0000, 3.0000	0.0000, 3.0000	0.0000, 3.0000	0.0000, 3.0000	0.0000, 3.0000
Baseline SES-CD						
N	165	169	168	502	130	51
Mean (SD)	14.8 (7.71)	15.8 (7.64)	15.5 (8.10)	15.4 (7.81)	12.9 (6.63)	12.8 (7.15)
Median	13.0	14.0	14.0	14.0	11.0	11.0
Min, Max	4, 35	4, 40	4, 41	4, 41	4, 35	6, 33
CD location per SES-CD – n (%)						
Ileal only	24 (14.5)	22 (13.0)	20 (11.9)	66 (13.1)	21 (16.2)	12 (23.5)
Colonic only	67 (40.6)	62 (36.7)	70 (41.7)	199 (39.6)	41 (31.5)	11 (21.6)
Ileal-colonic	74 (44.8)	85 (50.3)	78 (46.4)	237 (47.2)	68 (52.3)	28 (54.9)
Baseline hs-CRP (mg/L)						
N	162	164	164	490	128	50
Mean (SD)	19.251 (24.5274)	19.531 (23.0139)	20.630 (26.0916)	19.806 (24.5336)	13.907 (16.7167)	14.946 (18.2150)
Median	8.875	10.700	9.345	9.595	6.955	7.895
Min, Max	0.20, 96.70	0.20, 110.00	0.20, 124.00	0.20, 124.00	0.20, 89.30	0.36, 99.40

	Cohort 1				Cohort 2	Cohort 3
Variable	**PBO** (N = 165) n (%)	**UPA 15 mg** (N = 169) n (%)	**UPA 30 mg** (N = 168) n (%)	**Total** (N = 502) n (%)	**PBO** (N = 130) n (%)	**UPA 30 mg** (N = 51) n (%)
Baseline FCP (µg/g)						
N	156	151	148	455	120	48
Mean (SD)	1866.8 (2655.81)	3200.5 (5315.40)	2663.3 (4320.95)	2568.5 (4253.61)	1623.8 (2467.19)	1999.4 (4362.95)
Median	1102.5	1658.0	1221.0	1284.0	763.5	760.5
Min, Max	30, 17033	30, 28800	30, 28800	30, 28800	30, 16886	31, 28800
Draining fistulas (yes, no) – n (%)						
Yes	8 (4.8)	17 (10.1)	11 (6.5)	36 (7.2)	6 (4.6)	2 (3.9)
No	157 (95.2)	151 (89.9)	157 (93.5)	465 (92.8)	124 (95.4)	49 (96.1)
Missing	0	1	0	1	0	0
Non-draining fistulas (yes, no) – n (%)						
Yes	17 (10.3)	20 (11.9)	8 (4.8)	45 (9.0)	10 (7.7)	5 (9.8)
No	148 (89.7)	148 (88.1)	160 (95.2)	456 (91.0)	120 (92.3)	46 (90.2)
Missing	0	1	0	1	0	0
Baseline corticosteroid use (yes, no) – n (%)						
Yes	61 (37.0)	63 (37.3)	63 (37.5)	187 (37.3)	50 (38.5)	17 (33.3)
No	104 (63.0)	106 (62.7)	105 (62.5)	315 (62.7)	80 (61.5)	34 (66.7)

	Cohort 1				Cohort 2	Cohort 3
Variable	**PBO** (N = 165) n (%)	**UPA 15 mg** (N = 169) n (%)	**UPA 30 mg** (N = 168) n (%)	**Total** (N = 502) n (%)	**PBO** (N = 130) n (%)	**UPA 30 mg** (N = 51) n (%)
Baseline immunosuppressant use (yes, no) – n (%)						
Yes	11 (6.7)	5 (3.0)	9 (5.4)	25 (5.0)	5 (3.8)	3 (5.9)
No	154 (93.3)	164 (97.0)	159 (94.6)	477 (95.0)	125 (96.2)	48 (94.1)

CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; FCP = fecal calprotectin; hs-CRP = high sensitivity C-reactive protein; ITT1 = intent-to-treat population for Cohort 1; max = maximum; min = minimum; PBO = placebo; SD = standard deviation; SES-CD = Simple Endoscopic Score for Crohn's disease; TNF = tumor-necrosis factor; UPA = upadacitinib a 0-no pain, 1-mild, 2-moderate, 3-severe.

Prior Use of CD-Related Medications:

Use of any prior CD-related medication was reported by 100% of subjects in the ITT1 population. The most frequently reported prior CD related medications used in Cohort 1 were azathioprine (58.8% of subjects from the placebo group and 55.0% - 59.5% of subjects from the upadacitinib 15 mg and upadacitinib 30 mg groups) and infliximab (51.5% of subjects from the placebo group and 58.6% - 58.9% of subjects from the upadacitinib 15 mg and upadacitinib 30 mg groups).

Table 32 Crohn's Disease-Related Biologic Medications Taken Prior to Baseline (ITT1, ITT2, and ITT3 Populations) Study M14-430

	Cohort 1				Cohort 2	Cohort 3
Generic Name (WHO 2021 Q1)	**PBO** (N = 165) n (%)	**UPA 15 mg** (N = 169) n (%)	**UPA 30 mg** (N = 168) n (%)	**Total** (N = 502) n (%)	**PBO** (N = 130) n (%)	**UPA 30 mg** (N = 51) n (%)
Adalimumab	80 (48.5)	72 (42.6)	92 (54.8)	244 (48.6)	67 (51.5)	32 (62.7)
Certolizumab	2 (1.2)	5 (3.0)	1 (0.6)	8 (1.6)	2 (1.5)	0
Certolizumab pegol	14 (8.5)	11 (6.5)	14 (8.3)	39 (7.8)	5 (3.8)	5 (9.8)
Infliximab	85 (51.5)	99 (58.6)	99 (58.9)	283 (66.4)	61 (46.9)	30 (58.8)
Ustekinumab	50 (30.3)	44 (26.0)	50 (29.8)	144 (28.7)	34 (26.2)	23 (45.1)
Vedolizumab	39 (23.6)	43 (25.4)	45 (26.8)	127 (25.3)	29 (22.3)	13 (25.5)

Extent of Exposure

Among all subjects in Cohort 1, the mean duration of exposure to the blinded study drug was 245.0 days for upadacitinib 15 mg, 265.6 days for upadacitinib 30 mg, and 175.2 days for placebo. Among all subjects in Cohort 2, the mean duration of exposure to the blinded study drug was 184.3 days for placebo. Among all subjects in Cohort 3, the mean duration of exposure to the blinded study drug was 250.4 days for upadacitinib 30 mg.

Outcomes and estimation

Primary Efficacy Endpoints Study M14-430

The co-primary endpoints of clinical remission and endoscopic response for both upadacitinib 15 mg and upadacitinib 30 mg compared to placebo were met for both the US/FDA and EU/EMA regulatory purposes. At Week 52, a statistically significantly greater (p-value < 0.0001) proportion of subjects in both the upadacitinib 15 mg and upadacitinib 30 mg groups achieved the co-primary endpoint of clinical remission (by CDAI for the US/FDA and by PROs in the EU/EMA) compared to placebo group. At Week 52, a statistically significantly greater (p-value < 0.0001) proportion of subjects in both the upadacitinib 15 mg and upadacitinib 30 mg groups achieved endoscopic response, (for both US/FDA and EU/EMA), compared to the placebo group.

Table 33 Co-Primary Efficacy Variables for US and EU at Week 52 (NRI-C, ITT1 Population)

Treatment	N	Responder (NRI-C) n (%)	[95% CI][a]	Missing Due to COVID-19	Response Rate Diff Compared to Placebo Adjusted Diff (%)[b]	[95% CI][c]	P-value[c]
Clinical Remission per CDAI (US)							
PBO	165	25 (15.1)	[9.6, 20.6]	1			
UPA 15 mg	169	63 (37.3)	[30.0, 44.6]	0	23.7	[15.2, 32.1]	<0.0001
UPA 30 mg	168	80 (47.6)	[40.1, 55.2]	0	32.8	[23.9, 41.6]	<0.0001
Clinical Remission per PROs (EU)							
PBO	165	24 (14.4)	[9.0, 19.8]	1			
UPA 15 mg	169	60 (35.5)	[28.3, 42.7]	0	21.9	[13.7, 30.0]	<0.0001
UPA 30 mg	168	78 (46.4)	[38.9, 54.0]	0	31.8	[23.2, 40.3]	<0.0001
Endoscopic Response							
PBO	165	12 (7.3)	[3.3, 11.2]	3			
UPA 15 mg	169	47 (27.6)	[20.8, 34.4]	4	21.0	[13.6, 28.4]	<0.0001
UPA 30 mg	168	67 (40.1)	[32.7, 47.6]	1	33.7	[26.0, 41.3]	<0.0001

CDAI = Crohn's Disease Activity Index; CI = confidence interval; EU = European Union; ITT = intent-to-Treat; NRI-C = non-responder imputation while incorporating multiple imputation to handle missing data due to coronavirus (COVID-19); PBO = placebo; PROs = patient-reported outcomes of average daily very soft or liquid stool frequency and abdominal pain score; UPA = upadacitinib; US = United States

a. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.

b. Risk difference = (UPA – placebo). Adjusted risk difference is calculated based on the Cochran-Mantel-Haenszel test adjusting for stratification factors.

c. Adjusted treatment difference, 95% CI and p-values for comparison of binary endpoints between upadacitinib and placebo were calculated using CMH test adjusted for randomization stratification factors. Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) was performed for the analyses.
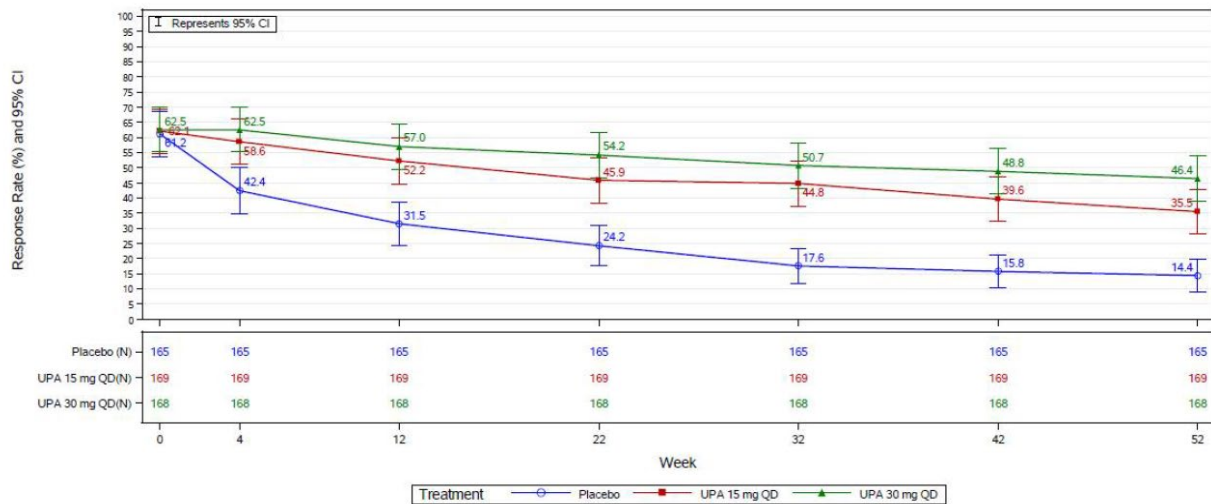
Figure 15 Summary of Achievement of SF/APS Clinical Remission over Time (ITT1; NRI-C)

Secondary Efficacy Variables Study M14-430

The key secondary endpoints (i.e., endpoints under the overall type I error control) shows that, upadacitinib 15 mg and upadacitinib 30 mg have are more effective compared to placebo for resolution of clinical symptoms, reduction in mucosal inflammation as measured by endoscopy and improvements in quality of life (QoL). A majority of endpoints were statistically significant for both upadacitinib 15 mg versus placebo and upadacitinib 30 mg versus placebo for both US/FDA and EU/EMA regulatory purposes.

Clinical response 100 (CR-100) (defined as decrease of at least 100 points in CDAI from Baseline) was achieved at Week 52, with statistically significant differences observed for upadacitinib 15 mg QD versus placebo and upadacitinib 30 mg QD versus placebo. Among subjects who had achieved clinical remission at Week 0, a significantly higher proportions of subjects maintained clinical remission at Week 52 in the upadacitinib 15 mg and upadacitinib 30 mg groups, compared to placebo. Statistically significantly higher improvement in fatigue (defined as change from Baseline in Functional Assessment of Chronic Illness therapy [FACIT]-Fatigue score) at Week 52 was achieved with upadacitinib 30 mg versus placebo while numerically higher improvement was noted for upadacitinib 15 mg versus placebo. Moreover, steroid-free clinical remission, irrespective of steroid use at Baseline, endoscopic remission and deep remission (defined as clinical remission and endoscopic remission) were also achieved at Week 52, with statistically significant differences observed for upadacitinib 15 mg QD versus placebo and upadacitinib 30 mg QD versus placebo.

Patient reported outcome (PRO) questionnaires that summarize QoL (by Inflammatory Bowel Disease Questionnaire [IBDQ]) also showed overall statistically significantly higher improvement in upadacitinib 15 mg versus placebo and upadacitinib 30 mg versus placebo at Week 52 (**Table 34** and **Table 35**). CD-related hospitalizations were numerically lower in the upadacitinib 15 mg group versus placebo and

upadacitinib 30 mg versus placebo. Additionally, while the total number of subjects analyzed was small, a statistically significantly higher proportion of subjects had resolution of their extra-intestinal manifestations (EIMs) in the upadacitinib 30 mg group versus placebo at Week 52, and a numerically higher proportion of subjects resolved their EIMs in the upadacitinib 15 mg group versus placebo.

Table 34 Summary of Key Secondary Efficacy Endpoints Under the Overall Type I Error Control, US/FDA (ITT1Population)

Study M14-430

	Endpoints	PBO (N = 165) % (n)[a] or LS MEAN (SE)	UPA 15 mg (N = 169) % (n)[a] or LS MEAN (SE)	UPA 30 mg (N = 168) % (n)[a] or LS MEAN (SE)	Adjusted Treatment Difference 95% CI[b] UPA 15 mg – PBO	Adjusted Treatment Difference 95% CI[b] UPA 30 mg – PBO	p-Value[b] UPA 15 mg vs. PBO	p-Value[b] UPA 30 mg vs. PBO
1	Clinical remission per PROs at Week 52 (NRI-C)	24 (14.4)	60 (35.5)	78 (46.4)	21.9	31.8	< 0.0001***	< 0.0001***
2	CR-100 at Week 52 (NRI-C)	25 (15.2)	70 (41.4)	86 (51.2)	27.1	36.4	< 0.0001***	< 0.0001***
3	Endoscopic remission at Week 52 (NRI-C)	9 (5.5)	32 (19.1)	48 (28.6)	14.4	23.6	< 0.0001***	< 0.0001***
4	Steroid-free use for CD at least 90 days prior to Week 52 and clinical remission per CDAI at Week 52 (NRI-C)	24 (14.5)	62 (36.7)	78 (46.4)	23.8	32.2	< 0.0001***	< 0.0001***
5	Clinical remission per CDAI and endoscopic remission at Week 52	6 (3.7)	25 (14.8)	39 (23.2)	12.2	19.8	0.0001***	< 0.0001***
6	Clinical remission per CDAI at Week 52, among subjects with clinical remission per CDAI at Week 0	N = 94 20 (21.2)	N = 101 50 (49.5)	N = 92 60 (65.2)	31.6	43.4	0.0001***	< 0.0001***
7	Steroid-free use for CD at least 90 days prior to Week 52 and clinical remission per CDAI at Week 52 (population: ITT1 subjects taking corticosteroids for CD at induction baseline) (NRI-C)	N = 61 3 (4.9)	N = 63 25 (39.7)	N = 63 25 (39.7)	35.4	32.3	< 0.0001***	< 0.0001***

	Endpoints	PBO (N = 165) % (n)[a] or LS MEAN (SE)	UPA 15 mg (N = 169) % (n)[a] or LS MEAN (SE)	UPA 30 mg (N = 168) % (n)[a] or LS MEAN (SE)	Adjusted Treatment Difference 95% CI[b] UPA 15 mg – PBO	Adjusted Treatment Difference 95% CI[b] UPA 30 mg – PBO	p-Value[b] UPA 15 mg vs. PBO	p-Value[b] UPA 30 mg vs. PBO
8	Change from induction baseline in IBDQ at Week 52 (MMRM)	N = 41 46.4 (4.02)	N = 78 59.3 (3.22)	N = 94 64.5 (3.15)	12.9 (4.3, 21.4)	18.1 (9.8, 26.4)	0.0033**	< 0.0001***
9	Change from induction baseline in FACIT-Fatigue at Week 52 (MMRM)	N = 40 12.0 (1.34)	N = 78 14.3 (1.05)	N = 94 16.1 (1.02)	2.3 (-0.6, 5.2)	4.1 (1.3, 6.9)	0.1149	0.0039**
10	Exposure-adjusted Rate for CD-related hospitalization through Week 52 (AO)	12.0022	11.2249	7.8282	-0.78 (-10.3985, 8.8440)	-4.17 (-13.0553, 4.7074)	0.8742	0.3570
11	Resolution of EIMs at Week 52, (ITT1 subjects with EIMs at induction baseline) (NRI-C)	N = 66 10 (15.2)	N = 61 15 (24.6)	N = 73 26 (35.6)	9.6	22.0	0.1476	0.0007***

AO = as observed; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CR-100 = Decrease of at least 100 points in CDAI from Baseline; EIM = extra-intestinal manifestation; FACIT = Functional Assessment of Chronic Illness Therapy; FDA = Food and Drug Administration; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT = intent-to-treat; LS = least squares; MMRM = mixed effect model repeat measurement; NRI-C = Non-responder imputation while incorporating multiple imputation to handle missing data due to COVID-19; PBO = placebo; PROs = patient-reported outcomes of average daily very soft or liquid stool frequency and abdominal pain score; SE = standard error; UPA = upadacitinib; US = United States

* P-value ≤ 0.05; ** P-value ≤ 0.01; *** P-value ≤ 0.001

a. The % (n) represents the synthesized results from multiple imputation.

b. Adjusted treatment difference, 95% CI and p-values for comparison of binary endpoints between upadacitinib and placebo were calculated using CMH test adjusted for randomization stratification factors; 95% CI and p-values for comparison of continuous endpoints between upadacitinib and placebo were calculated using MMRM with baseline, treatment, visit, treatment by visit interaction and stratification factors in the model; 95% CI and p-values

for comparison of exposure-adjusted rate for CD-related hospitalization between upadacitinib and placebo were calculated using normal approximation to binomial distribution.

Table 35   Summary of Key Secondary Efficacy Endpoints Under the Overall Type I Error Control, EU/EMA (NRI-C)(ITT1 Population) Study M14-430

	Endpoints	PBO (N = 165) % (n)[a] or LS MEAN (SE)	UPA 15 mg (N = 169) % (n)[a] or LS MEAN (SE)	UPA 30 mg (N = 168) % (n)[a] or LS MEAN (SE)	Adjusted Treatment Difference 95% CI[b] UPA 15 mg – PBO	Adjusted Treatment Difference 95% CI[b] UPA 30 mg – PBO	p-Value[b] UPA 15 mg vs. PBO	p-Value[b] UPA 30 mg vs. PBO
1	Clinical remission per CDAI at Week 52 (NRI-C)	25 (15.1)	63 (37.3)	80 (47.6)	23.7	32.8	< 0.0001***	< 0.0001***
2	Endoscopic remission at Week 52 (NRI-C)	9 (5.5)	32 (19.1)	48 (28.6)	14.4	23.6	< 0.0001***	< 0.0001***
3	Change from induction baseline in IBDQ at Week 52 (MMRM)	N = 41 46.4 (4.02)	N = 78 59.3 (3.22)	N = 94 64.5 (3.15)	12.9 (4.3, 21.4)	18.1 (9.8, 26.4)	0.0033**	< 0.0001***
4	CR-100 at Week 52 (NRI-C)	25 (15.2)	70 (41.4)	86 (51.2)	27.1	36.4	< 0.0001***	< 0.0001***
5	Steroid-free use for CD at least 90 days prior to Week 52 and clinical remission per PROs at Week 52 (NRI-C)	24 (14.4)	59 (34.9)	75 (44.6)	21.3	30.0	< 0.0001***	< 0.0001***
6	Steroid-free use for CD at least 90 days prior to Week 52 and clinical remission per PROs at Week 52 (population: ITT1 subjects taking corticosteroids for CD at induction baseline) (NRI-C)	N = 61 3 (4.9)	N = 63 24 (38.1)	N = 63 24 (38.1)	33.0	33.6	< 0.0001***	< 0.0001***
7	Clinical remission per PROs at Week 52 among subjects with clinical remission per PROs at Week 0	N = 101 20 (19.6)	N = 105 53 (50.5)	N = 105 63 (60.0)	31.9	39.7	<0.0001***	<0.0001***

	Endpoints	PBO (N = 165) % (n)[a] or LS MEAN (SE)	UPA 15 mg (N = 169) % (n)[a] or LS MEAN (SE)	UPA 30 mg (N = 168) % (n)[a] or LS MEAN (SE)	Adjusted Treatment Difference 95% CI[b] UPA 15 mg – PBO	Adjusted Treatment Difference 95% CI[b] UPA 30 mg – PBO	p-Value[b] UPA 15 mg vs. PBO	p-Value[b] UPA 30 mg vs. PBO
8	Change from induction baseline in FACIT-Fatigue at Week 52 (MMRM)	N = 40 12.0 (1.34)	N = 78 14.3 (1.05)	N = 94 16.1 (1.02)	2.3 (-0.6, 5.2)	4.1 (1.3, 6.9)	0.1149	0.0039**
9	Clinical remission per PROs and endoscopic remission at Week 52	7 (4.3)	23 (13.7)	38 (22.6)	10.0	18.2	0.0011**	< 0.0001***
10	Exposure-adjusted Rate for CD-related hospitalization through Week 52 (AO)	12.0022	11.2249	7.8282	-0.78 (-10.3985, 8.8440)	-4.17 (-13.0553, 4.7074)	0.8742	0.3570
11	Resolution of EIMs at Week 52, (ITT1 subjects with EIMs at induction baseline) (NRI-C)	N = 66 10 (15.2)	N = 61 15 (24.6)	N = 73 26 (35.6)	9.6	22.0	0.1476	0.0007***

Footnote please see Table 34.

Other Efficacy Variables Study M14-430

Overall, these endpoints offer supportive data to the co-primary and key secondary endpoints under the overall Type I error control. Symptom improvement was shown by achievement of clinical remission [per CDAI or PROs], mean change from Baseline in CDAI, abdominal pain score (APS), or stool frequency (SF), achievement of CR-100, enhanced clinical response, and mean change from Baseline in FACIT-Fatigue.

Treatment effects with respect to more stringent endoscopic measures, including
SES-CD 0-2, week 52 (cohort 1)
Placebo (N=165) 3.0%, 95%CI [0.4, 5.6]
UPA 15 mg QD (N=169) 11.2%, 95%CI [6.5, 16.0], diff with Placebo 8.7%, 95%CI [3.2, 14.1], P-value= 0.0018**
UPA 30 mg QD (N=168) 21.4%, 95%CI [15.2, 27.7], diff with Placebo 18.9%, 95%CI [12.5, 25.4], P-value= <0.0001***

Further, absence of ulcers (SES-CD ulcerated surface subscore of 0 among subjects with ulcers at Baseline), endoscopic remission and steroid-free were also observed at Week 52 with upadacitinib 15 mg and 30 mg groups compared with placebo.

Additionally, decreases in the biomarkers of fecal calprotectin (FCP) and high sensitivity C-reactive protein (hs-CRP) were sustained through Week 52 for upadacitinib versus placebo. Finally, QoL improvement, shown by improvements in IBDQ, WPAI-CD, EQ-5D-5L, SF-36, and Crohn's Symptom Severity (CSS) scores were observed over time for upadacitinib versus placebo.

Cohort 2 (placebo) and Cohort 3 (Upadacitinib 30 mg) Efficacy

At Week 52, 22.7% and 41.2% of subjects in Cohort 2 (placebo) and Cohort 3 (upadacitinib 30 mg), respectively, were in clinical response per PROs.

Study M14-430 Substudy 1 (Maintenance)

The following paragraphs have been submitted by the MAH. In Study M14-430 Substudy 1 Cohort 1, results demonstrated that in subjects who achieved SF/APS clinical response after 12-week induction treatment with upadacitinib 45 mg, both upadacitinib maintenance doses of 15 mg and 30 mg were effective in reaching long-term treatment targets. Higher proportions of subjects treated with upadacitinib 15 mg and 30 mg achieved the co-primary endpoints of clinical remission (per CDAI and per SF/APS) and endoscopic response at Week 52 compared with placebo. A significantly greater proportion of subjects treated with upadacitinib maintained clinical remission at Week 52 compared with placebo. Steroid-free clinical remission was achieved irrespective of steroid use at Baseline of induction. Improvement in fatigue and resolution of EIMs were achieved with upadacitinib 30 mg compared to placebo. The results of objective assessments, including endoscopic endpoints and inflammatory markers (FCP, hs-CRP), underscore the importance of continuing upadacitinib as maintenance therapy. The improvements in QoL were maintained through 52 weeks of maintenance treatment. Stringent treatment goals were also achieved, including deep remission, absence of ulcers by endoscopy (US)/mucosal healing (EU), and Simple Endoscopic Score for Crohn's Disease (SES-CD) 0-2. Overall, there was a clear dose-response, with higher efficacy observed in the upadacitinib 30 mg dose group than in the 15 mg dose group.

Among subgroups, the clinical remission and endoscopic response results were consistent with the overall results. A greater treatment effect for the upadacitinib 30 mg dose relative to the 15 mg dose was observed in subgroups of subjects with more severe and high disease burden (i.e., CDAI > 300 at Baseline, those who presented with elevated FCP and hs-CRP, and with prior biologic failure).

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36   Summary of Efficacy for Study M14-431

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Biologic Therapy			
Study identifier	M14-431		
Design	The study consists of a Screening Period (approximately 5 weeks), a 12-Week Induction Period, a 12-Week Extended Treatment Period, and a 30-day follow-up for subjects who do not enroll into Study M14-430. **Induction Period** is a 12-week period consisting of 2 parts: • Part 1: a randomized, double-blind, placebo-controlled Induction Period, eligible subjects were randomized in a 2:1 ratio to upadacitinib 45 mg once daily (QD) or matching placebo for 12 weeks. • Part 2: an open-label, single-arm active Induction Period. After enrollment in Part 1 was complete, additional subjects were enrolled in Part 2 to receive upadacitinib 45 mg QD for 12 weeks. **Extended Treatment Period** is a 12-week period for subjects who do not achieve clinical response at Week 12 of the Induction Period which consists of 3 cohorts: • Cohort 1: Subjects who received placebo in Part 1 were eligible to receive double-blind upadacitinib 45 mg QD for 12 weeks (until Week 24). • Cohort 2: Subjects who received upadacitinib in Part 1 were eligible to receive double-blind upadacitinib 30 mg QD for 12 weeks (until Week 24). • Cohort 3: Subjects who received upadacitinib in Part 2 were eligible to receive open-label upadacitinib 30 mg QD for 12 weeks (until Week 24).		
	Duration of main phase:		12 weeks (double-blind 12-week Induction Period [Part 1])
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority of upadacitinib 45 mg QD vs. placebo at Week 12		
Treatment groups for primary and ranked secondary endpoints	Upadacitinib 45 mg QD (UPA 45 mg QD)		Upadacitinib 45 mg QD for 12 weeks
	Placebo (PBO)		Matching placebo
Endpoints and definitions	Co-primary endpoint	Clinical remission per PROs	Achievement of clinical remission per PROs at Week 12
	Co-primary endpoint	Endoscopic response	Achievement of endoscopic response at Week 12
	Key Secondary endpoint	Clinical remission per CDAI	Achievement of clinical remission per CDAI at Week 12
	Key Secondary endpoint	Clinical remission per PROs	Achievement of clinical remission per PROs at Week 4
	Key Secondary endpoint	Endoscopic remission	Achievement of endoscopic remission at Week 12

	Key Secondary endpoint	Steroid-free and clinical remission per PROs	Discontinuation of corticosteroid use for CD and achievement of clinical remission per PROs at Week 12 among subjects taking corticosteroids for CD at Baseline
	Key Secondary endpoint	FACIT-Fatigue	Change from baseline in FACIT-Fatigue total score at Week 12
	Key Secondary endpoint	IBDQ	Change from baseline in IBDQ total score at Week 12
	Key Secondary endpoint	CR-100	Achievement of CR-100 at Week 2
	Key Secondary endpoint	CR-100	Achievement of CR-100 at Week 12
	Key Secondary endpoint	CD-related hospitalization	Occurrence of hospitalizations due to CD during Part 1
	Key Secondary endpoint	Resolution of EIMs	Achievement of resolution of EIMs at Week 12 among subjects with any EIMs at baseline
Database lock	23 November 2021		
Analysis population and time point description	The Intent-to-Treat (ITT1) population is defined as all randomized subjects who received at least one dose of double-blind study drug during the 12-week double-blind Induction Period (Part 1).		
Results and Analysis			
Analysis description	Co-primary and Key Secondary Endpoints Analyses		
	Treatment group	Upadacitinib 45 mg QD (UPA 45 mg QD)	Placebo (PBO)
	Number of subjects	324	171
	Clinical remission per PROs at Week 12 (NRI-C), N (%)	324 (39.8%)	171 (14.0%)
	Endoscopic response at Week 12 (NRI-C), N (%)	324 (34.6%)	171 (3.5%)
Descriptive statistics and estimate variability	Clinical remission per CDAI at Week 12 (NRI-C), N (%)	324 (38.9%)	171 (21.1%)
	Clinical remission per PROs at Week 4 (NRI-C), N (%)	324 (32.4%)	171 (9.4%)
	Endoscopic remission at Week 12 (NRI-C), N (%)	324 (19.1%)	171 (2.3%)
	Steroid-free and clinical remission per PROs at Week 12 (NRI-C), N (%)	108 (37.0%)	60 (6.7%)

	Change from baseline in FACIT-Fatigue at Week 12 (MMRM), LS-Mean Change from Baseline [95% CI]	11.4 [10.1, 12.8]	3.9 [2.0, 5.8]
	Change from baseline in IBDQ at Week 12 (MMRM), LS-Mean Change from Baseline [95% CI]	46.0 [41.7, 50.2]	21.6 [15.7, 27.6]
	CR-100 at Week 2 (NRI-C), N (%)	324 (33.2%)	171 (12.4%)
	CR-100 at Week 12 (NRI-C), N (%)	324 (50.5%)	171 (27.5%)
	Occurrence of CD-related hospitalization through Week 12 (AO), N (%)	324 (6.2%)	171 (8.8%)
	Resolution of EIMs at Week 12, in subjects with any EIMs at baseline (NRI-C), N (%)	131 (32.8%)	60 (21.7%)
	Clinical remission per PROs at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	25.9%
		95% CI	[18.7%, 33.1%]
		P-value	< 0.0001
	Endoscopic response at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	31.2%
		95% CI	[25.5%, 37.0%]
		P-value	< 0.0001
	Clinical remission per CDAI at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	17.9%
		95% CI	[10.0%, 25.8%]
		P-value	< 0.0001
	Clinical remission per PROs at Week 4 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	23.3%
		95% CI	[16.6%, 29.9%]
		P-value	< 0.0001
	Endoscopic remission at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	16.8%
		95% CI	[12.0%, 21.6%]
		P-value	< 0.0001
	Steroid-free and clinical remission per PROs at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	30.2%
		95% CI	[19.4%, 41.0%]
		P-value	< 0.0001
	Change from baseline in FACIT-Fatigue at Week 12 (MMRM)	Comparison groups	UPA vs PBO
		Difference	7.5
		95% CI	[5.2, 9.8]

		P-value	< 0.0001
	Change from baseline in IBDQ at Week 12 (MMRM)	Comparison groups	UPA vs PBO
		Difference	24.3
		95% CI	[17.2, 31.5]
		P-value	< 0.0001
	CR-100 at Week 2 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	20.7%
		95% CI	[13.7%, 27.8%]
		P-value	< 0.0001
	CR-100 at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	22.8%
		95% CI	[14.4%, 31.2%]
		P-value	< 0.0001
	Occurrence of CD-related hospitalization through Week 12 (AO)	Comparison groups	UPA vs PBO
		Difference	-2.6%
		95% CI	[-7.6%, 2.4%]
		P-value	0.2834
	Resolution of EIMs at Week 12, in subjects with any EIMs at baseline (NRI-C)	Comparison groups	UPA vs PBO
		Difference	11.5%
		95% CI	[-1.5%, 24.4%]
		P-value	0.0833

Table 37   Summary of Efficacy for Study M14-433

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Conventional and/or Biologic Therapies			
Study identifier	M14-433		
Design	The study consists of a Screening Period (approximately 5 weeks), a 12-Week Induction Period, a 12-Week Extended Treatment Period, and a 30-day follow-up for subjects who do not enroll into Study M14-430. **Induction Period (Part1)** is a 12-week randomized, double-blind, placebo-controlled period. Eligible subjects were randomized in a 2:1 ratio to upadacitinib 45 mg once daily (QD) or matching placebo for 12 weeks. **Extended Treatment Period (Part2)** is a 12-week period for subjects who do not achieve clinical response at Week 12 of the Induction Period which consists of 2 cohorts: • <u>Cohort 1</u>: Subjects who received placebo during Part 1 and did not achieve clinical response at Week 12 were eligible to receive double-blind induction treatment with upadacitinib 45 mg QD for 12 weeks (until Week 24). • <u>Cohort 2</u>: Subjects who received upadacitinib during Part 1 and did not achieve clinical response at Week 12 were eligible to receive double-blind upadacitinib 30 mg QD for 12 weeks (until Week 24).		
	Duration of main phase:		12 weeks (double-blind 12-Week Induction Period [Part 1])
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority of upadacitinib 45 mg QD vs. placebo at Week 12		
Treatment groups for primary and ranked secondary endpoints	Upadacitinib 45 mg QD (UPA 45 mg QD)		Upadacitinib 45 mg QD for 12 weeks
	Placebo (PBO)		Matching placebo
Endpoints and definitions	Co-primary endpoint	Clinical remission per PROs	Achievement of clinical remission per PROs at Week 12
	Co-primary endpoint	Endoscopic response	Achievement of endoscopic response at Week 12
	Key Secondary endpoint	Clinical remission per CDAI	Achievement of clinical remission per CDAI at Week 12
	Key Secondary endpoint	Clinical remission per PROs	Achievement of clinical remission per PROs at Week 4
	Key Secondary endpoint	Endoscopic remission	Achievement of endoscopic remission at Week 12
	Key Secondary endpoint	Steroid-free and clinical remission per PROs	Discontinuation of corticosteroid use for CD and achievement of clinical remission per PROs at Week 12 among subjects taking corticosteroids for CD at Baseline
	Key Secondary endpoint	FACIT-Fatigue	Change from baseline in FACIT-Fatigue total score at Week 12

	Key Secondary endpoint	IBDQ	Change from baseline in IBDQ total score at Week 12
	Key Secondary endpoint	CR-100	Achievement of CR-100 at Week 2
	Key Secondary endpoint	CR-100	Achievement of CR-100 at Week 12
	Key Secondary endpoint	CD-related hospitalization	Occurrence of hospitalizations due to CD during Part 1
	Key Secondary endpoint	Resolution of EIMs	Achievement of resolution of EIMs at Week 12 among subjects with any EIMs at baseline

Database lock	17 February 2022
Analysis population and time point description	The Intent-to-Treat (ITT1) population is defined as all randomized subjects who received at least one dose of double-blind study drug during the 12-Week double-blind Induction Period (Part 1).

Results and Analysis

Analysis description	Co-primary and Key Secondary Endpoints Analyses		
	Treatment group	Upadacitinib 45 mg QD (UPA 45 mg QD)	Placebo (PBO)
	Number of subjects	350	176
	Clinical remission per PROs at Week 12 (NRI-C), N (%)	350 (50.7%)	176 (22.2%)
	Endoscopic response at Week 12 (NRI-C), N (%)	350 (45.5%)	176 (13.1%)
	Clinical remission per CDAI at Week 12 (NRI-C), N (%)	350 (49.5%)	176 (29.1%)
	Clinical remission per PROs at Week 4 (NRI-C), N (%)	350 (35.7%)	176 (14.8%)
Descriptive statistics and estimate variability	Endoscopic remission at Week 12 (NRI-C), N (%)	350 (28.9%)	176 (7.4%)
	Steroid-free and clinical remission per PROs at Week 12 (NRI-C), N (%)	126 (44.4%)	64 (12.5%)
	Change from baseline in FACIT-Fatigue at Week 12 (MMRM), LS-Mean Change from Baseline [95% CI]	11.3 [10.0, 12.5]	5.0 [3.2, 6.8]
	Change from baseline in IBDQ at Week 12 (MMRM), LS-Mean Change from Baseline [95% CI]	46.3 [42.5, 50.0]	24.4 [19.0, 29.8]
	CR-100 at Week 2 (NRI-C), N (%)	350 (32.2%)	176 (20.4%)
	CR-100 at Week 12 (NRI-C), N (%)	350 (56.6%)	176 (37.3%)

	Occurrence of CD-related hospitalization through Week 12 (AO), N (%)	350 (3.7%)	176 (5.1%)
	Resolution of EIMs at Week 12, in subjects with any EIMs at baseline (NRI-C), N (%)	151 (28.5%)	78 (20.9%)
	Clinical remission per PROs at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	28.7%
		95% CI	[20.9%, 36.4%]
		P-value	< 0.0001
	Endoscopic response at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	33.0%
		95% CI	[26.2%, 39.9%]
		P-value	< 0.0001
	Clinical remission per CDAI at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	20.8%
		95% CI	[12.7%, 28.8%]
		P-value	< 0.0001
	Clinical remission per PROs at Week 4 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	21.2%
		95% CI	[14.3%, 28.2%]
		P-value	< 0.0001
	Endoscopic remission at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	21.8%
		95% CI	[15.8%, 27.8]
		P-value	< 0.0001
	Steroid-free and clinical remission per PROs at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	32.6%
		95% CI	[21.5%, 43.7%]
		P-value	< 0.0001
	Change from baseline in FACIT-Fatigue at Week 12 (MMRM)	Comparison groups	UPA vs PBO
		Difference	6.3
		95% CI	[4.2, 8.3]
		P-value	< 0.0001
	Change from baseline in IBDQ at Week 12 (MMRM)	Comparison groups	UPA vs PBO
		Difference	21.8
		95% CI	[15.6, 28.1]
		P-value	< 0.0001
	CR-100 at Week 2 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	11.7%
		95% CI	[4.2%, 19.2%]
		P-value	0.0022

	CR-100 at Week 12 (NRI-C)	Comparison groups	UPA vs PBO
		Difference	19.8%
		95% CI	[11.3%, 28.4%]
		P-value	< 0.0001
	Occurrence of CD-related hospitalization through Week 12 (AO)	Comparison groups	UPA vs PBO
		Difference	-1.4%
		95% CI	[-5.2%, 2.4%]
		P-value	0.4494
	Resolution of EIMs at Week 12, in subjects with any EIMs at baseline (NRI-C)	Comparison groups	UPA vs PBO
		Difference	9.0%
		95% CI	[-1.9%, 19.9%]
		P-value	0.1044

Table 38   Summary of Efficacy for Study M14-430 Substudy 1

| Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Maintenance and Long-Term Extension Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Crohn's Disease Who Completed the Studies M14-431 or M14-433 |||

Study identifier	M14-430		
Design	The study consists of two sub-studies: Substudy 1 is the 52-week randomized, double-blind, placebo-controlled maintenance study. Substudy 2 is the 240-week long-term extension study. **Substudy 1 (Maintenance Study)** consists of 3 cohorts: - Cohort 1: Subjects who received the 12-week induction treatment with upadacitinib 45 mg (including those who did not achieve clinical response with placebo and then received upadacitinib 45 mg for 12 weeks) and achieved clinical response in Studies M14-431 or M14-433 were re-randomized to either upadacitinib 30 mg QD, upadacitinib 15 mg QD, or matching placebo in a 1:1:1 ratio. - Cohort 2: Subjects who received the 12-week induction treatment with placebo and achieved clinical response in Studies M14-431 or M14-433 continued to receive placebo. - Cohort 3: Subjects who did not achieve clinical response after the 12-week induction treatment with upadacitinib 45 mg, received the 12-week extended treatment with upadacitinib 30 mg and achieved clinical response in Studies M14-431 or M14-433, continued to receive upadacitinib 30 mg QD.		
	Duration of Main phase:		52 weeks (randomized, double-blind maintenance study [Substudy 1 Cohort 1])
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority of upadacitinib vs. placebo at Week 52		
Treatment groups for primary and ranked secondary endpoints	Upadacitinib 30 mg QD (UPA 30 mg QD)		Upadacitinib 30 mg QD for 52 weeks
	Upadacitinib 15 mg QD (UPA 15 mg QD)		Upadacitinib 15 mg QD for 52 weeks
	Placebo (PBO)		Matching placebo
Endpoints and definitions	Co-primary endpoint	clinical remission per PROs	Achievement of clinical remission per PROs at Week 52
	Co-primary endpoint	endoscopic response	Achievement of endoscopic response at Week 52
	Key Secondary endpoint	clinical remission per CDAI	Achievement of clinical remission per CDAI at Week 52
	Key Secondary endpoint	endoscopic remission	Achievement of endoscopic remission at Week 52
	Key Secondary endpoint	IBDQ	Change from induction baseline in IBDQ at Week 52
	Key Secondary endpoint	CR-100	Achievement of CR-100 at Week 52
	Key Secondary endpoint	steroid-free and clinical remission per PROs	Without corticosteroid use for CD at least 90 days prior to Week 52 and achievement of clinical remission per PROs at Week 52
	Key Secondary endpoint	steroid-free and clinical remission per PROs	Discontinuation of corticosteroid use for CD at least 90 days prior to Week 52 and achievement of clinical remission per PROs at Week 52 among subjects taking corticosteroids for CD at Induction Baseline

	Key Secondary endpoint	Clinical remission per PROs	Achievement of clinical remission per PROs at Week 52 among subjects with clinical remission per PROs at Week 0
	Key Secondary endpoint	FACIT-Fatigue	Change from induction baseline in FACIT-Fatigue at Week 52
	Key Secondary endpoint	Clinical remission per PROs and endoscopic remission	Achievement of clinical remission per PROs and endoscopic remission at Week 52
	Key Secondary endpoint	CD-related hospitalization	Occurrence of exposure-adjusted CD-related hospitalizations during the 52-Week double-blind maintenance period
	Key Secondary endpoint	Resolution of EIMs	Achievement of resolution of EIMs at Week 52 among subjects with any EIMs at Induction Baseline

Database lock	23 April 2022		
Analysis population and time point description	The Intent-to-Treat (ITT1) population is defined as the first 502 subjects randomized in Cohort 1 who received at least 1 dose of study drug in Substudy 1. The ITT1 population is the primary analysis population for the M14-430 Substudy 1.		

Results and Analysis

Analysis description	Co-primary and Key Secondary Endpoints Analyses		
	Treatment group	UPA 30 mg QD	UPA 15 mg QD	Placebo (PBO)

Descriptive statistics and estimate variability	Treatment group	UPA 30 mg QD	UPA 15 mg QD	Placebo (PBO)
	Number of subjects	168	169	165
	Clinical remission per PROs at Week 52 (NRI-C), N (%)	168 (46.4%)	169 (35.5%)	165 (14.4%)
	Endoscopic response at Week 52 (NRI-C), N (%)	168 (40.1%)	169 (27.6%)	165 (7.3%)
	Clinical remission per CDAI at Week 52 (NRI-C), N (%)	168 (47.6%)	169 (37.3%)	165 (15.1%)
	Endoscopic remission at Week 52 (NRI-C), N (%)	168 (28.6%)	169 (19.1%)	165 (5.5%)
	Change from induction baseline in IBDQ at Week 52 (MMRM), LS-Mean Change from Baseline [95% CI]	64.5 [58.3, 70.7]	59.3 [52.9, 65.6]	46.4 [38.5, 54.3]
	CR-100 at Week 52 (NRI-C), N (%)	168 (51.2%)	169 (41.4%)	165 (15.2%)
	Steroid-free and clinical remission per PROs at Week 52 (NRI-C), N (%)	168 (44.6%)	169 (34.9%)	165 (14.4%)

Steroid-free and clinical remission per PROs at Week 52 among subjects taking corticosteroids for CD at Induction Baseline, (NRI-C), N (%)	63 (38.1%)	63 (38.1%)	61 (4.9%)
Clinical remission per PROs at Week 52 among subjects with clinical remission per PROs at Week 0, N (%)	105 (60.0%)	105 (50.5%)	101 (19.6%)
Change from baseline in FACIT-Fatigue at Week 52 (MMRM), LS-Mean Change from Baseline [95% CI]	16.1 [14.1, 18.1]	14.3 [12.2, 16.4]	12.0 [9.4, 14.7]
Clinical remission per PROs and endoscopic remission at Week 52, N (%)	168 (22.6%)	169 (13.7%)	165 (4.3%)
Occurrence of CD-related hospitalization through Week 52 (AO), n/100PY	7.8	11.2	12.0
Resolution of EIMs at Week 52 among subjects with any EIMs at induction baseline) (NRI-C, N (%)	73 (35.6%)	61 (24.6%)	66 (15.2%)

Clinical Remission per PROs at Week 52 (NRI-C)	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
	Difference	31.8%	21.9%
	95% CI	[23.2%, 40.3%]	[13.7%, 30.0%]
	P-value	< 0.0001	< 0.0001
Endoscopic Response at Week 52 (NRI-C)	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
	Difference	33.7%	21.0%
	95% CI	[26.0%, 41.3%]	[13.6%, 28.4%]
	P-value	< 0.0001	< 0.0001
Clinical Remission per CDAI at Week 52 (NRI-C)	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
	Difference	32.8%	23.7%
	95% CI	[23.9%, 41.6%]	[15.2%, 32.1%]
	P-value	< 0.0001	< 0.0001
Endoscopic remission at Week 52 (NRI-C)	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
	Difference	23.6%	14.4%
	95% CI	[16.1%, 31.0%]	[7.7%, 21.0%]
	P-value	< 0.0001	< 0.0001
Change from induction baseline in IBDQ at Week 52 (MMRM)	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
	Difference	18.1	12.9

		95% CI	[9.8, 26.4]	[4.3, 21.4]
		P-value	< 0.0001	0.0033
	CR-100 at Week 52 (NRI-C)	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
		Difference	36.4%	27.1%
		95% CI	[27.5%, 45.2%]	[18.3%, 35.8%]
		P-value	< 0.0001	< 0.0001
	Steroid-free and clinical remission per PROs at Week 52 (NRI-C)	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
		Difference	30.0%	21.3%
		95% CI	[21.4%, 38.6%]	[13.1%, 29.5%]
		P-value	< 0.0001	< 0.0001
	Steroid-free and clinical remission per PROs at Week 52 among subjects taking corticosteroids for CD at induction baseline (NRI-C)	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
		Difference	33.6%	33.0%
		95% CI	[21.4%, 45.8%]	[20.4%, 45.6%]
		P-value	< 0.0001	< 0.0001
	Clinical remission per PROs at Week 52 among subjects with clinical remission per PROs at Week 0	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
		Difference	39.7%	31.9%
		95% CI	[27.8%, 51.7%]	[20.1%, 43.6%]
		P-value	< 0.0001	< 0.0001
	Change from induction baseline in FACIT-Fatigue at Week 52 (MMRM)	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
		Difference	4.1	2.3
		95% CI	[1.3, 6.9]	[-0.6, 5.2]
		P-value	0.0039	0.1149
	Clinical remission per PROs and endoscopic remission at Week 52	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
		Difference	18.2%	10.0%
		95% CI	[11.3%, 25.0%]	[4.0%, 16.0%]
		P-value	< 0.0001	0.0011
	Occurrence of CD-related hospitalization through Week 52 (AO)	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
		Difference	-4.2	-0.8
		95% CI	[-13.1, 4.7]	[-10.4, 8.8]
		P-value	0.3570	0.8742
	Resolution of EIMs at Week 52, in subjects with any EIMs at baseline (NRI-C)	Comparison groups	UPA 30 mg QD vs PBO	UPA 15 mg QD vs PBO
		Difference	22.0%	9.6
		95% CI	[9.3%, 34.8%]	[-3.4%, 22.6%]
		P-value	0.0007	0.1476

Analysis performed across trials (pooled analyses and meta-analysis)

The results of the integrated analysis for induction are consistent with the results of the individual studies at Week 12. Please see tables below. Improvements with upadacitinib 45 mg treatment were shown in multiple measures of disease activity and symptoms when compared with placebo. Please see below for the integrated analyses sets. Chosen data are presented in this section.

Table 39   Summary of Integrated Analysis Sets

Integrated Analysis Set	Definition	Objective/Analyses	Pooled Studies	Analyses and Summarized Treatment Groups
Placebo-controlled 12-Week Induction Period – ISE1	ISE1 includes all randomized subjects who received at least one dose of study drug in the DB 12-Week Induction Period from the two global Phase 3 induction studies: Studies M14-431 and M14-433. This is the primary integrated analysis set for the primary and key secondary endpoints during the 12-Week Induction Period (Part 1).	**Short-term** – Used for the efficacy assessment of short-term induction treatment with UPA 45 mg QD vs PBO	M14-431 (Part 1) M14-433 (Part 1)	Upadacitinib 45 mg QD Placebo
Extended Treatment Period – ISE2	ISE2 includes all subjects who were not clinical responders to UPA 45 mg QD at the entry of Extended Treatment Period and received at least one dose of study drug in the Extended Treatment Period from the two global Phase 3 induction studies: Studies M14-431 and M14-433.	**Short-term** – Used for the efficacy assessment of short-term UPA treatment for subjects who were not responders to UPA or PBO in the 12-Week Induction Period	M14-431 (Part 3) M14-433 (Part 2)	Upadacitinib 30 mg QD
Maintenance and Long-Term Therapy – ISE3	ISE3 includes subjects who received at least one dose of UPA in Phase 3 maintenance Study M14-430 Substudy 1 Cohort 1. This analysis set integrates the efficacy data from subjects in UPA 30 mg QD and UPA 15 mg QD in Study M14-430 Substudy 1 and the long-term efficacy data from Study M14-430 Substudy 2. Data after the open-label UPA 30 mg QD rescue therapy will not be included in this analysis.	**Long term** – Used for the efficacy assessment of long-term UPA 15 mg QD or 30 mg QD maintenance and long-term treatment	M14-430 Substudy 1 Cohort 1 M14-430 Substudy 2 Cohort 5	Upadacitinib 15 mg QD Upadacitinib 30 mg QD
Open-label UPA 30 mg QD rescue therapy – ISE_OL30	ISE_OL30 includes Cohort 1 subjects who received at least one dose of the rescue therapy of open-label UPA 30 mg QD in Study M14-430. This analysis set includes the efficacy data after receiving open-label UPA 30 mg QD.	**Upadacitinib Rescue Therapy** Used for the efficacy assessment of UPA 30 mg QD rescue therapy	M14-430 Substudy 1 M14-430 Substudy 2	By cohort/ treatment group

Table 40   Baseline characteristics, selected variables M14-431 and M14-433 (ISE1 population)

Variables	Placebo (N = 347)	UPA 45 mg (N = 674)	Total (N = 1021)
Crohn's disease duration (years)			
Mean (SD)	9.4978 (8.1053)	10.6226 (9.5955)	10.2404 (9.1280)
Median	7.5565	7.6988	7.6331
Min, Max	0.2765, 46.2752	0.0575, 55.1677	0.0575, 55.1677
Prior biologics use/failure history (Bio-IR status), n (%)			
Bio-IR	248 (71.5)	485 (72.0)	733 (71.8)
Non-Bio-IR	99 (28.5)	189 (28.0)	288 (28.2)
Prior biologics failure history – n (%)			
n (Bio-IR)	248	485	733
1	95 (38.3)	184 (37.9)	279 (38.1)
2	79 (31.9)	144 (29.7)	223 (30.4)
≥ 3	74 (29.8)	157 (32.4)	231 (31.5)

Variables	Placebo (N = 347)	UPA 45 mg (N = 674)	Total (N = 1021)
Average daily abdominal pain score			
n	347	673	1020
Mean (SD)	1.8517 (0.6909)	1.8721 (0.6850)	1.8652 (0.6867)
Median	2.0000	2.0000	2.0000
Min, Max	0.0000, 3.0000	0.0000, 3.0000	0.0000, 3.0000
Baseline hs-CRP (mg/L)			
n	339	660	999
Mean (SD)	17.534 (23.0394)	18.335 (23.4029)	18.064 (23.2717)
Median	7.890	8.835	8.660
Min, Max	0.20, 126.00	0.20, 144.00	0.20, 144.00
Baseline FCP (µg/g)			
n	320	617	937
Mean (SD)	1987.2 (2967.68)	2226.4 (3935.55)	2144.7 (3634.25)
Median	1023.5	924.0	962.0
Min, Max	30, 24234	30, 28800	30, 28800
Draining fistulas – n (%)			
Yes	22 (6.3)	44 (6.5)	66 (6.5)
No	325 (93.7)	629 (93.5)	954 (93.5)
Missing	0	1	1
Non-draining fistulas – n (%)			
Yes	29 (8.4)	56 (8.3)	85 (8.3)
No	318 (91.6)	617 (91.7)	935 (91.7)
Missing	0	1	1
Baseline CD-related corticosteroid use (yes, no) – n (%)			
Yes	124 (35.7)	234 (34.7)	358 (35.1)
No	223 (64.3)	440 (65.3)	663 (64.9)
Baseline CD-related immunosuppressant use (yes, no) – n (%)			
Yes	16 (4.6)	37 (5.5)	53 (5.2)
No	331 (95.4)	637 (94.5)	968 (94.8)

Note: Percentages calculated on non-missing values.

A total of 495 and 526 subjects were randomized in Study M14-431 (Bio-IR population) and Study M14-433 (Non-Bio-IR and Bio-IR populations), respectively, the two confirmatory Phase 3 induction studies. These studies evaluated the efficacy and safety of upadacitinib 45 mg compared to placebo as induction therapy for 12 weeks in subjects with moderately to severely active CD (

Figure **7**).

In Study M14-433, 45.4% of enrolled subjects were Bio-IR and 54.6% were Non-Bio-IR. Study M14-431, by design, only enrolled subjects with prior inadequate response and intolerance to biologics, with 60.8% of subjects having failed at least 2 biologics.

The primary efficacy analysis for these studies was the ITT1 population as presented under each study above. Twelve weeks of treatment with upadacitinib 45 mg QD was superior to placebo as an induction therapy across the co-primary efficacy endpoints for both induction studies (p-values < 0.0001); statistically significantly higher proportions of subjects in the upadacitinib 45 mg groups achieved the co-primary endpoints of clinical remission (defined by CDAI for the US/FDA and by SF/APS in the EU/EMA).

A majority of key secondary endpoints were also achieved, reduction in mucosal inflammation, and improvements in QoL with IBDQ, under the overall Type I error control.

Table 41   Disease Activity and Symptoms Results: Upadacitinib 45 mg QD (Placebo-Controlled Induction Treatment Analysis Set) (NRI-C, ISE1)

	PBO N = 347 n (%)	UPA 45 mg N = 674 n (%)	Response Rate Difference Compared to Placebo		
			Adjusted Diff	(95% CI)[a]	P-Value[b]
Primary Endpoints					
CDAI clinical remission at Week 12 (US)	87 (25.1)	299 (44.3)	19.3	(13.7, 25.0)	< 0.0001
SF/APS Clinical remission at Week 12 (EU)	63 (18.2)	307 (45.5)	27.4	(22.1, 32.7)	< 0.0001
Key Secondary Endpoints					
Steroid-free CDAI clinical remission at Week 12 (US)	n = 124 17 (13.7)	n = 234 91 (38.9)	25.3	(17.0, 33.6)	< 0.0001
Steroid-free SF/APS clinical remission at Week 12 (EU)	n = 124 12 (9.7)	n = 234 96 (41.0)	31.5	(23.7, 39.2)	< 0.0001
CR-100 at Week 2	57 (16.5)	220 (32.6)	16.0	(10.9, 21.2)	< 0.0001
CR-100 at Week 12	113 (32.5)	362 (53.7)	21.3	(15.3, 27.3)	< 0.0001
CDAI Clinical remission at Week 4 (US)	78 (22.4)	226 (33.5)	11.3	(5.9, 16.7)	< 0.0001
SF/APS Clinical remission at Week 4 (EU)	42 (12.1)	230 (34.1)	22.2	(17.4, 27.0)	< 0.0001
Change from Baseline FACIT-Fatigue total score Week 12, (LS Mean)	n = 262 4.5	n = 582 11.4	6.9	(5.3, 8.4)	< 0.0001
Resolution of EIMs at Week 12 in subjects with EIMs at Baseline	n = 138 29 (21.1)	n = 282 86 (30.5)	10.3	(1.9, 18.6)	0.0158

a.   Point estimate and 95% CI for treatment difference are based on CMH for categorical endpoints and MMRM for continuous endpoints.

b.   P-values without overall Type-I error control in the integrated summary of efficacy.

Figure 16 Summary of Achievement of SF/APS Clinical Remission Over Time (NRI-C) (ISE1 Population)
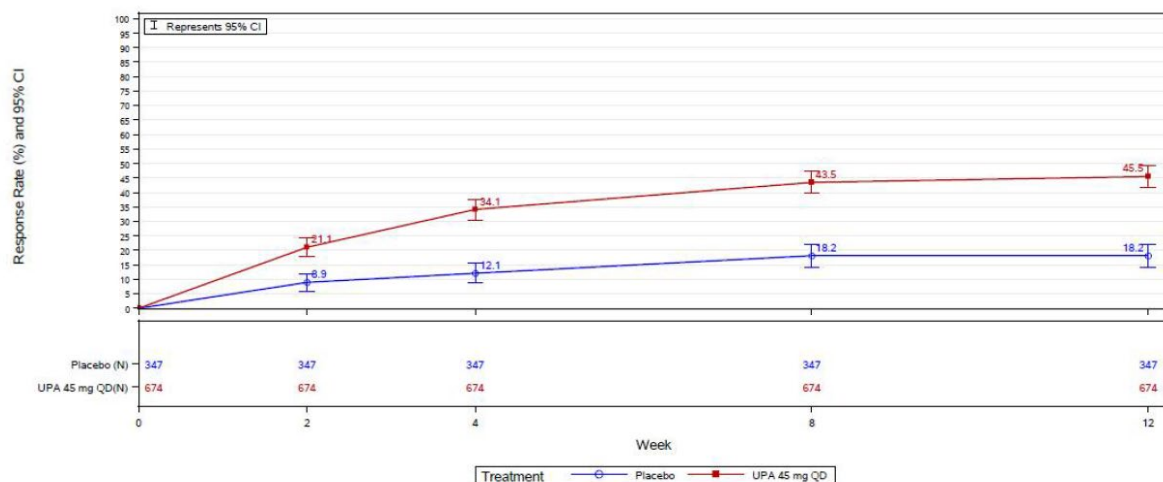
Table 42   Endoscopic co-primary endpoint study M14-431 and M14-433 (ISE1)

	PBO N = 347 n (%)	UPA 45 mg N = 674 n (%)	Response Rate Difference Compared to Placebo		
			Point Estimate	(95% CI)[a]	P-Value[b]
Co-Primary Endpoint					
Endoscopic response at Week 12	29 (8.4)	271 (40.3)	32.2	(27.6, 36.7)	< 0.0001
Key Secondary Endpoint					
Endoscopic remission at Week 12	17 (4.9)	163 (24.2)	19.4	(15.5, 23.2)	< 0.0001

a.   Point estimate and 95% CI for treatment difference are based on CMH.

b.   P-values without overall Type-I error control in the integrated summary of efficacy.

Table 43 Summary of Subgroup Results for Co-Primary Endpoints: Bio-IR and Non-Bio-IR Subjects inStudy M14-433 (NRI-C, ITT1)

	Bio-IR			Non-Bio-IR		
	PBO N = 78 n (%)	UPA 45 mg N = 161 n (%)	Adjusted Treatment Difference (95% CI)[a]	PBO N = 98 n (%)	UPA 45 mg N = 189 n (%)	Adjusted Treatment Difference (95% CI)[a]
CDAI clinical remission at Week 12 (Co-primary US, key secondary EU)	12 (15.6)	71 (43.9)	28.3 (17.0, 39.5)	39 (39.8)	103 (54.3)	14.5 (2.4, 26.5)
SF/APS clinical remission at Week 12 (Co-primary EU, key secondary US)	11 (14.1)	75 (46.8)	32.7 (21.8, 43.7)	28 (28.6)	102 (54.1)	25.5 (14.1, 36.9)
Endoscopic response at Week 12	7 (9.0)	61 (37.9)	29.0 (19.1, 38.8)	16 (16.3)	98 (52.0)	35.7 (25.5, 45.9)

a.   95% CI for difference calculated using normal approximation to the binomial distribution. The calculations are based on NRI-C or NRI only if there are no missing data due to COVID-19.

Table 44 Disease Activity and Symptoms: Upadacitinib 45 mg QD (Placebo-Controlled Induction Treatment Analysis Set) for Bio-IR (NRI-C, ISE1)

	PBO		UPA 45 mg		Response Rate Difference Compared to Placebo	
	N	n (%) or LS Mean (SE)	N	n (%) or LS Mean (SE)	Point Estimate	(95% CI)[a]
Primary Endpoints						
CDAI Clinical remission at Week 12 (US)	248	48 (19.4)	485	197 (40.5)	21.1	(14.8, 27.4)
SF/APS Clinical remission at Week 12 (EU)	248	35 (14.1)	485	205 (42.2)	28.0	(22.0, 33.9)
Endoscopic response at Week 12	248	13 (5.3)	485	173 (35.7)	30.7	(25.8, 35.7)
Key Secondary Endpoints						
Steroid free and CDAI clinical remission at Week 12	96	10 (10.5)	178	65 (36.5)	26.2	(17.3, 35.1)
CDAI Clinical remission at Week 4	248	42 (17.1)	485	149 (30.7)	13.7	(7.8, 19.7)
CR-100 at Week 2	248	33 (13.3)	485	162 (33.4)	20.1	(14.2, 25.9)
CR-100 at Week 12	248	67 (26.9)	485	258 (53.2)	26.4	(19.5, 33.2)
Clinical remission per SF/APS at Week 4	248	19 (7.7)	485	157 (32.4)	25.0	(19.8, 30.2)
Steroid free and clinical remission per SF/APS at Week 12	96	6 (6.3)	178	67 (37.6)	31.5	(23.4, 39.7)
Endoscopic remission at Week 12	248	7 (2.8)	485	95 (19.6)	16.7	(12.7, 20.8)
Change from Baseline in FACIT-Fatigue at Week 12	185	3.8 (0.79)	418	11.6 (0.55)	7.8	(6.0, 9.6)
Change from Baseline in IBDQ total score at Week 12	186	20.228 (2.4460)	420	46.644 (1.7085)	26.416	(20.722, 32.061)
CD-related hospitalizations at Week 12 (AO)	248	20 (8.1)	485	28 (5.8)	-2.3	(-6.3, 1.7)
Resolution of EIMs at Week 12	96	15 (15.8)	206	65 (31.6)	16.7	(7.3, 26.1)

a. Point estimate and 95% CI for treatment difference are based on CMH for categorical endpoints and MMRM for continuous endpoints.

Results of Subjects Enrolled in the Extended Treatment Period

Overall, 122 subjects who did not achieve clinical response to upadacitinib 45 mg QD at Week 12 received upadacitinib 30 mg for an additional 12 weeks. Integrated data from the 2 induction studies showed that 52.7% of subjects receiving upadacitinib 45/30 mg achieved SF/APS clinical response at Week 24. In addition, 29.8% and 24.7% of subjects receiving upadacitinib 45/30 mg achieved clinical remission per CDAI and per SF/APS, respectively, at Week 24, and 13.2% of subjects achieved endoscopic response at Week 24 (**Table 45**).

Among subjects who achieved clinical response at Week 24, enrolled in Cohort 3 of Study M14-430, and were included in this analysis as of the 30 March 2022 data cut-off, the efficacy results were generally maintained after 52 weeks of maintenance treatment

Table 45 Efficacy Results of Subjects Enrolled in the Extended Treatment Period (NRI-C, ISE2)

	Upadacitinib 45/30 mg QD	
Endpoint	Week 24 of Induction Studies N = 122	Week 52 of M14-430 Cohort 3 N = 51
Subjects (%) with:		
CDAI clinical remission	29.8	23.5
SF/APS Clinical remission	24.7	25.5
Endoscopic response	13.2	21.6
SF/APS Clinical response	52.7	41.2

Table 46 Summary of Co-Primary and Key Secondary Endpoints at Week 52 for Maintenance Study M14-430 Substudy 1 (NRI-C, ITT1 Population)

Treatment Endpoint (at Week 52)	PBO N = 165 Estimate	UPA 15 mg N = 169 Estimate	Differences Compared with Placebo Point Estimate (95% CI)[a]	P-Value	UPA 30 mg N = 168 Estimate	Differences Compared with Placebo Point Estimate (95% CI)[a]	P-Value
Co-primary Endpoints							
CDAI Clinical remission (co-primary US, secondary EU), %	15.1	37.3	23.7 (15.2, 32.1)	< 0.0001[b]	47.6	32.8 (23.9, 41.6)	< 0.0001[b]
SF/APS Clinical remission (co-primary EU, secondary US), %	14.4	35.5	21.9 (13.7, 30.0)	< 0.0001[b]	46.4	31.8 (23.2, 40.3)	< 0.0001[b]
Endoscopic response (co-primary), %	7.3	27.6	21.0 (13.6, 28.4)	< 0.0001[b]	40.1	33.7 (26.0, 41.3)	< 0.0001[b]
Key Secondary Endpoints							
Endoscopic Remission, %	5.5	19.1	14.4 (7.7, 21.0)	< 0.0001[b]	28.6	23.6 (16.1, 31.0)	< 0.0001[b]
Corticosteroid-free CDAI clinical remission among all subjects (US), %	14.5	36.7	23.8 (15.5, 32.1)	< 0.0001[b]	46.4	32.2 (23.4, 40.9)	< 0.0001[b]
Corticosteroid-free CDAI clinical remission among subjects on steroid at Baseline (US), %	(n = 61) 4.9	(n = 63) 39.7	35.4 (23.3, 47.5)	< 0.0001[b]	(n = 63) 39.7	32.3 (20.1, 44.5)	< 0.0001[b]
Corticosteroid-free SF/APS clinical remission among all subjects (EU), %	14.4	34.9	21.3 (13.1, 29.5)	< 0.0001[b]	44.6	30.0 (21.4, 38.6)	< 0.0001[b]
Corticosteroid-free SF/APS clinical remission among subjects on steroid at Baseline (EU), %	(n = 61) 4.9	(n = 63) 38.1	33.0 (20.4, 45.6)	< 0.0001[b]	(n = 63) 38.1	33.6 (21.4, 45.8)	< 0.0001[b]
CR-100 %	15.2	41.4	27.1 (18.3, 35.8)	< 0.0001[b]	51.2	36.4 (27.5, 45.2)	< 0.0001[b]

Treatment Endpoint (at Week 52)	PBO N = 165 Estimate	UPA 15 mg N = 169 Estimate	Differences Compared with Placebo Point Estimate (95% CI)[a]	P-Value	UPA 30 mg N = 168 Estimate	Differences Compared with Placebo Point Estimate (95% CI)[a]	P-Value
Maintenance of CDAI Clinical remission (US), %	(n = 94) 21.2	(n = 101) 49.5	31.6 (19.6, 43.6)	< 0.0001[b]	(n = 92) 65.2	43.4 (31.4, 55.5)	< 0.0001[b]
Maintenance of SF/APS Clinical remission (EU), %	(n = 101) 19.6	(n = 105) 50.5	31.9 (20.1, 43.6)	< 0.0001[b]	(n = 105) 60.0	39.7 (27.8, 51.7)	< 0.0001[b]
Change from Baseline in FACIT-Fatigue (MMRM), LS Mean	(n = 40) 12.0	(n = 78) 14.3	2.3 (-0.6, 5.2)	0.1149	(n = 94) 16.1	4.1 (1.3, 6.9)	0.0039[b]
Change from Baseline in IBDQ (MMRM), LS Mean	(n = 41) 46.4	(n = 78) 59.3	12.9 (4.3, 21.4)	0.0033[b]	(n = 94) 64.5	18.1 (9.8, 26.4)	< 0.0001[b]
CDAI Clinical remission and endoscopic remission (US), %	3.7	14.8	12.2 (6.3, 18.1)	0.0001[b]	23.2	19.8 (13.0, 26.6)	< 0.0001[b]
SF/APS Clinical remission and endoscopic remission (EU), %	4.3	13.7	10.0 (4.0, 16.0)	0.0011[b]	22.6	18.2 (11.3, 25.0)	< 0.0001[b]
CD-related hospitalization during maintenance (AO), %	12.0	11.2	-0.8 (-10.4, 8.8)	0.8742	7.8	-4.2 (-13.1, 4.7)	0.3570
Resolution of EIMs in subjects with EIMs at BL, %	(n = 66) 15.2	(n = 61) 24.6	9.6 (-3.4, 22.6)	0.1476	(n = 73) 35.6	22.0 (9.3, 34.8)	0.0007[b]

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A total of 450 subjects who achieved clinical response after 12-week treatment with upadacitinib 45 mg and were re-randomized to and received 15 mg or 30 mg were included in the analyses (ISE3 population) with a follow up to 196 weeks as of the data cut-off. The number of subjects tends to decrease over time and is low beyond Week 100 as Study M14-430 is ongoing and most subjects have not yet reached the later visits as of the data cut-off.

The results of the integrated analysis support consistent, sustained improvements in disease activity and symptoms during treatment with upadacitinib 15 mg or 30 mg as maintenance/long-term therapy, with results maintained from Week 52 through Week 100.

Summary of Achievement of Clinical Remission per PROs at Scheduled Visits (AO) (ISE3 Population) Week 100

Week 100

UPA 15 mg QD N=38, n=32 (84.2% (95%CI) [72.6, 95.8]

UPA 30 mg QD N=53, n= 39 (73.6%) 95%CI) [61.7, 85.5]

Integrated Maintenance (Substudy 1) and LTE (Substudy 2) Results

The results support consistent, sustained improvement in disease activity and symptoms (clinical remission, clinical response), endoscopic assessments (endoscopic response, endoscopic remission), and improvements in QoL during treatment with upadacitinib 15 mg or 30 mg as maintenance/long-term therapy, with results maintained from Week 52 through Week 100. Greater efficacy was noted with upadacitinib 30 mg compared with 15 mg, overall, across all endpoints.

Among subjects who experienced inadequate response and received open-label (OL) upadacitinib 30 mg as rescue therapy, percentages of subjects achieving CR-100 and clinical remission increased from 12 to 24 weeks after receiving the rescue therapy for those initially on placebo and upadacitinib 15 mg. Additionally, subjects who received rescue treatment had improvement in the markers of inflammation hs-CRP and FCP.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

With this submission, the MAH seeks to add a new indication for Rinvoq (Upadacitinib) for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. This application is supported by data from two phase 3 induction studies (M14-431 and M14-433) and one phase 3 maintenance study (M14-430 Substudy 1) which were all double-blind, randomised, placebo-controlled multi-centre studies (**Figure 6** and

Table 3).

Additional information is provided from the dose finding study (M13-740) and the ongoing long term extension study (M14-430 Substudy 2).

These studies have been performed in both the US and EU as there are different expectances on the clinical outcomes where CDAI is used for the FDA analyses and PRO 2 is used for EU analyses.

As stated in the EMA Guideline (CPMP/EWP/2284/99 Rev. 2 *Guideline on the development of new medicinal products for the treatment of Crohn's disease*) "*to fulfil a claim for the treatment of Crohn's disease, it is expected that at least two confirmatory trials are provided*". This is considered as fulfilled. The MAH also received Scientific Advice at the CHMP (EMEA/H/SA/3190/5/2017/II and clarification letter EMA/660515/2018), where the study design with two replicate phase 3 induction studies (M14-431 and M14-433) and one phase 3 maintenance study (M14-430 Substudy 1) was discussed and approved. Most of the CHMP advice were followed with some minor deviations discussed below.

The dose finding study (M13-740) included a double-blind (DB) placebo-controlled 16-week induction treatment that assessed the safety, efficacy, and pharmacokinetics versus placebo followed by a 36-week DB maintenance (extension) period. Subjects who completed Study M13-740 were eligible to enrol in the ongoing LTE Study M14-327.

Dose selection was informed by the analysis of the 16-week safety, efficacy, pharmacokinetic, and exposure-response data from Phase 2 CD Study M13-740, which evaluated 5 induction doses of upadacitinib using the immediate-release (IR) formulation (3, 6, 12, or 24 mg twice daily [BID] or 24 mg QD) versus placebo. The results from Study M13-740 demonstrated the clinical and endoscopic efficacy of upadacitinib compared to placebo across several endpoints with doses of 6 mg BID and higher. Pharmacokinetic analyses have shown that the 12 mg BID and 24 mg BID doses of the IR formulation provided similar daily exposures to the 30 mg QD and 60 mg QD dose of the extended-release (ER) formulation, respectively. Simulations based on the exposure-response analyses showed that doses higher than 45 mg QD (e.g., 60 mg QD) were predicted to provide minimal additional efficacy (2% to 5% increase), while a dose lower than 45 mg QD (e.g., 30 mg QD) predicted 5% to 7% lower efficacy for the endoscopic endpoints compared to the 45 mg QD dose.

Based on pathophysiology and data from other targeted immunomodulatory therapies, a lower dose for maintenance was expected to be effective once the initial high disease burden is reduced. Therefore, after induction treatment with 45 mg QD, 15 mg and 30 mg QD doses were chosen for maintenance treatment.

The upadacitinib 6 mg BID and 12 mg BID doses used in the maintenance dose selection CD Phase 2 Study M13-740 showed statistically significantly higher endoscopic response at Week 12/16 compared to placebo. Following induction with upadacitinib 45 mg QD, lower doses of upadacitinib 15 mg QD and 30 mg QD were therefore expected to maintain efficacy while minimizing dose dependent risks that may be observed with long-term use of higher doses.

The chosen dosing regimen for the phase 3 study programme was considered adequate by the CHMP. The induction dosing regimen was discussed and endorsed in the CHMP advice.

The Phase 3 program includes two induction studies (Study M14-431 and Study M14-433) which consist of an initial DB 12-week induction period with upadacitinib 45 mg with an unequal randomisation 2:1 for active treatment: placebo (ISE1 combined analyses induction studies). There was a possibility for additional 12-week extended treatment period with (1) upadacitinib 30 mg for subjects who did not achieve clinical response to upadacitinib 45 mg, or (2) upadacitinib 45 mg for subjects who did not achieve clinical response to placebo, at Week 12 of the induction Period. Study M14-431 also included an OL induction cohort to ensure a sufficient number of responders for Study

M14-430. This is accepted but it was recommended in the CHMP scientific advice that OL cohort should be stratified in the maintenance study by the previous study source which has been performed. This has been performed by the MAH.

Further, the separation of the conventional failure and biologic failure subgroups is endorsed. However, it would have been preferred from a clinical perspective to add an arm with active treatment, in study M14-433 to provide relevant evidence on the added clinical value after a 12-week induction treatment period with respect to the current standard of treatment in patients that have not previously failed biologics. However, this was not considered necessary with regard to an overall conclusion on benefit risk. Therefore, the lack of an active control arm in study M14-433 is acceptable.

The two Phase 3 induction studies included adult subjects ⩾ 18 and ⩽ 75 years of age with a confirmed diagnosis of CD for at least 3 months and moderately to severely active CD, with average daily very soft stool frequency (SF) score ⩾ 4 or average daily abdominal pain score (APS) ⩾ 2.0, and a centrally-read SES-CD ⩾ 6 (or ⩾ 4 for subjects with isolated ileal disease), excluding the narrowing component.

The use of the PRO-2 criteria for AP and (soft) SF, and the use of the endoscopic appearance of the mucosa (the SES-CD) for inclusion of patients into a CD trial was discussed and accepted in the CHMP advice, and takes sufficiently account of the changing paradigms of CD treatment with the importance of symptoms and mucosal appearance, both for the definition of the severity of the disease, as well as the evaluation of efficacy (e.g. as reflected in the CHMP CD guideline).

The chosen inclusion criteria, equal or higher than 4 for the stool frequency of stools with a baseline Bristol stool scale score of 6-7, or an average daily abdominal pain score of equal to or higher than 2 is accepted and in line with the CHMP advice. As CDAI was used historically the MAH has calculated that these inclusion criteria were met by 85% to 92% of subjects with baseline CDAI 220 to 450 based on pooled data from adalimumab studies.

The inclusion and exclusion were similar but not identical in the two induction studies:

- Study M14-431: Subjects should have had an inadequate response or intolerance to one or more biologic agents (Bio-IR) for CD (adalimumab, certolizumab, infliximab, ustekinumab, vedolizumab, and/or natalizumab). To be considered Bio-IR, subjects were required to meet criteria for types, doses, and durations of prior CD treatment as defined in the protocol.

- Study M14-433: Subjects should have had an inadequate response or intolerance to conventional therapies but had not failed biologic therapy (Non-Bio-IR population) and/or one or more biologic agents for CD (Bio-IR population).

The definitions of the inadequate response or intolerance to prior treatments is acceptable and in line with the CHMP advice and the EU SmPCs for induction regimens. Of note, certolizumab pegol has not a Crohn indication in the EU. At the CHMP's request, the MAH has clarified the use of immunosuppressants at baseline which was low and the timing when immunosuppressants were stopped (except MTX).

Steroids were allowed but should be tapered beginning after 4 weeks of induction treatment. At the CHMP's request, the MAH has provided the information concerning steroid usage during the induction and maintenance studies. In the induction studies patients in the active treatment groups that were treated with steroids at baseline had numerically higher doses compared to placebo but during the 12-week induction treatment duration the standardized dose and proportion of patients were lower in the active treatment groups. This also holds true for the maintenance study at least for the median standardized steroid dose. However, the mean, but not the median, standardized steroid dose was

practically equal in the active treatment groups compared to placebo. The reason for this is unclear but may be explained by some outliers.

Concerning rescue treatment during the maintenance study, the lowest proportion of patients receiving rescue treatment with steroids was in the group treated with 30 mg UPA. In the placebo group a high proportion of patients received rescue treatment where 45.5% received OL UPA 30mg and 18.2% received steroids. The corresponding figures for the 15mg UPA treatment was 26.6% and 13.6% and in the 30 mg maintenance treatment group 21.4% received open-label UPA as rescue treatment and 6.5% received steroids.

In summary, it is agreed with the MAH that subject treated with active UPA for induction received lower steroid doses. This holds true for the median values in the maintenance study as well, although in the maintenance study the subjects had practically the same standardized mean steroid dose (approx. 13.5 mg prednisolone equivalent) during the study. This may be explained by outliers. Further, there were fewer subjects on steroids in the active treatment group both in induction and maintenance active treatment compared to placebo.

Section 4.2 of the SmPC states that "*In patients who have responded to treatment with upadacitinib, corticosteroids may be reduced and/or discontinued in accordance with standard of care.*"

The co primary endpoints used in the induction studies were:

•   Proportion of subjects with clinical remission per SF/APS at Week 12, and

•   Proportion of subjects with endoscopic response at Week 12.

Clinical response was defined per SF/APS ($\geqslant$ 30% decrease in average daily very soft or liquid SF and/or $\geqslant$ 30% decrease in average daily APS and both not worse than baseline), clinical remission per SF/APS (average daily very soft or liquid SF $\leqslant$ 2.8 and not worse than baseline and average daily APS $\leqslant$ 1 and not worse than baseline) and enhanced SF/APS clinical response ($\geqslant$ 60% decrease in average daily very soft or liquid SF and/or $\geqslant$ 35% decrease in average daily APS) and both not worse than baseline. The clinical response criteria are acceptable to the CHMP.

Endoscopic response is defined as decrease in SES-CD > 50% from Baseline of the induction study (or for subjects with an SES-CD of 4 at Baseline of the induction study, at least a 2 point reduction from Baseline), as scored by central reviewer.

Endoscopic remission is defined as SES-CD <= 4 and at least 2-point reduction from Baseline and no subscore > 1 in any individual variable, as scored by central reviewer. The endoscopic remission criteria are not so stringent as would have been expected. Please see below.

The co primary endpoints are accepted although endoscopic remission would be the recommended endoscopic endpoint as discussed in the EMA CD guideline. But, for an induction study at a relatively early time point this may be acceptable. Further, endoscopic remission is a highly ranked secondary endpoint in the induction studies. In addition, there are more key secondary endpoints including proportion of subjects with clinical remission per CDAI (CDAI < 150) at week 12, proportion of subjects with clinical remission per PROs at Week 4 and proportion of subjects who discontinue corticosteroid use for CD and achieve clinical remission at Week 12, in subjects taking corticosteroids for CD at Baseline.

However, the same co-primary endpoints are applied for the maintenance study evaluated at week 52. Here the endoscopic remission would be a more appropriate endpoint. Further, as discussed in the CHMP advice it is considered that even the definition of endoscopic remission is not so strong as

expected. The international organisation of IBD (IOIBD) has proposed a definition of SES-CD≤2. This endpoint is presented but not as a high ranked secondary endpoint.

In addition, there are several highly ranked secondary endpoints such as proportion of subjects with clinical remission per CDAI (CDAI < 150), corticosteroid free remission, change in IBDQ and change in FACIT. The remaining secondary endpoints is considered adequate and especially the endpoint steroid free clinical remission is highly important. It would have been preferred to at least have the stringent endpoint for endoscopic remission SES-CD 0-2 as a higher ranked endpoint as the data is available.

The definition of the disease severity for SES-CD score is 0-2 points healed, 3-6 points mild disease, 7-16 points, moderate disease and severe disease>16. However, these are not defined for response of therapy.

To conclude, the MAH has chosen the co-primary endpoint endoscopic response although endoscopic remission is the preferred endpoint in the updated EMA GL and also suggested in the CHMP advice. However, as several stringent endoscopic assessments including endoscopic remission (SES-CD $\leqslant$ 4 and at least a 2-point reduction versus baseline and no subscore > 1 in any individual variable) and mucosal heling (SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore $\geqslant$ 1 at baseline) showed statistically significant and clinically relevant results this has been considered acceptable by the CHMP.

This is one of the first MAAs for CD where PROs are used as a co-primary endpoint together with effect on intestinal mucosal inflammation as described in the updated EMA guidelines. This brings some uncertainty concerning the relevance of the endpoints. However, the PROs stool frequency and abdominal pain are often the most bothersome symptoms for the patients suffering from CD. The earlier CDAI score used in clinical trials for CD treatment includes these symptoms as well but also general wellbeing, the presence of extraintestinal symptoms, the presence of a palpable abdominal mass and has several limitations including a complex calculation and high score has been shown even for patient with irritable bowel syndrome (IBS). Therefore, with any of these symptoms score it is crucial to combine the clinical score with an endoscopic assessment as a co-primary endpoint which is the case in these studies. Further, the CDAI score was included as a ranked secondary endpoint in the EU and the co primary endpoint it the separate SAP for US/FDA. This makes it possible to a certain limit to compare the results for SF/APS and CDAI considering that CDAI has been used as an endpoint in previous applications for treatments of Crohn's disease in EU as well.

In general, the baseline demographics and baseline characteristics were similar in the treatment group in all main studies. However, there were slightly more men in the studies which is not in line with the general epidemiology of Crohn's disease. At the CHMP's request, the MAH has indicated that one important factor for that less than half the subjects included in the study were female could be related to the strict contraception requirements for women of childbearing potential. As older studies usually have had a slightly higher proportion of women compared to men these requirements may have been strengthened by time. Further, the MAH has provided the results of the primary endpoint comparing the results between females and males. According to the MAH results are consistent among female vs male subjects but numerically, it seems that a higher proportion of men responded to treatment with UPA. This was considered acceptable by the CHMP and the issue was not further pursued.

Baseline characteristics for patients that proceeded to the maintenance studies were similar to the patients in the induction studies.

The sample size calculations and assumptions seem adequate. The number of subjects included is in line with earlier procedures and approvals concerning treatment in Crohn´s disease.

The randomisation and blinding procedures are acceptable.

Within each study, different sets of primary and key secondary endpoints were defined for US/FDA and EU/EMA regulatory purposes. This is acceptable to CHMP.

Each of the SAPs for the phase 3 studies was finalized prior to the respective database unblinding.

All three phase 3 studies include several study parts and/or cohorts of patients. Several analysis populations have been defined accordingly. The ITT1 population is the population addressing the primary objective in each of the studies.

The primary estimand for the primary endpoints for each of the phase 3 studies handles the intercurrent Event (ICE) premature discontinuation of study drug with a treatment policy approach and initiation or dose escalation of CD-related corticosteroids with a composite approach. This is acceptable to the CHMP.

The handling of missing data due to COVID-19 is acceptable since it seems reasonable to assume such data to be missing at random (MAR). The missing data handling for binary endpoints is in line with the composite estimand. The MMRM method used for continuous endpoints is dependent on the MAR assumption.

The overall type I error rate of the primary and the ranked secondary endpoints are controlled using the fixed-sequence multiple testing procedure. In the Maintenance study, alpha is split between the doses and a graphical procedure is applied. For each study those methods are standard and uncontroversial. In this context, the Maintenance study is regarded as a separate study although incorporating the same subjects as in the induction studies. This is acceptable since the maintenance study is considered to address a different scientific question.

At the CHMP's request, the MAH addressed the question of whether "inadequate response or lost response" relates to historical flares of the disease only, or to the current episode of high disease activity. The MAH was asked to discuss whether such a distinction of the patients can be made, and in case this is possible, analyse the subgroups for the main efficacy parameters. The MAH describes that the start date of the current episode of moderately to severely active Crohn's disease (CD) was not captured, and sites were not required to distinguish between current or historical treatment failures. As most subjects had failed two or more treatments, the number of subjects who had failed only conventional therapies or only a biologic, either in the past or recently, likely be inconclusive. This is accepted as in clinical practice, medications that has failed historically would seldom be prescribed again.

In addition, a clarification of the definition of resolution of EIM, hereunder to clarify what kind of extra intestinal manifestations that improved/resolved and how the resolution was measured was requested by the CHMP. The MAH described how EIMs were analysed and further provided analyses of classic and arthopathy EIMs separately. Clinically relevant benefits of the resolution of EIMs were seen both in induction and maintenance study. This is an important finding and data on resolution of extra-intestinal manifestation has been included in Section 5.1 of the SmPC.

Efficacy data and additional analyses

Induction studies M14-431 and M 14-433

In the summary of efficacy, the MAH has presented the combined data from these studied stratified on bio experience. The results from these studies were similar and are discussed in conjunction in this section.

A total of 495 and 526 subjects were randomized in Study M14-431 (Bio-IR population) and Study M14-433 (Non-Bio-IR and Bio-IR populations), respectively.

In Study M14-433, 45.4% of enrolled subjects were Bio-IR and 54.6% were Non-Bio-IR. Study M14-431, by design, only enrolled subjects with prior inadequate response and intolerance to biologics, with 60.8% of subjects having failed at least 2 biologics

Study M14-431 included patients with incomplete response to biologic therapies. At week 12 the results for the clinical remission co-primary endpoint showed that 39.8% of subjects treated with 45mg upa QD achieved clinical remission per PROs compared to 14% of the placebo. In the endoscopic co primary endpoint endoscopic response, 34.6% of patients in active treatment responded compared to 3.5% in the placebo group. For the US/FDA clinical co primary endpoint CDAI remission the corresponding figures were 38.9 % for active treatment and 21,1% for placebo. All these analyses had high statistical significance with p<0.0001.

Induction study M14-433 included patients with inadequate response or intolerance to conventional therapies but had not failed biologic therapy (Non-Bio-IR population) and/or one or more biologic agents for CD (Bio-IR population). At week 12 the results for the co primary clinical endpoints showed that 50.7% of patients in active treatment responded with clinical remission per PROs compared to placebo 22.2%. For the co primary endpoint endoscopic response 45.5% responded in active treatment arm compared to 13.1% in placebo group. The corresponding figures for CDAI was 49.5% in active treatment with 29.1% in the placebo group.

In both induction studies all the key secondary clinical endpoints such as corticosteroid free clinical remission and QoL showed highly statistically significance and clinically relevant results.

Concerning the important endpoint key secondary endoscopic remission 19.1% reached this endpoint in study M14-431 compared to 2.3% in the placebo group. In study M14-433 the corresponding results were 28.9% and 7.4% respectively. In addition, the more stringent endoscopic remission endpoint (SES-CD ulcerated surface subscore-mucosal healing) showed beneficial results for active treatment where 17% reached this endpoint in study M13-431 compared to 0 patients in placebo group. In study M14-433 the corresponding figures were 25%& and 55 respectively p<0.0001.

The induction dosing 45 mg QD in 12 weeks is acceptable. However, the proposal for extended induction treatment "*For patients who have not achieved adequate therapeutic benefit after the initial 12-week induction, prolonged induction for an additional 12 weeks with a dose of 30 mg once daily may be considered. For these patients, upadacitinib should be discontinued if there is no evidence of therapeutic benefit after 24 weeks of treatment*" was further discussed at the CHMP's request:

The patients in the extended treatment had longer treatment duration, were generally older but had approximately the same CDAI and SES-CD score. Interestingly the mean baseline laboratory values for (hs)CRP and FCP were lower in the extended treatment group. This might imply that, apart from being a treatment effect, some of these patients rather may suffer from a more permanent bowel impairment such as fibrosis. Therefore, the MAH was requested to further analyze if the patients responding to extended treatment had any signs of higher inflammatory burden such as objective laboratory markers (hs-CRP, FCP) to evaluate if that would be a possible option to guide the profession when deciding if a patient is a candidate for extended treatment. However, these analyses showed no support for using hs-CRP and FCP to guide which patients that may be appropriate for extended treatment.

Further the MAH describes that over half of the patients receiving extended treatment achieved clinical SF/APS response and about a quarter of the patients reached clinical remission in SF/APS score at

week 24. In addition, in the 35 subjects who had no improvement in SF nor in APS from Baseline to Week 12 one third achieved SF/APS clinical response at Week 24.

The MAH states that there were no major differences in safety profiles between the 12-week induction with upadacitinib 45 mg and the 24-week treatment with upadacitinib 45 mg/30 mg, with the exception of overall SAEs (primarily driven by worsening of CD). Further, there were no GI perforations during the extended treatment for the 122 subjects receiving extended treatment 30mg QD after 45 mg QD induction treatment. See also 2.5.2.

In conclusion, there seems to be a certain number of patients who benefit from extended treatment. Therefore, it could be beneficial for some patients to have the opportunity of extended treatment in this difficult to treat population. This is adequately reflected in the Section 4.2 of the SmPC.

The results of the combined analyses of the induction studies for the primary and key secondary endpoints are in line with the results from the separate induction studies.

Study M14-430 (Maintenance)

The first 502 subjects who were randomized and received at least one dose of study drug in Study M14-430 Substudy 1 Cohort 1 were included in the ITT1 Population for the primary efficacy analysis. Among these subjects, 75.9% completed study treatment.

Maintenance treatment with upadacitinib 15 mg or 30 mg was superior to placebo in achieving clinical remission (per CDAI and per SF/APS) and endoscopic response at Week 52. Most key secondary endpoints under the pre-defined strategy for overall Type-I error control were achieved with upadacitinib 15 mg and 30 mg treatment compared with placebo. Superiority was observed for endoscopic remission and the more stringent endpoint of deep remission (combined clinical and endoscopic remission), as well as for steroid-free clinical remission irrespective of steroid use at baseline. The result for the higher dose was overall more robust but clinically relevant results were found also for the lower maintenance dose.

However, the definition of endoscopic co-primary endpoint at week 52 is not the most relevant as it is preferred to aim at endoscopic remission instead of response because it is assumed that it is important to achieve healing of the mucosa to prevent long-term structural complications in the bowel. However, as the totality of data especially including the more strictly defined endoscopic endpoints clinical remission SES-SD <4 and also SES-CD 0-2 met statistically significance that was deemed as clinically relevant and therefore it is considered that the efficacy on intestinal mucosa is shown.

Most key secondary endpoints under the pre-defined strategy for overall Type-I error control were achieved with upadacitinib 15 mg and 30 mg treatment compared with placebo. Superiority was observed for endoscopic remission and the more stringent endpoint of deep remission (combined clinical and endoscopic remission), as well as for steroid-free clinical remission irrespective of steroid use at Baseline. Maintenance of clinical remission was achieved among subjects in clinical remission at Week 0. Improvements from Baseline for FACIT-Fatigue and resolution of EIMs continued with upadacitinib 30 mg maintenance therapy. Results of stringent endoscopic assessments (absence of ulcers by endoscopy [US]/mucosal healing [EU], SES-CD 0-2) and mean changes in markers FCP and hs-CRP support continued improvement of inflammation up to Week 52 on upadacitinib 15 mg or 30 mg QD.

The suggested maintenance dosing gives an opportunity to choose between 15 or 30 mg QD according to the patient's severity of disease and response to earlier treatment. This is accepted. However, as concluded in the JAK referral there are concerns regarding the 30 mg dose for long term treatment in patients with risk for MACE, malignancy and VTE. Hence, at the CHMP's request, a statement was included in the SmPC. See also 2.5.1.

The dosing recommendations for maintenance were therefore agreed as follows in Section 4.2 of the SmPC:

The recommended maintenance dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation:

- *A dose of 15 mg is recommended for patients at higher risk of VTE, MACE and malignancy (see section 4.4).*

- *A dose of 30 mg once daily may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy (see section 4.4) or who do not show adequate therapeutic benefit to 15 mg once daily.*

- *The lowest effective dose to maintain response should be used.*

The OLE is ongoing and relatively few individuals have reached the later visits. Data from week 100 indicates a sustained efficacy of treatment.

Altogether the clinical study programme in Crohn´s disease shows a robust clinical efficacy in nearly all chosen aspects of the disease.

The following indication was submitted by the MAH: "*Upadacitinib is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent, or for whom such therapies are not advisable.*"

This was in general acceptable based on the included patient population and vastly in line with other products with IBD indication including the UC indication for upadacitinib. However, the last section of the proposed indication "*or for whom such therapies are not advisable*" was not accepted by the CHMP as it is not in line with the population included. In response to the 1st Request for Supplementary Information (RSI), the MAH submitted a revised wording for the claimed indication in which this claim has been removed as requested by the CHMP: "*RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.*" The revised indication was acceptable to CHMP.

2.4.4. Conclusions on the clinical efficacy

The two pivotal induction studies demonstrated a clinically relevant and statistically significant superiority of Upadacitinib 45 mg compared to placebo in inducing the co-primary endpoint, clinical remission in patients with moderate to severe Crohn's disease. A superior efficacy was seen in symptomatic relieve already at week 2 (CR-100) and week 4 (SF/APS), and after 12 weeks of induction treatment with 45 mg upadacitinib QD, 45.5% of patients achieved clinical SF/APS remission with active treatment compared to 18.2% in the placebo group in the integrated analyses. Further, important clinical key secondary endpoints such as steroid free clinical remission and QoL showed highly statistically significant and clinically relevant result at week 12.

The co-primary endpoint endoscopic response has well demonstrated a significant difference between active treatment and placebo in the integrated induction analyses with 40.3% responders in active treatment compared to 8.4% in placebo group. For endoscopic remission the corresponding figures were 24.4% and 4.9% for active treatment and placebo. In addition, Upadacitinib provided a beneficial effect compared to placebo regarding the strictest endpoint, mucosal healing (SES-CD) at week 12

with a treatment difference of 17% and 20% respectively for study M14-431 and M14-433 compared to placebo This is an important finding.

In the maintenance study statistically significant (p<0.0001) and clinically relevant treatment differences between both Upadacitinib doses (15 mg and 30 mg) and placebo were observed for the co-primary and all key secondary endpoints with the exception of CD hospitalisation and effect on extraintestinal manifestations (EIM) for the 15 mg. There was a clear dose response showing more robust effect with the higher maintenance dosing. For example, clinical remission per SF/APS score was reached by 46.4% of patients treated with 30 mg maintenance dosing compared to 35.5% treated with 15 mg. The corresponding figure for placebo was 15.1%. Especially in patients with a high disease burden and in patients in need of a prolonged induction regimen, the 30 mg dose seemed to provide a more pronounced beneficial effect over the 15 mg dose. This is adequately reflected in the Section 4.2 of the SmPC.

At the CHMP's request, the MAH accepted to revise the indication as follows: "*RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent*."

The CHMP concluded that the efficacy shown in the clinical program investigating upadacitinib in the treatment of Crohn's disease is robust and clinically relevant.

2.5. Clinical safety

Introduction

The upadacitinib CD global clinical development program consists of a Phase 2 induction and maintenance study (Study M13-740), a Phase 2 OLE study (Study M14-327), two Phase 3 induction studies (Study M14-431 and Study M14-433), a Phase 3 maintenance study (Study M14-430 Substudy 1), and a LTE study (Study M14-430 Substudy 2).

The Phase 2 clinical development program evaluated 5 induction doses (3, 6, 12, and 24 mg BID and 24 mg QD) and 4 maintenance doses (3, 6 and 12 mg BID and 24 mg QD) of upadacitinib in Study M13-740 and 2 OLE doses (15 mg and 30 mg QD) in Study M14-327.

The Phase 3 clinical development program evaluated 1 induction dose of upadacitinib (45 mg once QD), and 2 maintenance/LTE doses of upadacitinib (15 mg and 30 mg QD). In the Phase 2 Study M13-740, upadacitinib was administered as an immediate-release formulation, while in the Phase 2 M14-327 and Phase 3 studies, upadacitinib was administered as the once-daily extended-release formulation.

To assess the safety of upadacitinib across clinical studies, subject data were integrated into 6 analysis sets**.** In addition, an additional analysis set was created for Study M14-430 Substudy 2 (M14-430_2), given that the CSR presented in the submission comprises Substudy 1 only. The M14-430_2 Analysis set includes only data collected within Study M14-430 Substudy 2:

Table 47 Integrated Safety Analysis Sets

Analysis Set	Analysis Set Rationale	Analyses	Pooled Studies	Summarized Treatment Groups	Treatment Comparisons[a]
Placebo-Controlled Induction (**PC_IND**)	This analysis set is to provide a comprehensive summary of safety for the primary 12-week induction period, including the estimation of treatment safety effect (UPA 45 mg versus PBO), for subjects in a randomized, DB, PBO-controlled setting.	Short-Term (12-week induction period, DB 45 mg UPA)	M14-433 (Part 1), M14-431 (Part 1)	• DB PBO QD • DB UPA 45 mg QD	• DB UPA 45 mg QD vs. DB PBO
Upadacitinib 45 mg Induction (**45_IND**)	This analysis set allows for estimation of event rates for all Phase 3 subjects exposed to UPA 45 mg.	Short-Term (12-week induction period, all 45 mg UPA)	M14-433 (Part 1 and 2), M14-431 (Part 1, 2, and 3)	• UPA 45 mg QD	• None
Extended Treatment Period (**EXT_TRT**)	This analysis set is to allow for safety assessment of 12 weeks of therapy at the UPA 30 mg dose for subjects who received 12 weeks of induction therapy at UPA 45 mg and did not achieve clinical response and to evaluate the 24-week safety profile compared to the 12-week safety profile within the same individual group of subjects.	Short-Term (12-week induction and 12-week extended periods, all 45 mg UPA followed by 30 mg UPA)	M14-433 (Parts 1 and 2), M14-431 (Parts 1, 2, and 3)	• UPA 45 mg/30 mg QD	• None

Analysis Set	Analysis Set Rationale	Analyses	Pooled Studies	Summarized Treatment Groups	Treatment Comparisons[a]
Randomized Responders Maintenance (**RESP_MAIN**)	The purpose of this analysis set is to conduct pairwise estimates of treatment safety effect for the 52-week maintenance period plus additional LTE time from Study M14-430 Substudy 2 for upadacitinib 30 mg QD vs. placebo and upadacitinib 15 mg QD vs. placebo.	Long-Term (maintenance and LTE periods, 30 mg and 15 mg UPA vs. PBO)	M14-430 Substudy 1 and 2	• DB PBO QD • DB UPA 15 mg QD • DB UPA 30 mg QD	• DB UPA 30 mg QD vs. DB PBO • DB UPA 15 mg QD vs. DB PBO
All Treated Responders by Subject (**ALL_TRT_RESP[subj]**)	This analysis set will be used to estimate event and incidence rates especially for uncommon or rare events, for cohorts of subjects across their entire treatment experience (induction, extended treatment, maintenance, and LTE).	Long-Term (induction, ET, maintenance, and LTE, all Phase 3 studies)	M14-433, M14-431, M14-430	Cohort A: PBO /PBO • PBO (induction) → PBO (maintenance/LTE) Cohort B: UPA 45 mg / PBO • UPA 45 mg (induction or ET) → PBO (maintenance) Cohort C: UPA 45 mg / 15 mg • UPA 45 mg (induction or ET) → UPA 15 mg (maintenance) Cohort D: UPA 45 mg / 30 mg[b] • UPA 45 mg (induction or ET) → UPA 30 mg (maintenance) Cohort E: RESC UPA 30 mg[c] Any UPA(Resp)[d]	• None

Analysis Set	Analysis Set Rationale	Analyses	Pooled Studies	Summarized Treatment Groups	Treatment Comparisons[a]
All Treated Maintenance by Dose (ALL_TRT_MAIN[dose])	The purpose of this analysis set is to provide a descriptive, long-term, non-randomized, summary of selected adverse events by UPA dose or PBO at onset of event across Phase 2 and Phase 3 maintenance/LTE periods.	Long-Term (maintenance and LTE, all Phase 2 and 3 studies)	M13-740, M14-327, M14-430	• PBO(pbo), PBO(45) UPA 15 mg QD, UPA 30 mg QD, All Other UPA Any UPA(Main/LTE)	• None
M14-430 Substudy 2 (M14-430_2)[e]	This analysis set will provide a limited safety assessment of all subjects who received at least 1 dose of study drug in Study M14-430 Substudy 2. Of note, all of the events reported in this dataset are also included in the (ALL_TRT_RESP[subj]) Analysis Set.	Long-Term (LTE periods, 30 mg and 15 mg UPA vs. PBO)	M14-430 Substudy 2	• DB PBO QD • DB UPA 15 mg QD • DB UPA 30 mg QD • OL/ RESC UPA 30 mg QD[f]	• None

a. Treatment comparison for overview of treatment-emergent adverse event (TEAE), overview of treatment-emergent AESI, TEAEs by decreasing frequency, and potentially clinically significant (PCS) laboratory values.
b. Also includes subjects who received UPA 45 mg during induction and did not achieve clinical response but responded to UPA 30 mg during the extended treatment period and received at least 1 dose of UPA 30 mg in maintenance or LTE.
c. Includes all subjects who initially received PBO during induction and in maintenance, lost response and then were rescued and received OL UPA 30 mg during maintenance or LTE. It also includes subjects who received UPA 45 mg during induction who were re-randomized to PBO or UPA 15 mg during maintenance and then lost response and were rescued with OL UPA 30 mg during maintenance or LTE.
d. Includes all Phase 3 subjects who met the analysis set entry criteria and received at least 1 dose of upadacitinib.
e. Includes only data collected within Study M14-430 Substudy 2.
f. Includes subjects who were rescued (in either Study M14-430 Substudy 1 or Substudy 2) and received OL UPA 30 mg QD in Cohort 5 along with subjects who received OL UPA 30 mg QD in Cohort 4, (regardless of what dose they were previously on, including DB UPA 30 mg).

Patient exposure

In the upadacitinib CD global Phase 3 studies, the short and long-term safety profile of upadacitinib in subjects with moderately to severely active CD is supported by data from 833 subjects who received at least 1 dose of upadacitinib and at least 1 dose of study drug during maintenance/LTE. This group of subjects had a mean duration of 75.4 weeks. Of these subjects, 536 (64.3%) and 244 (29.3%) had exposure to upadacitinib for at least 1 year and 2 years, respectively.

Table 48 *Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (PC_IND/45_IND Analysis Sets)*

	PC_IND Analysis Set		45_IND Analysis Set
Cumulative Duration	**Placebo (N = 347)**	**UPA 45 mg (N = 674)**	**UPA 45 mg (N = 938)**
		n (%)	
≥ 1 dose	347 (100)	674 (100)	938 (100)
≥ 4 weeks	332 (95.7)	660 (97.9)	916 (97.7)
≥ 8 weeks	318 (91.6)	641 (95.1)	891 (95.0)
≥ 12 weeks[a]	300 (86.5)	592 (87.8)	818 (87.2)
Mean duration in weeks (SD)	11.4 (2.45)	11.7 (2.01)	11.7 (2.07)

a. For the PC_IND Analysis Set, includes subjects who completed the Week 12 visit within 3 days of Day 84 (Week 12). For the 45_IND Analysis Set, includes subjects who completed the visit within 3 days of the actual scheduled time (i.e., Day 84 for the Week 12 visit and Day 168 for the Week 24 visit).

In the EXT_TRT Analysis Set, there were 142 subjects who received at least 1 dose of UPA 45 mg QD during the 12-week induction period, did not achieve clinical response, and received at least 1 dose of UPA 30 mg QD in the 12-week extended treatment period. The mean (SD) exposure to upadacitinib 45 mg/30 mg was 22.8 (2.85) weeks.

Table 49 Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (RESP_MAIN Analysis Set)

Cumulative Duration	Placebo (N = 223)	UPA 15 mg (N = 221)	UPA 30 mg (N = 229)
	n (%)		
≥ 1 dose	223 (100)	221 (100)	229 (100)
≥ 4 weeks	216 (96.9)	214 (96.8)	226 (98.7)
≥ 8 weeks	176 (78.9)	192 (86.9)	210 (91.7)
≥ 12 weeks	153 (68.6)	181 (81.9)	201 (87.8)
≥ 16 weeks	123 (55.2)	171 (77.4)	185 (80.8)
≥ 20 weeks	112 (50.2)	166 (75.1)	180 (78.6)
≥ 24 weeks	94 (42.2)	147 (66.5)	171 (74.7)
≥ 39 weeks (about 9 months)	64 (28.7)	116 (52.5)	140 (61.1)
≥ 52 weeks (about 1 year)[a]	46 (20.6)	89 (40.3)	107 (46.7)
≥ 78 weeks (about 1.5 years)	25 (11.2)	47 (21.3)	73 (31.9)
≥ 104 weeks (about 2 years)	14 (6.3)	41 (18.6)	49 (21.4)
≥ 130 weeks (about 2.5 years)	5 (2.2)	22 (10.0)	17 (7.4)
≥ 156 weeks (about 3 years)	1 (0.4)	5 (2.3)	4 (1.7)
Mean duration in weeks (SD)	32.4 (33.36)	53.2 (45.55)	59.5 (44.24)
Duration in PY	138.3	225.3	261.3

a.   Includes subjects who completed the Week 52 visit within 3 days of Day 364 (Week 52).

Table 50 Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (ALL_TRT_RESP[subj] Analysis Set

| Cumulative Duration | PBO/ PBO[b] (N = 161) | Induction Dose UPA 45 mg[a] | | | RESC UPA 30 mg[f] (N = 336) | Any UPA(Resp)[g] (N = 833) |
		UPA 45 mg/ PBO[c] (N = 223)	UPA 45 mg/ 15 mg[d] (N = 221)	UPA 45 mg/ 30 mg[e] (N = 300)		
			n (%)			
≥ 1 dose	161 (100)	223 (100)	221 (100)	300 (100)	336 (100)	833 (100)
≥ 4 weeks	161 (100)	223 (100)	221 (100)	300 (100)	328 (97.6)	831 (99.8)
≥ 8 weeks	161 (100)	223 (100)	221 (100)	300 (100)	314 (93.5)	827 (99.3)
≥ 12 weeks	161 (100)	223 (100)	221 (100)	300 (100)	301 (89.6)	812 (97.5)
≥ 16 weeks	155 (96.3)	216 (96.9)	212 (95.9)	295 (98.3)	282 (83.9)	744 (89.3)
≥ 20 weeks	131 (81.4)	179 (80.3)	192 (86.9)	290 (96.7)	270 (80.4)	728 (87.4)
≥ 24 weeks	113 (70.2)	155 (69.5)	181 (81.9)	285 (95.0)	253 (75.3)	708 (85.0)
≥ 39 weeks (about 9 months)	70 (43.5)	86 (38.6)	142 (64.3)	263 (87.7)	195 (58.0)	634 (76.1)
≥ 52 weeks (about 1 year)	48 (29.8)	64 (28.7)	116 (52.5)	232 (77.3)	143 (42.6)	536 (64.3)
≥ 78 weeks (about 18 months)	23 (14.3)	32 (14.3)	60 (27.1)	143 (47.7)	96 (28.6)	323 (38.8)
≥ 104 weeks (about 2 years)	16 (9.9)	22 (9.9)	45 (20.4)	116 (38.7)	62 (18.5)	244 (29.3)
≥ 130 weeks (about 2.5 years)	7 (4.3)	5 (2.2)	28 (12.7)	70 (23.3)	24 (7.1)	142 (17.0)
≥ 156 weeks (about 3 years)	3 (1.9)	3 (1.3)	12 (5.4)	25 (8.3)	0	50 (6.0)
≥ 208 weeks (about 4 years)	0	0	2 (0.9)	1 (0.3)	0	3 (0.4)
Mean duration in weeks (SD)	47.0 (35.45)	44.7 (33.53)	65.4 (45.51)	88.2 (45.13)	56.9 (40.48)	75.4 (46.80)
Duration in PY	144.9	191.1	277.1	507.3	366.2	1203.4

Adverse events

Table 51 Overview of Subjects with Treatment-Emergent Adverse Events (PC_IND/45_IND Analysis Sets)

	PC_IND Analysis Set			45_IND Analysis Set
Subjects With	Placebo (N = 347) n (%)	UPA 45 mg (N = 674) n (%)	Treatment Comparison (95% CI)[a] UPA 45 mg – Placebo	UPA 45 mg (N = 938) n (%)
Any AE	216 (62.2)	439 (65.1)	--	612 (65.2)
COVID-19 AE[b]	1 (0.3)	5 (0.7)	0.4 (-0.6, 1.5)	15 (1.6)
Any SAE	29 (8.4)	54 (8.0)	-0.3 (-3.9, 3.3)	78 (8.3)
Any AE leading to discontinuation of study drug	19 (5.5)	33 (4.9)	-0.6 (-3.5, 2.4)	46 (4.9)
Any severe AE	35 (10.1)	57 (8.5)	-1.6 (-5.4, 2.2)	86 (9.2)
Any AE with reasonable possibility of being related to study drug[c]	78 (22.5)	222 (32.9)	10.5 (4.8, 16.1)	305 (32.5)
Any AE leading to death	0	0	0.0	0
Deaths[d]	0	1 (0.1)[e]	0.1 (-0.5, 0.8)	1 (0.1)

a. SSA risk difference between treatment groups.

b. The term includes PTs of "COVID-19" and "COVID-19 pneumonia" reported in the studies.

c. As assessed by investigator.

d. Includes both treatment-emergent and non-treatment-emergent deaths.

e. Death occurred > 30 days after last dose of study drug.

Table 52 Overview of Treatment-Emergent Adverse Events per 100 PY (PC_IND/45_IND Analysis Sets)

	PC_IND Analysis Set		45_IND Analysis Set
	Placebo (N = 347) (PY = 75.7)	UPA 45 mg (N = 674) (PY = 151.0)	UPA 45 mg (N = 938) (PY = 209.8)
EAER		E (E/100 PY)	
Any AE	593 (783.3)	1308 (866.1)	1732 (825.7)
COVID-19 AE[a]	1 (1.3)	5 (3.3)	15 (7.2)
Any SAE	38 (50.2)	69 (45.7)	102 (48.6)
Any AE leading to discontinuation of study drug	20 (26.4)	55 (36.4)	73 (34.8)
Any severe AE	45 (59.4)	76 (50.3)	118 (56.3)
Any AE with reasonable possibility of being related to study drug[b]	162 (214.0)	522 (345.6)	665 (317.0)
Any AE leading to death	0	0	0
EAIR		n/PY (n/100 PY)	
Deaths[c]	0/75.7	1/151.5 (0.7)[d]	1/210.2 (0.5)

a.   The term includes PTs of "COVID-19" and "COVID-19 pneumonia" reported in the studies.

b.   As assessed by investigator.

c.   Includes both treatment-emergent and non-treatment-emergent deaths.

d.   Death occurred > 30 days after last dose of study drug.

Note: PY is defined as the sum of the study drug duration in the 12-week induction period of all subjects normalized by 365.25 and rounded to 1 decimal place.

Table 53 Overview of Treatment-Emergent Adverse Events per 100 PY (EXT_TRT Analysis Set)

	End of DB Induction[a] (Week 0 – Week 12) (N = 142) (PY = 32.8) E (E/100 PY)	End of OL Extended Treatment[b] (Week 0 – Week 24) (N = 142) (PY = 62.0) E (E/100 PY)
EAER	**E (E/100 PY)**	
Any AE	301 (917.0)	517 (833.9)
COVID-19 AE[c]	1 (3.0)	3 (4.8)
Any SAE	17 (51.8)	40 (64.5)
Any AE leading to discontinuation of study drug	1 (3.0)	11 (17.7)
Any severe AE	19 (57.9)	40 (64.5)
Any AE with reasonable possibility of being related to study drug[d]	128 (390.0)	183 (295.2)
Any AE leading to death	0	1 (1.6)
EAIR	**n/PY (n/100 PY)**	
Deaths[e]	0/32.8	1/62.0 (1.6)[f]

a. All events and exposure time from 12-week induction studies (for the EXT_TRT Analysis Set).
b. All events and exposure time from the Induction and Extended Treatment Periods (for the EXT_TRT Analysis Set).
c. The term includes PTs of "COVID-19" and "COVID-19 pneumonia" reported in the studies.
d. As assessed by investigator.
e. Includes both treatment-emergent and non-treatment-emergent deaths.
f. Death occurred ≤ 30 days after last dose of study drug and was related to COVID-19 infection.

Table 54 *Overview of TEAEs per 100 PY (RESP_MAIN Analysis Set)*

	Placebo (N = 223) (PY = 138.3)	UPA 15 mg (N = 221) (PY = 225.3)	UPA 30 mg (N = 229) (PY = 261.3)	Differences	
				UPA 15 mg – Placebo	UPA 30 mg – Placebo
EAER	**E (E/100 PY)**			**Risk Difference (95% CI)**	
Any AE	554 (400.5)	723 (320.9)	767 (293.5)	-79.6 (-119.3, -39.9)	-106.9 (-144.4, -69.5)
Any COVID-19 AE[a]	10 (7.2)	23 (10.2)	36 (13.8)	3.0 (-3.4, 9.4)	6.5 (-0.4, 13.5)
Any SAE	44 (31.8)	38 (16.9)	47 (18.0)	-14.9 (-25.0, -4.9)	-13.8 (-23.7, -4.0)
Any AE leading to discontinuation of study drug	11 (8.0)	21 (9.3)	17 (6.5)	1.4 (-4.9, 7.6)	-1.4 (-6.9, 4.0)
Any severe AE	44 (31.8)	38 (16.9)	42 (16.1)	-14.9 (-25.0, -4.9)	-15.7 (-25.3, -6.2)
Any AE with reasonable possibility of being related to study drug[a]	139 (100.5)	197 (87.4)	202 (77.3)	-13.0 (-33.4, 7.3)	-23.2 (-42.2, -4.1)
Any AE leading to death	0	0	0	0.0	0.0

a. As assessed by investigator.
b. Includes both treatment-emergent and non-treatment-emergent deaths.
Note: This analysis set includes events from the 45 mg responders who entered Study M14-430 Substudy 1 (Cohort 1) and additional events for those subjects who completed Substudy 1 (Cohort 1) and rolled over to the long-term extension Study M14-430 Substudy 2 (corresponds to a subset of Cohort 5 from Substudy 2), while maintaining the same DB dose. Events begin at the first dose of study drug administered during the maintenance period. Events occurring within the induction period for these subjects are not included.

Table 55 Overview of TEAEs per 100 PY (ALL_TRT_RESP[subj] Analysis Set)

| | PBO/ PBO[b] (N = 161) (PY = 144.9) | Induction Dose UPA 45 mg[a] | | | RESC UPA 30 mg[f] (N = 336) (PY = 366.2) | Any UPA(Resp)[g] (N =833) (PY = 1203.4) |
		UPA 45 mg/PBO[c] (N = 223) (PY = 191.1)	UPA 45 mg/15 mg[d] (N = 221) (PY = 277.1)	UPA 45 mg/30 mg[e] (N = 300) (PY = 507.3)		
EAER			E (E/100 PY)			
Any AE	516 (356.2)	923 (482.9)	1064 (384.0)	1932 (380.8)	1308 (357.2)	4673 (388.3)
Any COVID-19 AE[h]	6 (4.1)	17 (8.9)	25 (9.0)	60 (11.8)	72 (19.7)	164 (13.6)
Any SAE	43 (29.7)	56 (29.3)	53 (19.1)	125 (24.6)	127 (34.7)	317 (26.3)
Any AE leading to discontinuation of study drug	16 (11.0)	11 (5.8)	21 (7.6)	45 (8.9)	42 (11.5)	108 (9.0)
Any severe AE	36 (24.8)	58 (30.3)	54 (19.5)	127 (25.0)	95 (25.9)	290 (24.1)
Any AE with reasonable possibility of being related to study drug[i]	109 (75.2)	273 (142.8)	335 (120.9)	558 (110.0)	315 (86.0)	1342 (111.5)
Any AE leading to death	0	0	0	0	1 (0.3)	1 (< 0.1)

Common Adverse Events

In the PC_IND Analysis Set, the most frequent TEAEs by SOC were infections and infestations (UPA 30.1%, placebo 18.2%), gastrointestinal disorders (UPA 25.4%, Placebo 31.7%), skin and subcutaneous tissue disorders (UPA 15.6%, Placebo 11.6%) and musculoskeletal and connective tissue disorders (UPA 8.3%, Placebo 14.4%). The most frequently reported TEAEs (≥ 5.0% of subjects) were acne, nasopharyngitis, anaemia, and headache in the upadacitinib 45 mg group and worsening of CD, arthralgia, and anaemia in the placebo group. Except for reports of worsening CD in the placebo group, no other TEAE PT occurred in ≥ 10% of subjects in any treatment group. Among the frequently reported TEAEs (≥ 2% of subjects), the frequency of acne, influenza, herpes zoster, and blood creatine phosphokinase increased were higher in the upadacitinib group compared with the placebo group, while worsening CD and arthralgia were more frequent in the placebo group compared with the upadacitinib group.

In the EXT_TRT Analysis Set, the EAERs for the most frequently reported TEAEs (≥ 10 E/100 PY) in the upadacitinib 45 mg/30 mg group through Week 24 were generally similar to rates reported during the initial 12 weeks of upadacitinib 45 mg treatment; except higher rates of worsening of CD (53.2 E/100 PY vs 39.6 E/100 PY), influenza (16.1 E/100 PY vs 12.2 E/ 100 PY), and herpes zoster(11.3 E/100 PY vs 9.1 E/100 PY).

In the RESP_MAIN Analysis Set, the most frequently reported TEAEs (≥ 10 E/100 PY) was Crohn's disease in the upadacitinib 15 mg group, COVID-19 in the upadacitinib 30 mg group, and anemia, Crohn's disease, nausea, and arthralgia in the placebo group. The EAERs of TEAEs reported at ≥ 5 E/100 PY in the placebo group were generally higher than or similar to those in the upadacitinib groups; exceptions included COVID-19 in both upadacitinib groups and upper respiratory tract infection in the upadacitinib 30 mg group, which occurred at a higher rate than in the placebo group.

In the ALL_TRT_RESP[subj] Analysis Set, the most frequently reported TEAEs (≥ 10 E/100 PY) were worsening of CD and nasopharyngitis in the upadacitinib 45 mg/15 mg cohort and worsening of CD in the upadacitinib 45 mg/30 mg cohort.

Table 56 TEAEs Reported in ≥ 2% of Subjects in Any Group by Decreasing Frequency (PC_IND/45_IND Analysis Sets)

MedDRA 24.0 Preferred Term	PC_IND Analysis Set			45_IND Analysis Set
	Placebo (N = 347) n (%)	UPA 45 mg (N = 674) n (%)	Treatment Comparison (95% CI)[a] UPA 45 mg – Placebo	UPA 45 mg (N = 938) n (%)
Any AE	216 (62.2)	439 (65.1)	--	612 (65.2)
Acne	5 (1.4)	39 (5.8)	4.4 (2.1, 6.6)	65 (6.9)
Nasopharyngitis	11 (3.2)	39 (5.8)	2.6 (0.0, 5.2)	46 (4.9)
Anaemia	18 (5.2)	38 (5.6)	0.5 (-2.5, 3.4)	50 (5.3)
Headache	16 (4.6)	35 (5.2)	0.6 (-2.2, 3.4)	46 (4.9)
Crohn's disease	41 (11.8)	33 (4.9)	-6.9 (-10.7, -3.1)	52 (5.5)
Nausea	16 (4.6)	30 (4.5)	-0.2 (-2.9, 2.6)	37 (3.9)
Upper respiratory tract infection	9 (2.6)	29 (4.3)	1.7 (-0.6, 4.1)	34 (3.6)
Pyrexia	9 (2.6)	28 (4.2)	1.6 (-0.7, 3.9)	38 (4.1)
Abdominal pain	17 (4.9)	23 (3.4)	-1.5 (-4.1, 1.2)	29 (3.1)
Blood creatine phosphokinase increased	4 (1.2)	20 (3.0)	1.8 (0.0, 3.6)	26 (2.8)
Influenza	2 (0.6)	20 (3.0)	2.4 (0.8, 4.0)	23 (2.5)
Constipation	5 (1.4)	17 (2.5)	1.1 (-0.8, 2.9)	26 (2.8)
Arthralgia	19 (5.5)	16 (2.4)	-3.1 (-5.8, -0.4)	23 (2.5)
Fatigue	10 (2.9)	16 (2.4)	-0.5 (-2.7, 1.7)	18 (1.9)
Herpes zoster	0	15 (2.2)	2.2 (0.9, 3.5)	20 (2.1)
Rash	10 (2.9)	15 (2.2)	-0.7 (-2.8, 1.5)	21 (2.2)
Cough	6 (1.7)	14 (2.1)	0.4 (-1.5, 2.2)	15 (1.6)
Vomiting	9 (2.6)	13 (1.9)	-0.7 (-2.7, 1.4)	14 (1.5)
Abdominal distension	7 (2.0)	12 (1.8)	-0.2 (-2.1, 1.7)	15 (1.6)
Back pain	14 (4.0)	11 (1.6)	-2.4 (-4.7, -0.0)	13 (1.4)
Diarrhoea	11 (3.2)	10 (1.5)	-1.7 (-3.8, 0.4)	13 (1.4)
Anal fistula	8 (2.3)	4 (0.6)	-1.7 (-3.5, 0.1)	5 (0.5)

a. SSA risk difference between treatment groups.

Notes: Subjects were counted once in each row, regardless of the number of events they may have had.

Percentages are displayed by decreasing frequency in the upadacitinib 45 mg group.

Table 57 *TEAEs Reported in ≥ 2% of Subjects in Any Group by Decreasing Frequency (Randomized Responder Maintenance Analysis Sets)*

Number and Percentage of Subjects with Treatment-Emergent Adverse Events
by Decreasing Frequency by Preferred Term
(Randomized Responders Maintenance Analysis Set)

	Placebo (N=223) n (%)	UPA 15 mg QD (N=221) n (%)	UPA 30 mg QD (N=229) n (%)	Treatment Comparison (95% CI) UPA 15 mg QD - PBO	Treatment Comparison (95% CI) UPA 30 mg QD - PBO
Preferred Term					
Any adverse event	172 (77.1)	174 (78.7)	188 (82.1)		
COVID-19	9 (4.0)	21 (9.5)	29 (12.7)	5.5 (0.8, 10.1)	8.6 (3.6, 13.7)
Crohn's disease	60 (26.9)	43 (19.5)	22 (9.6)	-7.4 (-15.3, 0.4)	-17.3 (-24.3, -10.3)
Pyrexia	6 (2.7)	15 (6.8)	20 (8.7)	4.1 (0.2, 8.0)	6.0 (1.8, 10.3)
Arthralgia	14 (6.3)	10 (4.5)	16 (7.0)	-1.8 (-6.0, 2.4)	0.7 (-3.9, 5.3)
Headache	4 (1.8)	7 (3.2)	15 (6.6)	1.4 (-1.5, 4.3)	4.8 (1.1, 8.4)
Upper respiratory tract infection	8 (3.6)	10 (4.5)	14 (6.1)	0.9 (-2.7, 4.6)	2.5 (-1.4, 6.5)
Herpes zoster	4 (1.8)	8 (3.6)	14 (6.1)	1.8 (-1.2, 4.8)	4.3 (0.8, 7.9)
Abdominal pain	10 (4.5)	13 (5.9)	12 (5.2)	1.4 (-2.7, 5.5)	0.8 (-3.2, 4.7)
Acne	7 (3.1)	4 (1.8)	12 (5.2)	-1.3 (-4.2, 1.6)	2.1 (-1.6, 5.8)
Nausea	14 (6.3)	10 (4.5)	11 (4.8)	-1.8 (-6.0, 2.4)	-1.5 (-5.7, 2.7)
Anaemia	14 (6.3)	7 (3.2)	11 (4.8)	-3.1 (-7.0, 0.8)	-1.5 (-5.7, 2.7)
Lymphocyte count decreased	5 (2.2)	3 (1.4)	11 (4.8)	-0.9 (-3.4, 1.6)	2.6 (-0.8, 5.9)
Nasopharyngitis	10 (4.5)	14 (6.3)	9 (3.9)	1.9 (-2.4, 6.1)	-0.6 (-4.3, 3.1)
Diarrhoea	8 (3.6)	10 (4.5)	9 (3.9)	0.9 (-2.7, 4.6)	0.3 (-3.2, 3.8)
Blood creatine phosphokinase increased	4 (1.8)	9 (4.1)	9 (3.9)	2.3 (-0.9, 5.4)	2.1 (-0.9, 5.2)
Fatigue	5 (2.2)	8 (3.6)	9 (3.9)	1.4 (-1.8, 4.5)	1.7 (-1.5, 4.9)
Rash	12 (5.4)	6 (2.7)	9 (3.9)	-2.7 (-6.3, 1.0)	-1.5 (-5.3, 2.4)
Aspartate aminotransferase increased	1 (0.4)	3 (1.4)	9 (3.9)	0.9 (-0.9, 2.7)	3.5 (0.8, 6.1)
Bronchitis	0	3 (1.4)	9 (3.9)	1.4 (-0.2, 2.9)	3.9 (1.4, 6.4)
Urinary tract infection	6 (2.7)	9 (4.1)	8 (3.5)	1.4 (-2.0, 4.7)	0.8 (-2.4, 4.0)
Alanine aminotransferase increased	0	5 (2.3)	8 (3.5)	2.3 (0.3, 4.2)	3.5 (1.1, 5.9)
Back pain	2 (0.9)	6 (2.7)	5 (2.2)	1.8 (-0.7, 4.3)	1.3 (-1.0, 3.5)
Insomnia	2 (0.9)	6 (2.7)	5 (2.2)	1.8 (-0.7, 4.3)	1.3 (-1.0, 3.5)
Vomiting	5 (2.2)	4 (1.8)	5 (2.2)	-0.4 (-3.1, 2.2)	-0.1 (-2.8, 2.7)
Influenza	4 (1.8)	4 (1.8)	5 (2.2)	0.0 (-2.5, 2.5)	0.4 (-2.2, 3.0)
Dizziness	2 (0.9)	4 (1.8)	5 (2.2)	0.9 (-1.2, 3.1)	1.3 (-1.0, 3.5)
White blood cell count decreased	1 (0.4)	4 (1.8)	5 (2.2)	1.4 (-0.6, 3.3)	1.7 (-0.4, 3.8)

Note: Treatment-emergent adverse events are adverse events with an onset date on or after the first dose of study drug in the maintenance period and up to 30 days past the last dose of study drug in the maintenance or LTE period (for subjects who were not rescued with OL UPA 30 mg) or until one day prior to rescue in the maintenance or LTE period (for subjects who were rescued with OL UPA 30 mg).
Subjects are counted once in each row, regardless of the number of events they may have had.
[A] Includes all subjects who responded to UPA 45 mg QD during induction and were re-randomized to PBO, UPA 15 mg QD or UPA 30 mg QD and entered into M14-430 substudy 1 (cohort 1).

Adverse Drug Reactions proposed for inclusion in the SmPC

The MAH states that assessment of the induction and maintenance data from the CD clinical program did not identify any new ADRs beyond those currently listed in the upadacitinib label. The rate of pneumonia was >1% in both upadacitinib 15 mg and 30 mg groups of the CD study resulting in a proposed labeling change to update the frequency from uncommon to common. The ADRs identified in the CD clinical program are presented for induction and maintenance treatment respectively below.

Table 58 *ADRs Identified During the CD Induction Period (PC_IND Analysis Sets)*

Adverse Drug Reaction[a] MedDRA 24.0 Preferred Term	PC_IND Analysis Set	
	Placebo N = 347 n (%)	UPA 45 mg N = 674 n (%)
Anemia (CMQ)	19 (5.5)	50 (7.4)
Folliculitis	1 (0.3)	9 (1.3)
Influenza	2 (0.6)	20 (3.0)
Neutropenia (CMQ)	1 (0.3)	14 (2.1)
Pyrexia	9 (2.6)	28 (4.2)
Herpes zoster (CMQ)	0	15 (2.2)
Herpes simplex (Group term)	4 (1.2)	18 (2.7)
Upper respiratory tract infection (Group term)	28 (8.1)	87 (12.9)
Blood creatine phosphokinase increased	4 (1.2)	20 (3.0)
Acne (Group term)	6 (1.7)	42 (6.2)
Pneumonia (Group term)	1 (0.3)	5 (0.7)
Oral candidiasis	0	5 (0.7)
Hypercholesterolemia (Group term)	0	7 (1.0)
Bronchitis (Group term)	0	6 (0.9)
Hyperlipidemia (Group term)	0	3 (0.4)

a.   Adverse Drug Reactions that are not based on CMQs or designated grouped terms are individual preferred terms.

Table 59 *ADRs Identified During the CD Maintenance Period (RESP_MAIN Analysis Set)*

Adverse Drug Reaction[b] MedDRA 24.0 Preferred Term	M14-430 Substudy 1 (Cohort 1)[a]		
	Placebo N = 223 n (%)	UPA 15 mg N = 221 n (%)	UPA 30 mg N = 229 n (%)
Fatigue	5 (2.2)	8 (3.6)	9 (3.9)
Headache (Group term)	4 (1.8)	8 (3.6)	15 (6.6)
Pyrexia	6 (2.7)	15 (6.8)	20 (8.7)
Neutropenia (CMQ)	1 (0.4)	3 (1.4)	5 (2.2)
Herpes zoster (CMQ)	5 (2.2)	9 (4.1)	14 (6.1)
Upper respiratory tract infection (Group term)	25 (11.2)	33 (14.9)	32 (14.0)
Blood creatine phosphokinase increased	4 (1.8)	9 (4.1)	9 (3.9)
Acne (Group term)	8 (3.6)	5 (2.3)	12 (5.2)
Pneumonia (Group term)	1 (0.4)	9 (4.1)	4 (1.7)
Oral candidiasis	1 (0.4)	1 (0.5)	2 (0.9)
Hypercholesterolemia (Group term)	0	4 (1.8)	1 (0.4)
Alanine aminotransferase increased	0	5 (2.3)	8 (3.5)
Aspartate aminotransferase increased	1 (0.4)	3 (1.4)	9 (3.9)
Bronchitis (Group term)	0	3 (1.4)	9 (3.9)
Hyperlipidemia (Group term)	0	4 (1.8)	2 (0.9)

a.   Includes all subjects who responded to UPA 45 mg QD during induction and were re-randomized to PBO, UPA 15 mg QD or UPA 30 mg QD and entered into M14-430 Substudy 1 (Cohort 1).

b.   Adverse Drug Reactions that are not based on CMQs or designated grouped terms are individual preferred terms.

Serious adverse event/deaths/other significant events

Deaths

Table 60 Listing of Deaths in CD Studies

Study Number at Time of Event Age/Sex/Race	Treatment at Event Occurrence	Onset Day[a]/ Days Since Last Dose of Study Drug	Treatment Sequence	Days Since First Dose on Study Drug	Cause of Death Preferred Term[b] (CAC Adjudicated Death)	Comments
Study M14-327: UPA 15 mg LTE						
M14-327 OLE 35/M/White	UPA 15 mg	806/469	Induction: Placebo Maintenance: UPA 12 mg BID Long-term extension: UPA 15 mg QD	806	Sepsis	The subject died 469 days after discontinuation of study drug due to post-surgery complications of acute renal failure, sepsis, jejunal perforation, abdominal, compartment syndrome, and necrotic bowel following loop ileostomy with adhesion lysis. The fatal event was assessed by the investigator as having no reasonable possibility of being related to study drug. Risk factors: Crohn's disease, obesity
UPA 45 mg Induction/15 mg Maintenance/LTE						
M14-431 (Part 3) 36/F/Asian	UPA 45 mg	164/159	Induction: UPA 45 mg	164	Infectious shock	The subject discontinued upadacitinib on Day 6 due to gastrointestinal hemorrhage, which resolved. Approximately 123 days after discontinuation of therapy, the subject experienced fever due to infection in the right lung, progressing to infectious shock. The subject died 159 days after the discontinuation of upadacitinib. The fatal event was assessed by the investigator as having no reasonable possibility of being related to study drug. Risk factors: malnutrition, anemia, adalimumab therapy post study discontinuation

Study Number at Time of Event Age/Sex/Race	Treatment at Event Occurrence	Onset Day[a]/ Days Since Last Dose of Study Drug	Treatment Sequence	Days Since First Dose on Study Drug	Cause of Death Preferred Term[b] (CAC Adjudicated Death)	Comments
M14-433 (Part 2) 64/M/White	UPA 30 mg	92/1	Induction: UPA 45 mg Extended Treatment: UPA 30 mg	97	COVID-19	The subject experienced COVID-19 on Day 92 of therapy and died on Day 97 of therapy. The reason of death was reported as COVID-19. The investigator assessed the death as having no reasonable possibility of being related to study drug. Risk factors: age, smoker (20 cigarettes/day for 40 years).
UPA 15 mg or 30mg Maintenance/LTE						
M14-430 (Maintenance) 46/M/White	Rescue UPA 30 mg	458/14	Induction: Placebo Maintenance: Placebo/Rescue UPA 30 mg	675	COVID-19 pneumonia	The subject experienced COVID-19 pneumonia on Day 583 of maintenance therapy and died on Day 591 of maintenance therapy. The reason of death was reported as COVID-19 pneumonia. The investigator assessed the death as having no reasonable possibility of being related to study drug. Risk factors: overweight, anemia, hypertension, pre-diabetic

a. Onset day is the number of days since first dose of study drug. For events that occurred with upadacitinib exposure, onset day was the number of days since first dose of upadacitinib.

Serious adverse events

In the PC_IND Analysis Set, the percentage of subjects with SAEs was similar in the upadacitinib 45 mg group (8.0%) compared with the placebo group (8.4%). Most SAEs were reported in no more than 1 subject in each group, except for worsening of CD (14 [2.1%] subjects in the upadacitinib 45 mg group and 15 [4.3%] subjects in the placebo group); GI haemorrhage and intestinal obstruction (3 [0.4%] subjects each in the upadacitinib 45 mg group); anal abscess (3 [0.4%] subjects in the upadacitinib 45 mg group and 3 [0.9%] subjects in the placebo group); and abdominal pain, ileus, and nephrolithiasis (2 [0.3%] subjects each in the upadacitinib 45 mg group).

In the EXT_TRT Analysis Set, the EAER of treatment-emergent SAEs increased with longer duration of exposure to upadacitinib, primarily driven by worsening of CD (64.5 E/100 PY through Week 24 compared with 51.8 E/100 PY during the initial 12 weeks of treatment). Fourteen SAEs of worsening

CD were reported through Week 24 (4 events with onset during the induction period with upadacitinib 45 mg and 10 events with onset during the extended treatment period with upadacitinib 30 mg). Through Week 24, the SAEs of intestinal obstruction and abdominal wall abscess were each reported twice. All other SAEs were reported only once.

In the RESP_MAIN Analysis Set, the EAER of treatment-emergent SAEs was higher in the placebo group (31.8 E/100 PY) compared with the upadacitinib 15 mg (16.9 E/100 PY) and 30 mg (18.0 E/100 PY) groups. The rates of SAEs of Crohn's disease were 8.0, 3.6, and 1.5 E/100 PY in subjects receiving placebo, 15 mg, and 30 mg, respectively. Most SAEs were reported no more than once in each group, except for worsening of CD (11 subjects in the placebo group, 8 subjects in the upadacitinib 15 mg group, and 4 subjects in the upadacitinib 30 mg group); anal abscess (4 events in the upadacitinib 15 mg group); anal fistula (3 events in the upadacitinib 30 mg group); constipation and nephrolithiasis (2 events each in the placebo group); ileus, appendicitis, and hydronephrosis (2 events each in the upadacitinib 15 mg group); and and anaemia, gastrointestinal haemorrhage, COVID-19 pneumonia, and cellulitis (2 events each in the upadacitinib 30 mg group).

Table 61 Treatment-Emergent SAEs Reported at ≥ 2 Events in any Upadacitinib 45 mg Induction Dose Cohort by Decreasing Frequency (ALL_TRT_RESP[subj] Analysis Set)

MedDRA 24.0 Preferred Term	PBO/PBO[b] (N = 161) (PY = 144.9)	UPA 45 mg/PBO[c] (N = 223) (PY = 191.1)	UPA 45 mg/15 mg[d] (N = 221) (PY = 277.1)	UPA 45 mg/30 mg[e] (N = 300) (PY = 507.3)	RESC UPA 30 mg[f] (N = 336) (PY = 366.2)	Any UPA(Resp)[g] (N = 833) (PY = 1203.4)
			Induction Dose UPA 45 mg[a]			
			E (E/100 PY)			
Any SAE	43 (29.7)	56 (29.3)	53 (19.1)	125 (24.6)	127 (34.7)	317 (26.3)
Crohn's disease	19 (13.1)	12 (6.3)	10 (3.6)	16 (3.2)	39 (10.7)	66 (5.5)
Anal fistula	1 (0.7)	1 (0.5)	0	5 (1.0)	3 (0.8)	8 (0.7)
Intestinal obstruction	1 (0.7)	1 (0.5)	1 (0.4)	5 (1.0)	2 (0.5)	9 (0.7)
COVID-19 pneumonia	0	0	1 (0.4)	5 (1.0)	5 (1.4)	11 (0.9)
Anal abscess	2 (1.4)	1 (0.5)	5 (1.8)	4 (0.8)	6 (1.6)	15 (1.2)
Gastrointestinal haemorrhage	0	2 (1.0)	1 (0.4)	3 (0.6)	1 (0.3)	6 (0.5)
Pneumonia	0	1 (0.5)	1 (0.4)	3 (0.6)	0	4 (0.3)
Nephrolithiasis	0	2 (1.0)	1 (0.4)	3 (0.6)	1 (0.3)	5 (0.4)
Ileal stenosis	0	0	0	2 (0.4)	1 (0.3)	3 (0.2)
Ileus	0	0	3 (1.1)	2 (0.4)	0	5 (0.4)
Anaemia	1 (0.7)	3 (1.6)	0	2 (0.4)	8 (2.2)	12 (1.0)
Small intestinal obstruction	2 (1.4)	1 (0.5)	1 (0.4)	2 (0.4)	2 (0.5)	5 (0.4)
Abdominal wall abscess	0	0	0	2 (0.4)	0	2 (0.2)
COVID-19	0	1 (0.5)	0	2 (0.4)	0	3 (0.2)
Cellulitis	0	1 (0.5)	0	2 (0.4)	1 (0.3)	3 (0.2)
Gastroenteritis	0	1 (0.5)	0	2 (0.4)	0	2 (0.2)
Perirectal abscess	0	0	0	2 (0.4)	0	2 (0.2)
Post procedural haemorrhage	0	0	0	2 (0.4)	0	2 (0.2)
Acute respiratory failure	0	0	0	2 (0.4)	0	2 (0.2)
Constipation	1 (0.7)	2 (1.0)	0	1 (0.2)	0	1 (<0.1)
Appendicitis	0	1 (0.5)	3 (1.1)	1 (0.2)	1 (0.3)	5 (0.4)
Hydronephrosis	0	0	2 (0.7)	0	0	2 (0.2)

a. Includes all subjects who received at least 1 dose of upadacitinib 45 mg during any part of induction. Subjects are further categorized by primary dose received during maintenance (or LTE).
b. All subjects who received PBO as initial study drug induction and received at least one dose of PBO during maintenance.
c. All subjects who received UPA 45 mg during induction or extended treatment period and received at least one dose of PBO during the maintenance period.
d. All subjects who received UPA 45 mg during induction and were re-randomized to UPA 15 mg during maintenance.
e. All subjects who received UPA 45 mg during induction and were re-randomized or assigned to UPA 30 mg during maintenance, plus subjects who received UPA 45 mg during induction.
f. Includes all subjects who were on PBO or UPA 15 mg and were rescued and received OL UPA 30 mg during maintenance or LTE.
g. Includes all Phase 3 subjects who met the analysis set entry criteria and received at least 1 dose of upadacitinib. Only events and exposure time associated with a dose of upadacitinib (during induction, extended treatment, maintenance, or LTE) are included.
Note: Rates are displayed by decreasing frequency in the upadacitinib 45 mg/30 mg cohort.

Adverse Events of Special Interest

Serious Infections:

In the PC_IND Analysis Set, the percentage of subjects with serious infections was similar in subjects receiving upadacitinib 45 mg and placebo (1.9% and 1.7%, respectively). The most commonly reported serious infections were of gastrointestinal infections, including PTs of abdominal wall abscess, anal abscess, colonic abscess, rectal abscess, and retroperitoneal abscess. The only serious infections by PT reported in ≥ 1 subject in any group was anal abscess reported in both treatment groups (3 in the upadacitinib 45 mg group and 3 in the placebo group). One subject in each treatment group had a serious infection that led to discontinuation of study drug. Results in the upadacitinib 45 mg group from the 45_IND Analysis Set were similar to those from the PC_IND Analysis Set (2.2% serious infections).

In the EXT_TRT Analysis Set, the EAER of serious infections with up to 24 weeks of induction and extended treatment (19.4 E/100 PY) was similar to the rate reported during the initial 12 weeks of induction treatment (21.3 E/100 PY)

In the RESP_MAIN Analysis Set, the EAERs of TEAEs of serious infections were lower in the upadacitinib 15 mg and 30 mg groups compared with the placebo group, with lower rates observed in the upadacitinib 15 mg group compared with upadacitinib 30 mg group (table below). Similar to the induction treatment gastrointestinal infections were the most commonly reported serious infections.

Table 62 Treatment-Emergent Serious Infection EAER per 100 PY (RESP_MAIN Analysis Set)

System Organ Class MedDRA 24.0 Preferred Term	M14-430 Substudy 1 (Cohort 1)[a]		
	Placebo (N = 223) (PY = 138.3)	UPA 15 mg (N = 221) (PY = 225.3)	UPA 30 mg (N = 229) (PY = 261.3)
	E (E/100 PY)		
Any TEAE	10 (7.2)	9 (4.0)	15 (5.7)
Infections and infestations	10 (7.2)	9 (4.0)	15 (5.7)
Abdominal infection	0	1 (0.4)	0
Abscess intestinal	1 (0.7)	0	1 (0.4)
Anal abscess	1 (0.7)	4 (1.8)	1 (0.4)
Appendicitis	1 (0.7)	2 (0.9)	1 (0.4)
Bartholin's abscess	1 (0.7)	0	0
Bursitis infective	0	0	1 (0.4)
COVID-19	0	0	1 (0.4)
COVID-19 pneumonia	0	0	2 (0.8)
Cellulitis	1 (0.7)	0	2 (0.8)
Colonic abscess	0	0	1 (0.4)
Gastroenteritis	1 (0.7)	0	1 (0.4)
Joint abscess	0	0	1 (0.4)
Osteomyelitis	1 (0.7)	0	0
Otitis externa	0	0	1 (0.4)
Pneumocystis jirovecii pneumonia	0	1 (0.4)	0
Pneumonia	1 (0.7)	1 (0.4)	1 (0.4)
Postoperative wound infection	1 (0.7)	0	0
Pyelonephritis acute	1 (0.7)	0	0
Rectal abscess	0	0	1 (0.4)

a. Includes all subjects who responded to UPA 45 mg during induction and were re-randomized to PBO, UPA 15 mg, or UPA 30 mg and entered into M14-430 Substudy 1 (Cohort 1).

Opportunistic Infection (Excluding Tuberculosis and Herpes Zoster)

Table 63 Treatment-Emergent Opportunistic Infections (Excluding Tuberculosis and Herpes Zoster) EAER per 100 PY (ALL_TRT_RESP[subj] Analysis Set)

System Organ Class MedDRA 24.0 Preferred Term	PBO/ PBO[b] (N = 161) (PY = 144.9)	Induction Dose UPA 45 mg[a]			RESC UPA 30 mg[f] (N = 336) (PY = 366.2)	Any UPA(Resp)[g] (N = 833) (PY = 1203.4)
		UPA 45 mg/ PBO[c] (N = 223) (PY = 191.1)	UPA 45 mg/15 mg[d] (N = 221) (PY = 277.1)	UPA 45 mg/30 mg[e] (N = 300) (PY = 507.3)		
		E (E/100 PY)				
Infections and infestations	0	0	2 (0.7)	2 (0.4)	2 (0.5)	6 (0.5)
Cytomegalovirus infection	0	0	1 (0.4)	0	0	1 (< 0.1)
Oesophageal candidiasis	0	0	0	1 (0.2)	0	1 (< 0.1)
Oral fungal infection	0	0	0	1 (0.2)	1 (0.3)	2 (0.2)
Pneumocystis jirovecii pneumonia	0	0	1 (0.4)	0	0	1 (< 0.1)
Pneumonia cryptococcal	0	0	0	0	1 (0.3)	1 (< 0.1)

a. Includes all subjects who received at least 1 dose of upadacitinib 45 mg during any part of induction. Subjects are further categorized by primary dose received during maintenance (or LTE).
b. All subjects who received PBO as initial study drug induction and received at least one dose of PBO during maintenance.
c. All subjects who received UPA 45 mg during induction or extended treatment period and received at least one dose of PBO during the maintenance period.
d. All subjects who received UPA 45 mg during induction period and were re-randomized to UPA 15 mg during maintenance.
e. All subjects who received UPA 45 mg during induction and were re-randomized to UPA 30 mg during maintenance. In addition, subjects who received UPA 45 mg during induction and did not achieve clinical response but responded to UPA 30 mg during the extended treatment period and received at least 1 dose of UPA 30 mg in maintenance or LTE are also included.
f. Includes all subjects who were on PBO or UPA 15 mg and were rescued and received OL UPA 30 mg during maintenance or LTE.
g. Includes all Phase 3 subjects who met the analysis set entry criteria and received at least 1 dose of upadacitinib. Only events and exposure time associated with a dose of upadacitinib (during induction, extended treatment, maintenance, or LTE) are included.

Active TB

No events of active TB were reported

Herpes Zoster

In the PC_IND Analysis Set, the number and percentage of subjects with TEAEs of herpes zoster was 15 (2.2%) in the upadacitinib 45 mg group; no subject reported a TEAE of herpes zoster in the placebo group. Among the reported cases of herpes zoster, one was severe, none were serious. Three herpes zoster events led to discontinuation of study drug and 10 events led to study drug interruption. Of the 15 cases of herpes zoster, 8 (53.3%) involved 1 dermatome, 5 (33.3%) involved 2 dermatomes, and 3 (20.0%) involved ≥ 3 dermatomes. Twenty total cases of herpes zoster were reported in the 45_IND Analysis Set and of the 5 additional cases, one resulted in study drug discontinuation, but none were severe or serious. None of the herpes zoster cases had non-cutaneous or ophthalmic involvement.

In the EXT_TRT Analysis Set, the EAER of TEAEs of herpes zoster increased with longer duration of exposure to study drug (11.3 E/100 PY [7 events cumulative] during 24 weeks of upadacitinib 45 mg/30 mg treatment compared with 9.1 E/100 PY [3 events] during the initial 12 weeks of upadacitinib 45 mg treatment). None of the events were considered severe or serious or led to discontinuation of study drug, but five events resulted in interruption of study drug.

In the RESP_MAIN Analysis Set, the EAER of herpes zoster was higher in the upadacitinib 30 mg group compared with the upadacitinib 15 mg and placebo groups. No events of herpes zoster were serious or led to discontinuation of study drug. One event each in the upadacitinib 15 mg and 30 mg groups was severe. Herpes zoster cutaneous involvement included 1 dermatome for subjects in the placebo group and 1 or 2 dermatomes for subjects in the upadacitinib 15 mg and 30 mg groups. One event in the placebo group had ophthalmic involvement. None of the herpes zoster cases reported in the upadacitinib groups had non-cutaneous or ophthalmic involvement.

In the ALL_TRT_RESP[subj] Analysis Set, the EAER of herpes zoster was similar among the upadacitinib cohorts. The EAERs for these cohorts were higher compared with subjects on placebo. Only 1 herpes zoster event, which occurred in the rescue upadacitinib 30 mg group, was serious.

During the study, the subject received upadacitinib 45 mg as induction treatment and placebo as maintenance treatment, followed by rescue therapy with OL upadacitinib 30 mg. On Day 144 of upadacitinib exposure, the subject began experiencing the TEAE of herpes zoster that was considered ongoing at data cutoff. The event was moderate and required hospitalization and study drug was interrupted. The investigator considered the TEAE of herpes zoster as having no reasonable possibility of being related to study drug. No herpes zoster TEAEs led to discontinuation of study drug, and most events were mild or moderate in severity. Most experienced events involving 1 or 2 dermatomes. Two subjects each in the upadacitinib 45 mg/30 mg and upadacitinib 45 mg/placebo cohorts and 4 subjects in the rescue upadacitinib 30 mg cohort experienced events involving 3 or more dermatomes. Four subjects experienced events with ophthalmic involvement (2 in the upadacitinib 45 mg/30 mg cohort and 1 each in the rescue upadacitinib 30 mg and upadacitinib 45 mg/placebo cohorts). No events involved CNS or other internal organs.

In the ALL_TRT_RESP[subj] Analysis Set, subgroup analysis by geographic region revealed a higher rate of herpes zoster in Asia (8.2 E/100 PY) compared to other regions (rates ranged from 3.6 to 5.3 E/100 PY). Analysis by age group for the any upadacitinib responders cohort revealed that subjects ≥ 50 to < 65 years of age had the highest rate of herpes zoster, followed by subjects < 50 years of age. The risk of herpes zoster was also higher in subjects with prior history of herpes zoster compared to those without. In the upadacitinib CD global clinical development program, approximately 7.0% of subjects who received at least 1 dose of upadacitinib indicated a prior history of zoster vaccination. The rate of herpes zoster events was observed to be lower in subjects who had history of zoster vaccination (2.1 E/100 PY) than in subjects who were unvaccinated (5.7 E/100 PY) The risk of subjects having herpes zoster events increased with time for subjects who received upadacitinib 45 mg during induction or extended treatment (up to Week 24). The cumulative incidence proportion over time was higher for those subjects who received 15 mg or 30 mg as maintenance or rescue treatment compared to the other treatment cohorts.

The EAERs of TEAEs of herpes zoster were highest in the rescue upadacitinib 30 mg group (13 events; 5.1 E/100 PY), followed in descending order by the upadacitinib 15 mg (3 events; 3.9 E/100 PY), upadacitinib 30 mg (4 events; 3.4 E/100 PY), and placebo (0 events) groups. No TEAEs of herpes zoster were serious or led to study drug discontinuation.

Hepatic Disorders
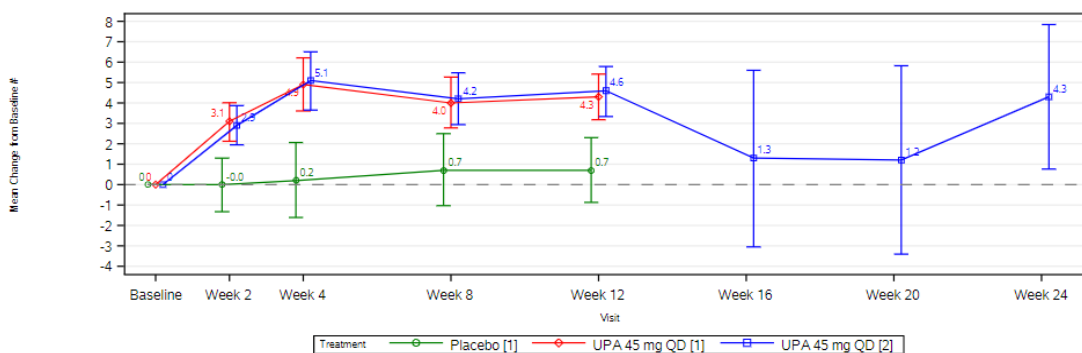
Figure 17 Plot of Mean Change from Baseline in Alanine aminotransferase (Placebo-Controlled Induction Analysis set and UPA 45 mg Induction Analysis Set

In the PC_IND Analysis Set, mean (SD) increases in ALT and AST at Week 12 from Baseline were observed for the upadacitinib 45 mg group, while values of ALT and AST generally remained unchanged from Baseline for the placebo group. Laboratory values of ALT or bilirubin increases were

mostly CTCAE Grade 2 elevations. Three (0.4%) subjects had a Grade 4 AST increase (≥ 20 × ULN) and no subject had a Grade 4 ALT increase. No placebo subjects experienced above a Grade 2 ALT, AST, or bilirubin value up through Week 12 of induction treatment. There was one case that met the criteria of biochemical Hy's Law. The details of the Hy's Law case who also had grade 4 AST elevation and the 2 additional subjects with Grade 4 AST increase are provided below:

- One subject in the upadacitinib 45 mg group of Study M14-431 met the criteria for biochemical Hy's Law case (ALT and/or AST > 3 × ULN and concurrent TBL > 2 × ULN). On Day 57 ALT levels rose to ≥ 5 × ULN (196 U/L), returned to just above the normal range at Day 64 (39 U/L), and then increased to ≥ 10 × ULN (630 U/L) the following day. The subject's AST levels were high (98 U/L) on Day 57, returned to normal range on Day 64 (32 U/L), and then increased to ≥ 20 × ULN (815 U/L) on Day 65, also an increase in bilirubin from within the normal range (13 μmol/L) on Day 64 to ≥ 2 × ULN (47 U/L) on Day 65 was observed. The subject had a concurrent AE of symptomatic cholecystolithiasis. By Day 77 ALT, AST, and bilirubin values were approaching or were within normal range: 42 U/L, 26 U/L, and 11 μmol/L, respectively. Study drug was interrupted for 9 days and then restarted, and event did not recur.

- One subject in the upadacitinib 45 mg group of Study M14-430 with a slightly above normal AST value (38 U/L) and a normal ALT value (40 U/L) at Baseline experienced an AST ≥ 20 × ULN(1334 U/L) and an ALT ≥ 10 × ULN (953 U/L) on Day 40, after experiencing septic shock on Day 39. At the next assessment on Day 44, AST and ALT values had decreased to ≥ 3 × ULN (159 U/L) and ≥ 5 × ULN (405 U/L), respectively. By Day 58 AST and ALT further decreased to 33 U/L (within the normal range) and 50 U/L (above ULN). Study drug was ongoing, and the subject had a relevant medical history of elevated liver function tests. Concomitant medications included paracetamol, hydrocodone, hydromorphone and lisinopril.

- One subject in the upadacitinib 45 mg group of Study M14-431 experienced elevations of AST and ALT on Days 29 and 32, respectively: AST of 464 U/L (≥ 10 × ULN) and 775 U/L (≥ 20 × ULN) and ALT of 79 U/L (above ULN) and 206 U/L (≥ 3 × ULN). This subject also experienced Grade 4 CPK elevations on Day 29 (47520 U/L) and Day 32 (40640 U/L). Values of AST and ALT at all other study visits, including Baseline, were within normal range.

The percentage of subjects with TEAEs of hepatic disorders was similar in the upadacitinib 45 mg group and the placebo group. The most frequently reported TEAEs of hepatic disorder (> 1 subject within a treatment group) were hepatic function abnormal, AST increased, ALT increased, and blood bilirubin increased in the upadacitinib 45 mg group and ALT increased and AST increased in the placebo group.

No serious TEAEs of hepatic disorder were reported. Treatment-emergent adverse events of hepatic disorders were primarily mild or moderate in severity. Two subjects in the upadacitinib 45 mg group and 1 subject in the placebo group discontinued study drug due to a TEAE of hepatic disorder.

In the EXT_TRT Analysis Set, there was no mean (SD) increase from Baseline in ALT observed with extended treatment of upadacitinib 45 mg/30 mg at Week 24. Slight mean (SD) increases from Baseline in AST were observed at Week 24 with the extended treatment of upadacitinib 45 mg/30 mg treatment compared to upadacitinib 45 mg at Week 12 (3.8 [15.93] and 3.1 [9.64] U/L, respectively). The number and percentages of subjects with ALT ≥ 5 × ULN and AST ≥ 5 × ULN were 4 (2.8%) and 5 (3.5%), respectively. The EAER of TEAEs of hepatic disorder in the upadacitinib 45 mg/30 mg group through Week 24 (11.3 E/100 PY [7 events]) was slightly lower than the rate observed during the initial 12 weeks of upadacitinib 45 mg treatment (15.2 E/100 PY [5 events]). No TEAE of hepatic disorder during the 24 weeks of treatment was severe, serious or led to discontinuation of study drug.

RESP_MAIN Analysis Set Mean increases in ALT and AST at Week 52 from Baseline were observed in all treatment groups, with larger mean (SD) increases occurring in the upadacitinib 15 mg (5.6 [17.45] U/L and 8.6 [12.02] U/L, respectively) and 30 mg (7.9 [22.60] U/L and 8.5 [15.63] U/L, respectively) groups compared with the placebo group (3.1 [10.51] U/L and 1.9 [6.84] U/L, respectively). The percentage of subjects with ALT or AST ≥ 5 × ULN was low and slightly higher in the upadacitinib 15 mg group compared with the upadacitinib 30 mg and placebo groups. ALT ≥ 10 × ULN was reported in 1 subject each in the upadacitinib 15 mg and placebo groups. One subject in the upadacitinib 15 mg group had transient elevations of AST ≥ 20 × ULN, however this subject experienced concurrent and one subject in the upadacitinib 30 mg group met the biochemical criteria for Hy's Law

The subject in M14-430 experienced transient Grade 3 ALT and AST elevations on Day 451: ALT (594 U/L [> 10.0 × ULN]), AST (1579 U/L [> 20.0 × ULN]), ALP (46 U/L), and Bilirubin (5 µmol/L) that improved on Day 466: ALT (81 U/L) and AST (53 U/L). The subject experienced concurrent AEs of ALT increased, AST increased, and rhabdomyolysis (induced by exercise) on Day 538. The subject had a relevant medical history of abnormal liver function. Concomitant medication included escitalopram. Study drug was ongoing.

In the ALL_TRT_RESP[subj] Analysis Set, mean increases in ALT and AST from Baseline were observed in the upadacitinib 45 mg/placebo, upadacitinib 45 mg/15 mg, and upadacitinib 45 mg/30 mg cohorts. The percentages of subjects with ALT ≥ 3 × ULN and AST ≥ 3 × ULN were higher in the upadacitinib 45 mg/30 mg cohort compared with the upadacitinib 45 mg/15 mg cohort. The percentages of subjects with ALT ≥ 5 × ULN were low (≤ 1.3%) and comparable between the upadacitinib 45 mg/30 mg and upadacitinib 45 mg/15 mg cohorts. The percentages of subjects with AST ≥ 5 × ULN were numerically higher in the upadacitinib 45 mg/30 mg cohort compared with the upadacitinib 45 mg/15 mg cohort (2.3% vs. 1.8%). ALT ≥ 10 × ULN were reported in no more than 1 subject in any mutually exclusive cohort (i.e., all cohorts except for the any upadacitinib responder's cohort). AST ≥ 10 x ULN was noted in 2 subjects in the upadacitinib 45 mg/30 mg cohort. According to the MAH, most elevations in ALT and/or AST were confounded by use of concomitant medications and relevant past medical history.

One subject, in the upadacitinib 45 mg/30 mg cohort, met the biochemical criteria for Hy's Law: ALT and/or AST > 3 × ULN and concurrent TBL > 2 × ULN (within 30 days). A second subject, in the rescue upadacitinib 30 mg cohort, was a borderline Hy's law case with ALT and AST > 3 × ULN and concurrent TBL > 1.5 × ULN. The details of these 2 cases are provided below.

- The subject in the upadacitinib 45 mg/30 mg cohort had ALT above the ULN (59 U/L), AST within the normal range (33 U/L), and TBL > 1.5 × ULN (37 µmol/L) at Baseline. On Day 312 ALT was > 3 × ULN (175 U/L), AST was above the ULN (101 U/L), and TBL was > 2 × ULN (45 U/L). All values had slightly decreased by Day 381 but were still above the ULN. By Day 451 ALT and AST values had decreased to 122 U/L and 65 U/L, respectively, and remained steady through the data cutoff. The subject has relevant past medical history of hepatic steatosis and Gilbert's syndrome. No concurrent AE was reported at the time of liver enzyme elevations, study drug was ongoing, and liver enzymes improved with no recurrence of event.

- The subject in the rescue upadacitinib 30 mg cohort had Baseline values of ALT, AST, and TBL of 71 U/L (above the ULN), 34 U/L (within normal range), and 15 μmol/L (within normal range), respectively. Throughout study treatment, the subject experienced ALT and AST values ranging from 82 to 155 U/L and from 65 to 164 U/L, respectively. At the last recorded visit, the subject had ALT and AST values > 3 × ULN (155 U/L and 116 U/L, respectively) and a TBL value > 1.5 × ULN (41 μmol/L), which was just under 2 × ULN (ULN = 21 μmol/L). Subject had relevant medical history of gallstones, obesity, and elevated liver function tests.

Anemia

In the upadacitinib CD global Phase 2 and Phase 3 studies, all subjects at study entry were required to have a haemoglobin value ≥ 9 g/dL (induction Studies M13-740, M14-431, and M14-433) or ≥ 8 g/dL (maintenance and LTE Studies M14-327 and M14-430). The protocols mandated interruption of study drug if a subject's haemoglobin value (confirmed by repeat testing) was < 8.0 g/dL or decreased ≥ 3.0 g/dL (or > 2.0 g/dL in study M13-740) from baseline without an alternative aetiology, until the haemoglobin values returned to the normal reference range or its baseline value.

In the PC_IND Analysis Set, mean (SD) decreases in hemoglobin at Week 12 from Baseline were observed and were numerically greater in the upadacitinib 45 mg group (-3.4 [13.87] g/L) compared with the placebo group (−1.0 [12.16] g/L). A greater number and percentage of subjects had Grade 3 hemoglobin decreases in the upadacitinib 45 mg group (18 [2.7%]) compared with the placebo group (5 [1.4%]). The percentage of subjects with TEAEs of anemia was numerically higher in the upadacitinib 45 mg group (7.4%) compared with the placebo group (5.5%). Most TEAEs of anemia were mild or moderate. Five subjects in the upadacitinib 45 mg and 1 subject in the placebo group had severe anemia. Two subjects in the upadacitinib 45 mg group and 1 subject in the placebo group had a serious TEAE of anemia.

Extended induction: In the EXT_TRT Analysis Set, a mean (SD) decrease in hemoglobin from Baseline, observed at Week 12 of upadacitinib 45 mg treatment (−6.4 [14.55] g/L), did not further decrease through Week 24 of upadacitinib 45 mg/30 mg treatment (−3.4 [15.31] g/L). Potentially clinically significant decreases in hemoglobin of ≥ Grade 3 occurred in 9 subjects in the EXT_TRT Analysis Set. The EAER of TEAEs of anemia decreased with longer duration of exposure to study drug (35.5 E/100 PY [22 events cumulative] during 24 weeks of upadacitinib 45 mg/30 mg treatment compared with 48.7 E/100 PY [16 events] during the initial 12 weeks of upadacitinib 45 mg treatment). One SAE of iron deficiency anemia was reported during the 24 weeks of upadacitinib 45 mg/30 mg treatment. One TEAE of anemia was severe and no TEAE of anemia led to discontinuation of study drug during the 24 weeks of treatment.

In the RESP_MAIN Analysis Set, mean hemoglobin values increased from Baseline in the upadacitinib groups and fluctuated slightly in the placebo group over time, where at Week 52, mean (SD) changes in hemoglobin from Baseline were 7.2 (17.51) g/L, 2.9 (15.93) g/L, and ˗2.8 (10.56) g/L for the upadacitinib 15 mg, upadacitinib 30 mg, and placebo groups, respectively A numerically higher percentage of subjects with Grade 3 hemoglobin decreases was noted in the upadacitinib 30 mg group compared to the placebo and upadacitinib 15 mg groups; however, the rate was numerically lower in the upadacitinib 15 mg group compared to the placebo group.

Neutropenia

In the PC_IND Analysis Set, a mean (SD) decrease in neutrophil count at Week 12 from Baseline were observed for the upadacitinib 45 mg group (−0.939 [2.7008] × 109/L). A small mean (SD) decrease was observed in the placebo group (−0.090 [2.3154] × 109/L). Grade 3 neutrophil count decreases were reported only in the upadacitinib 45 mg group (6/670 (0.9%). No Grade 4 decreases were observed. The percentage of subjects with TEAEs of neutropenia was higher in the upadacitinib 45 mg group (2.1%) compared with the placebo group (0.3%). All TEAEs of neutropenia were mild or moderate in severity and no subjects discontinued study drug due to a TEAE of neutropenia.

In the EXT_TRT Analysis Set, a mean (SD) decrease in neutrophil count from Baseline was generally maintained through Week 20 of upadacitinib 45 mg/30 mg treatment. One subject had a Grade 4 (< 0.5 × 109/L) neutrophil count (0.390 × 109/L) on Day 114 that returned to within normal range on Day 120 (3.891 × 109/L) and continued to rise and remained within normal range on Day 163 which was the last recorded value. The subject was reported as having an SAE of severe febrile neutropenia

that began on Day 117 of upadacitinib 30 mg treatment and ended on Day 122. The subject was hospitalized and treated with G-CSF, piperacillin-tazobactam, cefepime, and neutropenic diet. No other etiology for the fever was identified, the neutropenic fever resolved, and the subject was discharged from the hospital. The subject was discontinued from the study. The investigator considered the SAE as having a reasonable possibility of being related to study drug. No other TEAE of neutropenia was severe, serious or led to discontinuation of study drug. The EAER of TEAEs of neutropenia did not increase with longer duration of exposure to upadacitinib (6.5 E/100 PY [4 events cumulative] during 24 weeks of upadacitinib 45 mg/30 mg treatment compared with 9.1 E/100 PY [3 events] during the initial 12 weeks of upadacitinib 45 mg treatment)

In the RESP_MAIN Analysis Set, mean decreases in neutrophil count were observed in both upadacitinib and placebo groups at most timepoints during the treatment period. Grade 3 neutrophil count decreases were reported in the upadacitinib groups only. The percentage of subjects with Grade 3 neutrophil count decreases was higher in the upadacitinib 30 mg group compared with the upadacitinib 15 mg group (2.6% and 1.4%, respectively). No subject experienced a Grade 4 neutrophil count decrease. The EAER of TEAEs of neutropenia was higher in the upadacitinib 15 mg (3.1 E/100 PY) and 30 mg (2.3 E/100 PY) groups compared with the placebo (0.7 E/100 PY) group. No TEAE of neutropenia was serious or severe. One event of moderate neutropenia in the upadacitinib 30 mg group led to discontinuation of study drug and was considered by the investigator to have a reasonable possibility of being related to study drug.

Lymphopenia

In the PC_IND Analysis Set, no notable mean (SD) change from Baseline in lymphocyte count over the 12-week induction treatment was observed in the upadacitinib 45 mg group. Individual Grade 2 lymphocyte count decreases were reported more frequently with upadacitinib 45 mg compared with placebo treatment. The percentage of subjects with Grade 3 lymphocyte count decreases was 1.7% in the placebo group and 2.2% in the upadacitinib 45 mg group. One subject in the placebo group and no subjects in the upadacitinib 45 mg group experienced a Grade 4 lymphocyte count decrease. One subject from Study M14-431 who received DB placebo during Part 1 induction and DB upadacitinib 45 mg during Part 3 extended
treatment experienced a Grade 4 lymphocyte count on Day 145 that improved to Grade 2 by Day 168, the last reported lymphocyte value for this subject. No TEAE of lymphopenia or infectious AE was reported for this subject. The percentage of subjects with the TEAEs of lymphopenia was 2.3% and 1.6% for the placebo and upadacitinib 45 mg. Most TEAEs of lymphopenia were mild or moderate. No serious TEAE of lymphopenia and no discontinuations of study drug due to lymphopenia were reported in the upadacitinib 45 mg group. In the 45_IND Analysis Set, one subject experienced a severe TEAE of lymphopenia (reported as worsening lymphopenia) that resulted in discontinuation of study drug. The event was not serious and considered by the investigator to have no reasonable possibility of being related to study drug.

In the EXT_TRT Analysis Set, mean decreases in lymphocyte count from Baseline was generally maintained through Week 24 of upadacitinib 45 mg/30 mg treatment. Six Grade 3 lymphocyte count decreases were observed up to 24 weeks in subjects receiving upadacitinib 45 mg/30 mg. According to the MAH these decreases appeared to be transient. No Grade 4 lymphocyte count decreases were noted. The EAER of TEAEs of lymphopenia were similar between longer duration of exposure to upadacitinib (6.5 E/100 PY [4 events cumulative] during 24 weeks of upadacitinib 45 mg/30 mg treatment compared with 6.1 E/100 PY [2 events] during the initial 12 weeks of upadacitinib 45 mg treatment). No TEAE of lymphopenia was serious or led to discontinuation of study drug during the 24 weeks of treatment. During the initial 12 weeks of upadacitinib 45 mg treatment, 1 severe event (3.0

E/100 PY) of lymphopenia was reported versus 2 severe events cumulative (3.2 E/100 PY) during 24 weeks of upadacitinib 45 mg/30 mg treatment.

In the RESP_MAIN Analysis Set, mean changes in lymphocyte counts for the upadacitinib 15 mg and 30 mg groups fluctuated slightly above or below the Baseline value through Week 22 after which mean decreases from Baseline were observed through Week 52. At Week 52, the mean (SD) changes in lymphocyte count from Baseline were −0.450 (0.8348) and − 0.288 (0.5936) × 109/L for the upadacitinib 15 mg and 30 mg groups, respectively, which were greater than the −0.151 (0.5138) × 109/L seen in the placebo group.The percentage of subjects with Grade 3 lymphocyte count decreases were reported in a higher percentage in the upadacitinib 15 mg and 30 mg groups compared with the placebo group. No subject experienced a Grade 4 lymphocyte count decrease.

Creatine Phosphokinase Elevation

In the PC_IND Analysis Set, a mean (SD) increase at Week 12 from Baseline was observed for CPK in the upadacitinib 45 mg group (122.6 [540.87] U/L), while a mean (SD) decrease at Week 12 from Baseline was observed in the placebo group (−174.8 [2713.09] U/L). Grade 3 CPK increases were more frequent in the upadacitinib 45 mg compared with the placebo group. Grade 4 CPK increases were reported in < 2.0% of subjects in both the upadacitinib 45 mg and placebo groups. The percentage of subjects with TEAEs of CPK elevation (PT blood creatine phosphokinase increased) was higher in the upadacitinib 45 mg group (3.0%) compared with the placebo group (1.1%). Most TEAEs of CPK elevation were mild or moderate and no event was serious or led to discontinuation of study drug. No event of rhabdomyolysis was reported.

In the EXT_TRT Analysis Set, mean CPK values were elevated at Week 12 after upadacitinib 45 mg treatment and remained elevated through Week 24 of upadacitinib 45 mg/30 mg treatment. Five (3.5%) subjects experienced ≥ Grade 3 CPK elevation, 4 of whom experienced a Grade 4 elevation (. One subject from Study M14-431 had 2 consecutive elevated CPK values: 47520.00 U/L on Day 29 and 40640.00 U/L on Day 32, associated with exercise/other vigorous physical activity. By Day 40 the subject's CPK decreased to 161.00 U/L. Among the 4 subjects with Grade 4 elevation, associated conditions included 1 subject with septic shock, 1 subject who had a snowboarding accident with muscle strain reported, and 2 subjects with AST/ALT increases without other reported symptoms. The EAER of TEAEs of CPK elevation during 24 weeks of upadacitinib 45 mg/30 mg treatment through Week 24 (17.7 E/100 PY, 11 events cumulative) was lower than the rate observed during the initial 12 weeks of upadacitinib 45 mg treatment (21.3 E/100 PY,7 events)

In the RESP_MAIN Analysis Set, mean increases in CPK from Baseline for each treatment group were observed at most visits through Week 52. There was a dose-dependent increased percentage of subjects who experienced ≥ Grade 3 CPK elevation for upadacitinib; the rates of these elevated CPK were higher compared to the placebo group. Most Grade 3 and Grade 4 elevations of CPK were transient and returned to within normal range by the following assessment date.

- One subject receiving upadacitinib 30 mg presented with rhabdomyolysis at Day 868 that lasted 12 days. The rhabdomyolysis was considered to be a complication of COVID-19 infection. This subject also experienced concurrent acute kidney injury.

- One subject receiving upadacitinib 15 mg presented with a CPK elevation (70060 U/L) at Day 533, which was reported as exercise-induced rhabdomyolysis with no sign and symptoms by the investigator. The event resolved without treatment discontinuation. The investigator assessed the rhabdomyolysis as having a reasonable possibility of being related to study drug, with an alternative etiology of exercise or other vigorous physical activity.

Renal Dysfunction

In the PC_IND Analysis Set, a small mean increase (SD) at Week 12 from Baseline was observed for creatinine in the upadacitinib 45 mg group (4.9 [10.71] µmol/L), which was higher than the placebo group (1.3 [9.73] µmol/L). Grade 2 creatinine increases were reported at similar frequencies in the upadacitinib 45 mg (1.5%) and placebo (0.9%) groups. No Grade 3 or 4 increase in creatinine was reported in either treatment group in the PC_IND Analysis Set. Results in the upadacitinib 45 mg group from the 45_IND Analysis Set were similar to those from the PC_IND Analysis Set. One subject who received OL upadacitinib 45 mg as induction treatment in Study M14-431 (Part 2) experienced a Grade 4 (> 6.0 × ULN) increase in creatinine (6807 µmol/L). The Grade 4 increase coincided with an SAE of severe COVID-19 pneumonia. Study drug was interrupted due to the SAE.

In the EXT_TRT Analysis Set, mean (SD) increases in creatinine were reported at Week 12 of upadacitinib 45 mg induction treatment (4.9 [9.72] µmol/L) and at Week 24 of upadacitinib 45 mg/30 mg treatment (6.9 [9.30] µmol/L) One subject from Study M14-433 with a history of chronic kidney disease, experienced an SAE of severe renal dysfunction (PT of acute kidney injury) that began on Day 121 during upadacitinib 30 mg treatment after an SAE of upper respiratory tract infection. Study drug was discontinued due to this SAE and the investigator considered the acute kidney injury to have no reasonable possibility of being related to study drug. This same subject experienced a Grade 3 creatinine value of 385 µmol/L on Day 123 that was > 3.0 × Baseline value of 97 µmol/L. Creatinine for this subject decreased to 278 µmol/L (Grade 2) by Day 133. No other Grade 3 or Grade 4 increases in creatinine were reported

In the RESP_MAIN Analysis Set, mean increases from Baseline in serum creatinine were observed throughout the 52 weeks of maintenance treatment for the upadacitinib 15 mg and 30 mg groups, with smaller mean increases observed in the placebo group. At Week 52 the mean (SD) changes from Baseline in serum creatinine for the upadacitinib 15 mg, upadacitinib 30 mg, and placebo groups were 7.5 (10.87), 6.7 (10.50), and 0.4 (11.79) µmol/L, respectively. No subjects experienced Grade 3 or Grade 4 serum creatinine values during maintenance treatment. Grade 2 increases in creatinine were reported in 4.6%, 1.3%, and 1.4% of subjects in the upadacitinib 15 mg, upadacitinib 30 mg, and placebo, respectively. In the RESP_MAIN Analysis Set, 1 event (0.4 E/100 PY) and 3 events (2.2 E/100 PY) for the TEAEs of renal dysfunction occurred in the upadacitinib 30 mg and placebo groups, respectively. No TEAEs of renal dysfunction were reported in the upadacitinib 15 mg group. Two TEAEs of renal dysfunction (PT acute kidney injury) were serious: 1 in the upadacitinib 30 mg group and 1 in the placebo group. The serious TEAE of acute kidney injury in the upadacitinib 30 mg group was severe and considered by the investigator to have no reasonable possibility of being related to study drug The event began on Day 868 of Study M14-430 Substudy 1, lasted 4 days, and was considered a complicationof COVID-19 infection. This subject also experienced concurrent rhabdomyolysis.

Adjudicated GI perforation

In the upadacitinib CD global Phase 3 studies, subjects with a history of spontaneous GI perforation (other than appendicitis or mechanical injury), diverticulitis, or significantly increased risk for GI perforation per investigator judgment were excluded. In the upadacitinib CD Phase 2 studies (Studies M14-327 and M13-740) and Phase 3 studies, if a diagnosis of spontaneous GI perforation was confirmed (other than appendicitis or mechanical injury), the subject was permanently discontinued from study drug.

In the PC_IND Analysis Set, 1 event of GI perforation was reported in a subject on upadacitinib 45 mg. Additionally, 3 subjects who received placebo during the placebo-controlled period and did not respond to induction treatment experienced the events of GI perforation during the extended treatment period

with upadacitinib 45 mg. The 4 subjects had active or severe CD at the time of the GI perforation. All events of GI perforation were serious, severe, considered by the investigator to have a reasonable possibility of being related to study drug, and led to discontinuation of study drug.

In the RESP_MAIN Analysis Set, 3 adjudicated GI perforations were reported in 1 subject each in the placebo (0.7 E/100PYs), upadacitinib 15 mg (0.4 E/100PYs) and upadacitinib 30 mg (0.4 E/100PYs) groups. In addition, 4 subjects experienced events of GI perforation while receiving open-label upadacitinib 30 mg as rescue therapy during the maintenance period (2 had inadequate response to blinded 15 mg, 1 to blinded 30 mg, and one to placebo).

Overall, in the ALL_TRT_RESP[subj] Analysis Set, 1 subject in the upadacitinib 45 mg/placebo, 1 subject in the upadacitinib 45 mg/15 mg, 2 subjects in the upadacitinib 45 mg/30 mg (including 1 receiving blinded and OL rescue upadacitinib 30 mg), and 5 subjects rescued with OL upadacitinib 30 mg experienced events of adjudicated GI perforation. These events occurred when the subjects experienced active or severe CD or CD complications (stricture, obstruction) and reflect the higher risk of GI perforation in the CD patient population.

Additionally, 3 subjects experienced adjudicated GI perforations during the Phase 2 studies.

Patient characteristics of the cases with GI perforation are provided below:

1. UPA 45 mg 97 Days Since First Dose of Study Drug, 13 days since first dose of UPA. Intestinal perforation History of CD since 2015. On the start date of upadacitinib, endoscopy demonstrated very extensive CD involving rectum, left and right colon with large (0.5 to 2cm) and very large (> 2 cm) ulcers and impassable stenosis in the right colon not allowing the evaluation of the ileum. Prior meds: Adalimumab and ustekinumab Finding: CT showed free air in the right lower abdomen, small and large intestinal wall thickening. Pathology report revealed chronic ileitis with longitudinal ulcers of the ileum. Acute peritonitis due to possible perforation associated with probable CD. Investigator's comments: Reasonable possibility of being related to study drug Sponsor's comment: Event more likely related to pre-existing CD

2. UPA 45 mg 141 Days Since First Dose of Study Drug 59 days since first dose of UPA Ileal perforation History of CD since 2008 Prior med: Adalimumab Finding: CT showed wall thickening and enhancement of the terminal ileum with active inflammation; small volume of pneumoperitoneum adjacent to a loop of the terminal ileum consistent with ileal perforation. She underwent a laparoscopic small bowel resection of perforated ileum with ileostomy. Investigator's comments: Reasonable possibility of being related to study drug. Sponsor's comments: Event more likely related to active inflammation of the pre-existing Crohn's as noted in the CT scan of the abdomen and pelvis.

3. UPA 45 mg 64 Ind: UPA 45 mg 64 Intestinal perforation Yes Drug withdrawn, subject discontinued study. History of CD since 2009 Prior meds: Azathioprine and adalimumab Finding: CT showed localized contained perforation of the terminal ileum with severe disease involvement noted in 20 cm of the terminal ileum. Histopathology demonstrated the cecum with chronic active colitis, changes consistent with Crohn's ileitis with perforation, chronic active enteritis, and a segmental stricture. Investigator's comments: Reasonable possibility of being related to study drug Sponsor's comment: Event more likely related to pre-existing CD

4. UPA 45 mg 173 Ind: PBO, Ext: UPA 45 mg 92 Retro-peritoneal abscess Yes Drug withdrawn; subject prematurely discontinued study History: CD since 2011 and prior history of draining fistulas. Prior meds: 6-mercaptopurine, adalimumab, infliximab, vedolizumab, methotrexate, and ustekinumab Finding: CT showed extensive pericolonic inflammatory changes extending to musculature of the anterior abdominal wall and scattered foci of air without evidence of

discrete abscess. Histopathology revealed severe segmental and chronic colonic inflammation with fissural ulceration. Investigator's comments: Reasonable possibility of being related to study drug Sponsor's comment: Event more likely related to pre-existing CD

5. PBO 98 Ind: OL UPA 45 mg Main: PBO 87 Ileal perforation Yes Drug withdrawn, subject prematurely discontinued History of CD: > 20 years (1998), former smoker, previous bowel resection, severe CD; colonoscopy 10 days prior to event- impassable stricture. Prior meds: Infliximab and mesalazine Finding: CT revealed intraperitoneal fluid of moderate volume in the right parietocolic gutter and small gas bubbles suggestive of peritonitis. Post-surgical pathology revealed ileum with multiple foci of ulceration with perforation. Investigator's comment: No reasonable possibility of being related to study drug

6. UPA 15 mg 96 Ind: UPA 45 mg Main: UPA 15 mg 96 Intestinal perforation Yes Drug withdrawn, subject prematurely discontinued History of stenosing CD > 12 years; history of small bowel obstruction, bowel resection, pelvic abscess, and severe neo-terminal ileitis. Finding: 7 days prior to perforation, colonoscopy showed severely ulcerated neo-terminal ileum with large ulcers up to 2 cm and ulcerated surface of > 30% and passable ileal stricture. CT confirmed bowel perforation around his neo-terminal ileum. Investigator's comment: No reasonable possibility of being related to study drug

7. UPA 30 mg 159 Ind: OL UPA 45 mg Main: UPA 30 mg/Rescue UPA 30 mg 159 Ileal perforation Yes Drug interrupted History of stenosing CD for approximately 3 years. Prior meds: Adalimumab and budesonide Finding: Approximately 1 month prior to perforation, colonoscopy showed subtle aphthous ulceration in the rectum, left and right colon and impassable for endoscope stricture in the ileum. CT revealed active CD and perforation proximal to a bowel stricture; a segment of thickened and inflamed terminal ileum measuring 5 cm in length; and a gas locule. Post-surgical pathology showed small intestinal and colonic pieces with patchy mucosal ulceration. Subject was on blinded upadacitinib 30 mg, not responding, and rescued with OL upadacitinib 30 mg. Perforation occurred during rescue therapy. Investigator's comment: No reasonable possibility of being related to study drug; the subject had relevant risk factors of stricturing CD.

8. UPA 30 mg 221 Ind: UPA 45 mg Main: UPA 30 mg 221 Small intestine perforation Yes Drug withdrawn History of stenosing CD for 4 years. Finding: CT showed at least 2 focal luminal strictures, mild pneumoperitoneum, acute on chronic CD, partial ileal obstruction or hollow distal ileal perforation complicated with regional peritonitis. Post-surgical pathology revealed small intestine with transmural necrosis, multiple ulcers, acute and chronic inflammatory cell infiltration, vague aggregates of epithelioid histiocytes, scattered multinucleated giant cells, and fibrosis consistent with CD. Investigator's comments: No reasonable possibility of being related to study drug

9. Rescue UPA 30 mg 255 Ind: PBO Main: PBO/Rescue UPA 30 mg 146 Intestinal perforation Yes Drug interrupted History of stenosing CD for 4 years.
Finding: CT showed GI tract with inflammatory changes and obstruction at time of perforation. Subject had inadequate response to placebo and was rescued with OL upadacitinib 30 mg. Perforation occurred during rescue therapy. Investigator's comment: No reasonable possibility of being related to study drug

10. Rescue UPA 30 mg654 Ind: UPA 45 mg Main: UPA 15 mg/Rescue UPA 30 mg 654 Intestinal perforationYes Dose interrupted; subject prematurely discontinued due to associated pelvic abscess History of CD for approximately 3 years. The subject had a nonserious AE of pelvic abscess on Day 648.Prior med: Azathioprine Finding:

Histopathology showed picture suggestive of CD complicated with abscess formation. Investigator's comment: Reasonable possibility of being related to study drug Sponsor's comment: Event more likely related to pre-existing CD

11. Rescue UPA 30 mg385 Ind: UPA 45 mg Main: UPA 15 mg/Rescue UPA 30 mg385 Intestinal perforationYes Drug withdrawn, subject prematurely
discontinued History of stenosing CD for 19 years, enterocutaneous fistula, and intra-abdominal abscess. Prior meds: Infliximab, adalimumab, 6-mercaptopurine, certolizumab pegol, and ustekinumab Finding: CT showed colonic perforation in an area of complex sinus tracts and inflammation at the splenic flexure.Subject was inadequately responding to upadacitinib 15 mg and was rescued with OL upadacitinib 30 mg. Perforation occurred during rescue therapy. Investigator's comments: No reasonable possibility of being related to study drug; worsening of CD

12. UPA 24 mg 37 Ind: UPA 24 mg 37 Ileal perforation Yes Drug withdrawn; subject prematurely discontinued study History of CD since 2010.Prior meds: Infliximab, adalimumab, and vedolizumabFinding: Pathology showed colonic and small intestinal tissue with chronic active inflammation, ulceration, grandular distortion, fistula tract formation, focal perforation, and focal transmural chronic inflammation. Pathologic features compatible with clinical impression of CD. Small intestine to small intestine fistula tract
is identified. Pericolic abscess adjacent to ileocecal valve. Severe acute peritonitis. Serosal fibrous adhesions. Investigator's comments: No reasonable possibility of being related to study drug; progression of subject's underlying CD.

13. UPA 24 mg BID52 Ind: UPA 24 mg BID52 Small
intestinal perforationYes Subject prematurely discontinued study prior to event History of CD since 1981; history of bowel resection (1993).Prior meds: Infliximab, adalimumab and azathioprine Finding: CT showed several locules of extraluminal air adjacent to an inflamed segment of distal small bowel suspicious for microperforation. Pathology indicated small bowel, portion of ileum: 0.5×0.5 cm perforation site, 4.5 cm to the closest mucosal margin. Associated with a defect $2.5 \times 1.5 \times 0.9$ cm abscess cavity. The perforation and abscess cavity communicate with the overlying mucosa. Investigator's comments: No reasonable possibility of being related to study drug; worsening of CD

14. UPA 15 mg 525a Ind: UPA 6 mg BID Main: UPA 12 mg BID, LTE: OL UPA 15 mg/Esc. UPA 30 mg 635 Abdominal abscess. Drug withdrawn History of CD since 2007. Prior meds: Adalimumab and azathioprine Finding: CT showed acute colitis of transverse colon, uniocular cyst, mild wall thickening else wherein the colon, sinus tract, and abscess extending laterally from the mid-descending colon to the left colic gutter with associated $5 \times 14 \times 0.7$; and gas-filled sinus tract and large surrounding inflammation. Wall thickening of the terminal ileum could be due to acute or chronic Crohn's ileitis. There is a low-grade partial obstruction of the distal ileum at this site. 4×4.6 cm unilocular cyst of the left ovary. Investigator's comments: Reasonable possibility of being related to study drug Sponsor's comment: Event more likely related to pre-existing CD

Malignancy

In the PC_IND/45 IND and EXT_TRT Analysis Set, no TEAE of malignancy, malignancy excluding NMSC, NMSC, or lymphoma was reported.

In the RESP_MAIN Analysis Set, the EAIR of TEAEs of malignancy excluding NMSC was 0.4 n/100 PY (1 subject with metastatic ovarian cancer) in the upadacitinib 15 mg group, 1.1 n/100 PY (3 subjects: 1 subject with adenocarcinoma of colon, 1 subject with invasive lobular breast carcinoma, 1 subject with

pleomorphic malignant fibrous histiocytoma) in the upadacitinib 30 mg group, and 0.7 n/100 PY (1 subject with intraductal proliferative breast lesion reported as breast ductal carcinoma in situ) in the placebo group.

In the ALL_TRT_RESP[subj] Analysis Set, the EAIR of TEAEs of malignancy excluding NMSC was 0.4 n/100 PY (1 subject) and 1.2 n/100 PY (6 subjects; after correction of the one NMSC, 1.0 n/100 PY) in the upadacitinib 45 mg/15 mg and upadacitinib 45 mg/30 mg cohorts, respectively. Additionally, 1 subject (0.5 n/100 PY) in the upadacitinib 45 mg/placebo cohort and 3 subjects (0.8 n/100 PY) in the rescue upadacitinib 30 mg cohort experienced malignancy excluding NMSC. The overall incidence rate of malignancy excluding NMSC in the any upadacitinib group was 0.7 n/100 PY.

In the Phase 2 studies, 2 subjects experienced malignancy excluding NMSC during the maintenance treatment with upadacitinib 12 mg BID Overall, the malignancy excluding NMSC was reported slightly more frequently in subjects receiving upadacitinib 30 mg compared to upadacitinib 15 mg. However, the MAH states that based on the limited number and lack of pattern of the malignancy types, an increased risk of malignancy excluding NMSC with upadacitinib 30 mg compared to upadacitinib 15 mg cannot be concluded.

Adjudicated MACE

Table 64 Treatment-Emergent Adjudicated MACE EAER per 100 PY (ALL_TRT_RESP[subj] Analysis Set

Event Category Adjudicated Term	PBO / PBO[b] (N = 161) (PY = 144.9)	Induction Dose UPA 45 mg[a]			RESC UPA30 mg[f] (N = 336) (PY = 366.2)	Any UPA(Resp)[g] (N = 833) (PY = 1203.4)
		UPA 45 mg/PBO[c] (N = 223) (PY = 191.1)	UPA 45 mg/15 mg[d] (N = 221) (PY = 277.1)	UPA 45 mg/30 mg[e] (N = 300) (PY = 507.3)		
		E (E/100 PY)				
MACE[h]	0	0	0	0	2 (0.5)	2 (0.2)
CV death	0	0	0	0	0	0
Non-fatal MI	0	0	0	0	1 (0.3)	1 (<0.1)
Non-fatal stroke	0	0	0	0	1 (0.3)	1 (<0.1)

a. Includes all subjects who received at least 1 dose of upadacitinib 45 mg during any part of induction. Subjects are further categorized by primary dose received during maintenance (or LTE).
b. All subjects who received PBO as initial study drug induction and received at least one dose of PBO during maintenance.
c. All subjects who received UPA 45 mg during induction or extended treatment period and were re-randomized to PBO during the maintenance period.
d. All subjects who received UPA 45 mg during induction or extended treatment period and were re-randomized to UPA 15 mg during maintenance.
e. All subjects who received UPA 45 mg during induction or extended treatment and were re-randomized to UPA 30 mg during maintenance. In addition, subjects who received UPA 45 mg during induction and did not achieve clinical response but responded to UPA 30 mg during the extended treatment period and received at least 1 dose of UPA 30 mg in maintenance or LTE are also included.
f. All subjects who initially received PBO during induction and in maintenance, lost response and then were rescued and received OL UPA 30 mg during maintenance or LTE. It also includes subjects who received UPA 45 mg during induction who were re-randomized to PBO or UPA 15 mg during maintenance and then lost response and were rescued and received OL UPA 30 mg during maintenance or LTE.
g. Includes all Phase 3 subjects who met the analysis set entry criteria and received at least 1 dose of upadacitinib. Only events and exposure time associated with a dose of upadacitinib (during induction, extended treatment, maintenance, or LTE) are included.
h. MACE is defined as CV death, non-fatal MI, and non-fatal stroke.

In the PC_IND, 45 IND and EXT_TRT Analysis Sets, no upadacitinib-treated subjects had a TEAE of adjudicated MACE. One placebo-treated subject experienced an adjudicated other CV event (transient ischemic attack).

In the RESP_MAIN Analysis Set, no adjudicated MACE was reported in the upadacitinib 15 mg, upadacitinib 30 mg and placebo groups. In the Phase 3 maintenance/LTE treatment period, 2 events of adjudicated MACE (non-fatal stroke and non-fatal MI) were reported in 2 subjects receiving upadacitinib 30 mg as rescue therapy. The incidence rate of adjudicated MACE was 0.2 n/100 PY in all subjects who responded to induction treatment and received at least 1 dose of upadacitinib.

Additionally, there were 2 events (acute MI and pneumonia aspiration with abnormal cardiac enzymes) adjudicated as MACE reported in the Phase 2 studies. According to the MAH, all subjects with adjudicated MACE had at least one CV risk factor, such as hypertension, obesity, smoking history, and diabetes.

Adjudicated VTE:

In the PC_IND Analysis Set, no subjects receiving upadacitinib had a TEAE of adjudicated VTE.

In the RESP_MAIN Analysis Set, adjudicated thrombotic events were reported in 2 subjects (1 DVT in 1 subject and 1 other thrombosis event [PT hepatic vein thrombosis] in 1 subject) receiving upadacitinib 30 mg compared with no events in those receiving upadacitinib 15 mg or placebo.
In the Phase 3 clinical studies, a total of 3 subjects receiving upadacitinib 45 mg during induction and upadacitinib 30 mg during maintenance/LTE (0.6 n/100 PY) and 1 subject receiving placebo during induction and maintenance/LTE (0.7 n/100 PY) experienced adjudicated VTE. Additionally, adjudicated VTE (both DVT) were reported in 2 subjects (1 with upadacitinib 15 mg and 1 with rescue upadacitinib 30 mg) during the LTE Phase 2 study Two adjudicated other venous thrombotic events (hepatic vein thrombosis with upadacitinib 30 mg and superior mesenteric vein thrombosis with rescue upadacitinib 30 mg) and 1 adjudicated arterial thrombosis (upadacitinib 30 mg) were reported during the maintenance/LTE studies.

Fractures

Table 65 TEAEs of Fracture Reported in Subjects in Any Group (PC_IND/45_IND Analysis Sets)

| | PC_IND Analysis Set | | 45_IND Analysis Set |
| | Placebo (N = 347) | UPA 45 mg (N = 674) | UPA 45 mg (N = 938) |
MedDRA 24.0 Preferred Term	n (%) [SSA %]	n (%) [SSA %]	n (%)
Ankle fracture	0	1 (0.1) [0.1]	1 (0.1)
Femoral neck fracture	0	0	1 (0.1)
Fibula fracture	0	1 (0.1) [0.1]	1 (0.1)
Radius fracture	0	1 (0.1) [0.1]	1 (0.1)
Spinal compression fracture	0	0	1 (0.1)
Wrist fracture	0	1 (0.1) [0.1]	1 (0.1)

Note: Subjects were counted once in each row, regardless of the number of events they may have had.

In the 45_IND Analysis Set, 1 subject each (0.1%) in the upadacitinib 45 mg group had a TEAE of ankle fracture, femoral neck fracture, fibula fracture, radius fracture, spinal compression fracture and wrist fracture; no subjects in the placebo group had a TEAE of fracture. Two of the 6 events (femoral neck fracture and spinal compression fracture) were serious. All 6 events were considered by the investigator to have no reasonable possibility of being related to study drug and did not lead to study drug discontinuation. The SAEs of femoral neck fracture and spinal compression fracture occurred in 2 subjects following accidental falls. According to the MAH, the 2 subjects also had risk factors including medical history of osteoporosis, Cushing's syndrome, or concomitant use of glucocorticoids and of the 4 subjects with nonserious events of fracture, 1 had an alternative etiology (bike accident), and 3 had underlying risk factors, including history of menopause and concomitant medications of methotrexate, glucocorticoids, or SSRI or obesity.

In the RESP_MAIN Analysis Set, 1 subject each (≤ 0.5%) had a TEAE of lower limb fracture and stress fracture in the upadacitinib 15 mg group; foot fracture and upper limb fracture in the upadacitinib 30 mg group; and rib fracture in the placebo group All but one event (stress fracture of the femoral neck) were considered non-serious; all 5 events were considered by the investigator to have no reasonable possibility of being related to study drug and did not lead to study drug discontinuation

The SAE of stress fracture occurred on Day 393 of treatment in a subject with a history of osteoporosis and smoking in the upadacitinib 15 mg group; alternative etiology was reported as accidental fall.The remaining 4 non-serious events were reported in 3 male and 1 female subject. Ages ranged from 30 to 64 years old. Event time-to-onset (TTO) ranged from 127 to 872 days of upadacitinib treatment. According to the MAH, risk factor of concomitant medications (i.e., PPI) was identified in 2 subjects.

Table 66 TEAEs of Fracture Reported per 100 PY in any Treatment Group (ALL_TRT_RESP[subj]) Analysis Set

MedDRA 24.0 Preferred Term	PBO/ PBO[b] (N = 161) (PY = 144.9)	Induction Dose UPA 45 mg[a]			RESC UPA 30 mg[f] (N = 336) (PY = 366.2)	Any UPA(Resp)[g] (N = 833) (PY = 1203.4)
		UPA 45 mg/PBO[c] (N = 223) (PY = 191.1)	UPA 45 mg/15 mg[d] (N = 221) (PY = 277.1)	UPA 45 mg/30 mg[e] (N = 300) (PY = 507.3)		
	E (E/100 PY)					
Ankle fracture	0	1 (0.5)	0	0	0	1 (<0.1)
Comminuted fracture	0	0	0	0	1 (0.3)	1 (<0.1)
Femoral neck fracture	0	0	0	1 (0.2)	0	1 (<0.1)
Fibula fracture	0	0	0	1 (0.2)	0	1 (<0.1)
Foot fracture	0	0	0	2 (0.4)	0	2 (0.2)
Hand fracture	1 (0.7)	0	0	0	0	0
Lower limb fracture	0	0	1 (0.4)	0	0	1 (<0.1)
Radius fracture	0	1 (0.5)	0	0	0	1 (<0.1)
Rib fracture	0	1 (0.5)	0	0	3 (0.8)	3 (0.2)
Scapula fracture	0	0	0	1 (0.2)	0	1 (<0.1)
Spinal compression fracture	0	0	1 (0.4)	0	0	1 (<0.1)
Stress fracture	0	0	1 (0.4)	0	0	1 (<0.1)
Upper limb fracture	0	0	0	1 (0.2)	0	1 (<0.1)
Wrist fracture	0	0	1 (0.4)	0	1 (0.3)	2 (0.2)

a. Includes all subjects who received at least 1 dose of upadacitinib 45 mg during any part of induction. Subjects are further categorized by primary dose received during maintenance (or LTE).
b. All subjects who received PBO as initial study drug induction and received at least one dose of PBO during maintenance.

Laboratory findings

Hematology

Treatment-emergent adverse events of abnormal hematology laboratory values: hemoglobin, neutrophils, and lymphocytes were evaluated and reported in the section for the respective associated AESI. According to the MAH, there were no clinically meaningful differences seen for treatment with upadacitinib compared with placebo in the placebo-controlled safety analyses for changes in platelet counts, for subjects meeting criteria for PCS values for platelet counts, for shift analysis from Baseline to post-Baseline in platelet counts, or for TEAEs representing changes in platelet counts. In long-term analyses, similar results were seen with upadacitinib across treatment groups.

Clinical Chemistry

Treatment-emergent adverse events of abnormal laboratory clinical chemistry values
(ALT and AST, blood CPK, and creatinine) were evaluated and reported in the section for the respective associated AESI)

Safety in special populations

The following intrinsic factors were examined: gender, age, race, geographic region,
BMI category, renal impairment, and hepatic impairment.

Gender

In the PC_IND/45_IND Analysis Set, the rates of TEAEs overall, AEs leading to discontinuation of study drug, and AEs with a reasonable possibility of being related to study drug as assessed by the investigator were higher in females compared with males in the upadacitinib 45 mg group, while the rates for COVID-19 related AEs, SAE and severe TEAEs were generally similar between the gender subgroups. The rates of most AESI were generally similar between males and females, with the exception of CPK increases that were slightly higher in males compared to females. In the RESP_MAIN Analysis Set, the rates of TEAEs overall were higher in females compared to males across all treatment groups. However, according to the MAH no consistent trends were noticed for the rates of other AE categories between the gender subgroup

Age

PC_IND/45_IND Analysis Sets: Due to the small number of subjects $\geq$ 65 years age in the placebo group (9 subjects), no comparison between upadacitinib 45 mg and placebo was performed. Results are being presented for only the 45_IND Analysis Set. A total of 900 subjects were included in the < 65 years age subgroups, while 38 subjects were included in the $\geq$ 65 years age group for the 45_IND Analysis Set. According to the MAH, there was no consistent trend between age subgroups, except for a higher rate of TEAEs overall and TEAEs with a reasonable possibility of being related to study drug as assessed by the investigator in the < 65 years age group. Most AESI rates were similar between age groups, except for anemia, with a higher rate in the < 65 years age group (7.0%) compared to the $\geq$ 65 years age (2.6%), which should be interpreted with caution, given the small sample size in the elderly subgroup.

In the RESP_MAIN Analysis Set, a small number of subjects was included in the $\geq$ 65 years age group: placebo (N = 8), upadacitinib 15 mg (N = 7), and upadacitinib 30 mg (N = 8). For the placebo and upadacitinib 30 mg treatment groups, the rates of SAEs and severe TEAEs were higher in subjects $\geq$ 65 years (49.4 E/100PY and 37.0 E/100PY, respectively) compared to subjects < 65 years age (17.0 E/100PY and 15.4 E/100PY, respectively). For the upadacitinib 15 mg group, most AE categories were higher in the < 65 years age, except for the COVID 19-related events. In the <65 years age subgroup, the rates of TEAEs overall, SAEs, severe TEAEs, and TEAEs with a reasonable possibility of being related to study drug were lower among upadacitinib-treated subjects compared with placebo-treated subjects. In the $\geq$ 65 years age group, the rates of TEAEs overall, SAEs, severe TEAEs, and any AE with reasonable possibility of being related to study drug were lower among upadacitinib 15 mg-treated subjects compared to upadacitinib 30 mg-treated and placebo-treated subjects.

Race

In the PC_IND/45_IND Analysis Set, the rates of AEs in all categories were generally similar between White and non-White subgroups and the percentages of AESI between race subgroups were comparable, except for TEAE of anemia and neutropenia, which were higher in the non-White

subgroup. The rates of TEAEs overall, SAEs, TEAEs leading to discontinuation of study drug, severe TEAEs, and TEAEs with a reasonable possibility of being related to study drug were similar or numerically lower among upadacitinib treated subjects compared with placebo-treated subjects for both White and non-White subjects.

In the ALL_TRT_RESP[subj] Analysis Set, there was no consistent pattern or trend observed for the rates of TEAEs overall, SAEs, severe TEAEs, and TEAEs leading to discontinuation of study drug between Whites and non-Whites subgroups Similar to what was observed in the RESP_MAIN Analysis Set, the EAERs of TEAEs of neutropenia, lymphopenia and hepatic disorder were higher in non-White subjects compared to Whites subjects for most treatment groups.

Geographic Region

In the PC_IND Analysis Set, the rates for AE categories were generally similar between geographic region subgroups. Within both the NA and ROW subgroups, the rates of most AESI were similar between the geographic region subgroups, except for anemia, which was higher in the ROW (8.1%) compared to the NA subgroup (4.5%) in the upadacitinib 45 mg group. In the RESP_MAIN Analysis Set, and across treatment groups, there was no consistent pattern or trend observed for rates of SAEs, TEAEs leading to discontinuation of study drug, severe TEAEs, and TEAEs with a reasonable possibility of being related to study drug between NA and ROW. The rates of TEAEs overall were numerically higher in NA compared with ROW subjects across treatment groups In the NA subgroup, the rates of TEAEs overall and SAEs were lower in upadacitinib 15 mg-treated subjects compared to placebo-treated subjects, and the rate of severe TEAEs was lower among upadacitinib-treated subjects (15 mg and 30 mg) compared with placebo-treated subjects. Among the ROW subgroup, the rates of SAEs and TEAEs with reasonable possibility of being related to study drug were lower in upadacitinib 30 mg treated subjects than in the other groups, and the rates of TEAEs overall were lower among upadacitinib-treated (15 mg and 30 mg), compared to placebo-treated subjects the rates of most AESI were generally similar among geographic region subgroups. The EAERs of TEAEs of herpes zoster and lymphopenia were higher in ROW subjects across all treatment groups, while the rates for anemia were higher than in NA subjects in the placebo and upadacitinib 15 mg treatment groups.

BMI Category

Most subjects were non-obese (BMI < 30 kg/m2) at Baseline; thus, the sample size for obese subjects was smaller compared with non-obese subjects and therefore results should be interpreted with caution.

In the PC_IND Analysis Set, the rates for AE categories were generally similar between BMI subgroups. The rates of most AESI were similar between obese and non-obese subjects. For the upadacitinib 45 mg treatment group, a higher percentage of anemia was noticed in non-obese compared to obese subjects (8.3% vs. 2.7%, respectively); while the percentage for CPK elevation was higher in obese compared to non-obese subgroup (7.2% vs 2.1%, respectively) In the ALL_TRT_RESP[subj] Analysis Set, the rates of SAEs, TEAEs leading to discontinuation of study drug, severe TEAEs, and TEAEs with a reasonable possibility of being related to study drug were generally similar between BMI subgroups. The rates of TEAEs overall and COVID-19 related events were numerically higher in the obese subjects compared to non-obese ones.

Renal Impairment

In the upadacitinib clinical studies, subjects with estimated glomerular filtration (eGFR) rate < 30 mL/min/1.73 m2 were excluded. Most subjects had normal renal function or mild impairment at Baseline; thus, the sample size for the moderate renal impairment subgroup was smaller compared with the other 2 subgroups.

In the PC_IND/45_IND Analysis Sets, the rates for AEs categories were generally similar among renal function subgroups. The rates of most AESI were similar among the subgroups. In the RESP_MAIN Analysis Set, the rates of TEAEs overall were numerically higher in the normal renal function subjects, across all treatment groups. The rates of COVID-19-related events and severe TEAEs were higher than normal renal subjects in the mild renal impairment subjects for the upadacitinib 15 mg treatment group. Among the mild renal impairment subjects, rates of TEAEs overall were lower among upadacitinib 30 mg-treated subjects compared with placebo treated subjects. Among the impairment subjects, rates of TEAEs overall, SAEs, TEAEs leading to discontinuation of study drug, severe TEAEs, and TEAEs with reasonable possibility of being related to study drug were similar in upadacitinib-treated subjects and placebo-treated subjects In the mild renal impairment subgroup, the EAERs of COVID 19-related infections were similar between the placebo and upadacitinib 30 mg groups, and higher in upadacitinib 15 mg-treated subjects compared to placebo-treated subjects. Across the no renal impairment subjects, the EAERs of COVID 19-related infections were similar between upadacitinib-treated subjects and placebo-treated subjects. No AEs led to death and no deaths occurred among subjects with no renal impairment, mild renal impairment, or moderate renal impairment. In the RESP_MAIN Analysis Set, most of the rates of AESI were comparable among renal function subgroups. In the upadacitinib 15 mg treatment group, the rates of TEAEs of neutropenia, lymphopenia, CPK elevation and hepatic disorder were higher in subjects with no renal impairment, while the rates of serious infections and herpes zoster were higher in the mild renal impairment subgroup. In the upadacitinib 30 mg group, the rates of lymphopenia were higher in subjects with no renal impairment, while the rates of serious infection and hepatic disorder were higher in the mild renal impairment subgroup. In the ALL_TRT_RESP[subj] Analysis Set, most rates of TEAEs overall, SAEs, severe TEAEs, TEAEs leading to discontinuation of study drug and TEAEs with a reasonable possibility of being related to study drug were numerically higher in subjects with normal renal function, but still comparable to the other renal function subgroups

Hepatic Impairment

Most subjects had normal hepatic function at Baseline; few subjects had mild ormoderate hepatic impairment and no subjects had severe hepatic impairment. Only results from subjects with normal or mild hepatic function are presented.In the PC_IND/45_IND Analysis Sets, the rates for AE categories were generally similar among hepatic function subgroups, except for the rates of SAEs, which were higher in subjects with normal hepatic function, and TEAEs overall and TEAEs leading to discontinuation of study drug, which were higher in the mild hepatic impairment subgroup The rates of most AESI were similar between the subgroups, except for the percentages of herpes zoster, neutropenia, CPK elevation, and hepatic disorder, which were higher in subjects with mild hepatic impairment. In the RESP_MAIN Analysis Set, there was no consistent pattern or trend for the rates of AEs categories between the hepatic function subgroups. For the upadacitinib 15 mg treatment group, the rates of TEAEs overall and SAEs were higher in subjects with normal hepatic function, while the rates of TEAEs leading to discontinuation of study drug, severe TEAEs, and TEAEs with a reasonable possibility of being related to study drug were higher in the mild hepatic impairment subgroup. For the upadacitinib 30 mg treatment group, the rates of COVID 19-related events, SAEs, TEAEs leading to discontinuation of study drug, and severe TEAEs were higher in subjects with normal hepatic function, while the rates of TEAEs overall and TEAEs with a reasonable possibility of being related to study drug were higher in the mild hepatic impairment subgroup

In the ALL_TRT_RESP[subj] Analysis Set, there was no pattern or trend in the rates of TEAEs overall in subjects with mild hepatic impairment compared to the normal and moderate impairment subgroups. For the other AE categories, there was no pattern or trend of the rates between the subgroups

The following extrinsic factors were examined: prior biologic response status, number of prior biologics used, Baseline steroid use, and Baseline immunomodulator use (integrated long-term analysis sets only).

Prior Biologic Response Status

In the PC_IND and 45_IND Analysis Sets, the percentages of subjects with TEAEs overall and by individual AE category were higher in Bio-IR subjects compared with non-Bio-IR subjects. The percentages of subjects with AESI were generally comparable between Bio-IR and non-Bio-IR subjects. The percentage of subjects with serious infections was higher in Bio-IR subjects than non-Bio-IR subjects, whereas the opposite was observed for subjects with anemia and neutropenia. Across the RESP_MAIN Analysis Set and across treatment groups, there was no consistent pattern or trend observed for the rates of SAEs, severe TEAEs, and TEAEs leading to discontinuation of study drug between Bio-IR and non-Bio-IR subjects. The rates of TEAEs overall were higher in Bio-IR compared with non-Bio-IR subjects across upadacitinib treatment groups in theIn conclusion, the safety profile was generally similar between non-Bio-IR and Bio-IR subjects.

Number of Prior Biologics

In the PC_IND and 45_IND Analysis Sets, the percentages of subjects with TEAEs overall and by individual AE category were higher in subjects who received > 1 prior biologic compared to those who received ≤ 1 prior biologic, except for TEAE leading to discontinuation of study drug, which was comparable between groups

In the RESP_MAIN Analysis Set, the rates of TEAEs overall were numerically higher in the subjects who received > 1 prior biologic compared to those who received ≤ 1 prior biologic across the upadacitinib treatment groups. However, the rates for the other individual AE categories were comparable between the subgroups

Baseline Steroid Use

In the PC_IND and 45_IND Analysis Sets, the percentages of subjects with TEAEs overall, SAEs and severe AEs were higher between subjects who used steroids at Baseline than those who did not. Across the RESP_MAIN Analysis Set and ALL_TRT_RESP[subj] Analysis Set and across upadacitinib-treated subjects TEAEs were higher overall in steroid users compared to non-users. Additionally, SAEs, TEAEs leading to study drug discontinuation, and severe TEAEs were generally higher in steroid users

Baseline Immunomodulator Use

The number of subjects who used immunomodulators at Baseline was substantially smaller (16 subjects on placebo, 37 subjects on upadacitinib 45 mg [PC_IND], and 50 subjects on upadacitinib 45 mg [45_IND]) compared with the number of subjects who did not use immunomodulators at Baseline (331 subjects on placebo, 637 subjects on upadacitinib 45 mg [PC_IND], and 888 subjects on upadacitinib 45 mg. In the PC_IND and 45_IND Analysis Sets, the percentages of subjects with TEAEs overall and by individual AE category were higher in subjects who used immunomodulators at Baseline than those who did not, except for TEAEs with a reasonable possibility of being related to study drug as assessed by the investigator

Table 67 Pregnancy outcomes

Pregnancy Outcomes for Maternal Exposure Reports	N = 84
Total live births:	**32**
Live birth without congenital anomaly	32[a]
Live birth with congenital anomaly	0
Total fetal deaths:	**34**
Spontaneous Abortion	18
Stillbirth without fetal defects	0
Stillbirth with fetal defects	0
Ectopic pregnancy	1
Elective termination (no fetal defects or unknown)	15
Elective termination (with fetal defects)	0
Ongoing pregnancy	**11**
Lost to follow-up	**7**
Other (Molar and blighted ovum pregnancies)	**0**

a. Includes 1 infant born premature at 28 weeks gestation and 1 born premature at 34 weeks gestation, neither with reported complications.

Note: Based on cumulative exposure through 30 March 2022.

Safety related to drug-drug interactions and other interactions

According to the MAH the potential for drug-drug interactions between upadacitinib and commonly used concomitant medications as well as probe substrates for cytochrome P450 (CYP) enzymes was characterized in several Phase 1 studies. Based on the results of these studies, strong inducers of CYP3A (e.g., rifampin) reduce upadacitinib plasma exposures by approximately half while strong CYP3A inhibitors (e.g., ketoconazole) increase upadacitinib area under the concentration-time curve by 75% and maximum observed concentration (Cmax) by 70%. Concomitant administration of strong CYP2D6 inhibitors, OATP1B inhibitors, MTX, pH modifying medications, or statins have no effect on upadacitinib plasma exposures. Upadacitinib has no clinically relevant effects on plasma exposures of MTX, ethinylestradiol, levonorgestrel, statins, or drugs that are substrates for metabolism by CYP1A2, CYP2B6, CYP2D6, CYP2C19, CYP2C9, or CYP3A.

Discontinuation due to adverse events

In the PC_IND Analysis Set, the percentage of subjects with TEAEs leading to discontinuation of study drug was 4.9% in the upadacitinib 45 mg and 5.5% in the placebo group. Individual TEAEs leading to discontinuation of study drug were reported in no more than 1 subject in any group, except for worsening CD (11 [3.2%] subjects in the placebo group and 8 [1.2%] subjects in the upadacitinib 45 mg group) and gastrointestinal haemorrhage, herpes zoster, and paraesthesia (2 [0.3%] subjects each in the upadacitinib 45 mg group).

In the EXT_TRT Analysis Set, 11 (7.7%) subjects discontinued upadacitinib during the 24-week treatment period due to a TEAE; most discontinuations resulted from the TEAE of worsening of CD. The remaining discontinuations were due to the following TEAEs (1 subject each): leukopenia, abdominal abscess, and acute kidney injury.

In the RESP_MAIN Analysis Set, the EAER of TEAEs leading to discontinuation of study drug was highest in the upadacitinib 15 mg group (9.3 E/100 PY), followed by the placebo group (8.0 E/100 PY) and the upadacitinib 30 mg group (6.5 E/100 PY). The TEAEs by PT leading to discontinuation of study drug were reported no more than once in any group, except for worsening of CD (5 events in the placebo group, 5 events in the upadacitinib 15 mg group, 2 events in the upadacitinib 30 mg group) and acne (2 events in the upadacitinib 30 mg group).

In the ALL_TRT_RESP[subj] Analysis Set, the EAERs of TEAEs leading to discontinuation of study drug were slightly higher in the upadacitinib 45 mg/30 mg cohort (8.9 E/100 PY) compared to the upadacitinib 45 mg/15 mg cohort (7.6 E/100 PY). The TEAEs by PT leading to discontinuation of study drug were reported no more than once in either of these 2 cohorts, except for worsening of CD (5 events in the upadacitinib 45 mg/15 mg and 9 events in the upadacitinib 45 mg/30 mg cohorts) and anaemia, anal fistula, lung opacity, and acne (2 events each in the upadacitinib 45 mg/30 mg cohort). In subjects who received upadacitinib 30 mg as rescue medication and in subjects who were exposed to any dose of upadacitinib, the EAERs of TEAEs leading to discontinuation of study drug were 11.5 E/100 PY and 9.0 E/100 PY, respectively.

Post marketing experience

Upadacitinib 15 mg daily dose was first approved for the treatment of RA on 16 August 2019 (international birth date) in the US. Upadacitinib has been approved in RA in over 60 countries and was approved for treatment of PsA and AS in the EU on 25 January 2021 and in additional countries. Upadacitinib was also approved for the treatment of UC in the US on 16 March 2022. Upadacitinib (30 mg or 15 mg QD) was approved in the EU on 23 August 2021 and other countries for the treatment of adults and adolescents with AD. Through 30 June 2021, the estimated cumulative postmarketing exposure is 88,004 patient treatment years. AbbVie has been continuing to monitor potential new safety signals through its ongoing routine pharmacovigilance that includes weekly review of all postmarketing reports, serious and nonserious, received from all sources (including literature) and SAEs from clinical trials; quarterly review of data mining scores generated from the FDA's Adverse Event Reporting System database; and periodic reports (Periodic Safety Update Report, Development Safety Update Report, periodic adverse drug experience reports, etc.) with assessment of topics of interest, per mandated timelines, and postmarketing studies The overall safety of upadacitinib 15 mg QD therapy was evaluated through review of postmarketing reports (spontaneous, solicited, literature) received from 16 August 2019 through 22 April 2022. Search of the AbbVie global safety database retrieved 79,424 reports, which include 9,030 serious reports and 70,394 nonserious reports. Of the 70,394 nonserious reports, 95% (66,794 reports) were from solicited sources.

Review of the postmarketing safety data reported for upadacitinib to date demonstrated a similar safety profile as observed in the clinical studies for RA. The 79,424 cumulative postmarketing reports describe 182,601 events (13,759 serious and 168,842 nonserious). Of the 168,842 nonserious events, the most frequently reported AEs were in the SOC of general disorders and administration site conditions and musculoskeletal and connective tissue disorders. The most common reported AEs include pain (5%), arthralgia (4.46%), RA (4.33%), drug ineffective (3.23%) and pain in extremity (2.90%). Most of the postmarketing events are either expected for upadacitinib or commonly seen in the general population or patients with RA. Although drug ineffective is listed as one of the most frequently reported events, it is also not unexpected for a product once reaching market. Of the 13,759 serious events, the most frequently reported SAEs were in the SOCs of infections and infestations, surgical and medical procedures, general disorders and administration site conditions, and eye disorders. The most common reported SAEs by PT include COVID-19, surgery, hospitalization (2.53%), and pneumonia (2.50%); and death, knee arthroplasty, and cataract (1.58% each). The

reports of COVID-19 infection were reflective of the ongoing COVID-19 pandemic during the review period. Surgery, hospitalization, and knee arthroplasty are not unexpected in patients with RA. Pneumonia is a labeled event for upadacitinib. Reports with the generic PT Death described older patients (median age 58 years) with RA as the top indication (83%) and contained limited events details. Of the cataract reports, review of the available information provided that most of the patients were elderly (average age 66 years), which is a patient population with high prevalence and incidence of cataract. Additionally, many of these patients with cataracts were also on concomitant medications, such as steroids, which are known to cause cataract. Thus, excluding COVID-19, the type and pattern of SAEs reported were similar to what has been observed in the RA clinical trials for upadacitinib or expected for the patient populations indicated for upadacitinib or the general population. Although many of the postmarketing reports did not provide sufficient information to allow for an adequate assessment, review of the available data did not suggest any unusual findings on mortality, malignancy, and CV events including MACE and VTE. Besides the underlying medical condition, generally, the patients had at least 1 other risk factor observed for the development of these events while receiving upadacitinib.

According to the MAH, analysis of the safety data available from the postmarketing experience has not confirmed any new clinically important safety risks for upadacitinib.

2.5.1. Discussion on clinical safety

Rinvoq was approved for the treatment of rheumatoid arthritis (RA) in December 2019, and subsequently for treatment of psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) atopic dermatitis (AD) and recently (May 2022) for Ulcerative Colitis (UC). In UC, the induction dose is 45 mg for 8 weeks (with the option to prolong induction for additional 8 weeks for inadequate responders) followed by 15 or 30 mg as maintenance treatment. The proposed dose for the current indication Crohn disease (CD) is 45 mg as induction treatment for 12 weeks, followed by 15 mg or 30 mg as maintenance treatment. Thus, the proposed dosing regimen is similar, but not identical as the dose given for UC. The main difference is the proposed extended treatment, where patients with an insufficient response at week 12 are suggested to receive a lower dose (30 mg) for additional 12 weeks. After 24 weeks, it is suggested to stop treatment if no effect is seen. See discussion in 2.4.3.

The upadacitinib CD global clinical development program consists of a Phase 2 induction and maintenance study (Study M13-740), a Phase 2 OLE study (Study M14-327), two Phase 3 induction studies (Study M14-431 and Study M14-433), a Phase 3 maintenance study (Study M14-430 Substudy 1), and a LTE study (Study M14-430 Substudy 2).

In the upadacitinib CD global Phase 3 studies, the short and long-term safety profile of upadacitinib is supported by data from 833 subjects who received at least 1 dose of upadacitinib and at least 1 dose of study drug during maintenance/LTE. This group of subjects had a mean duration of 75.4 weeks. Of these subjects, 536 (64.3%) and 244 (29.3%) had exposure to upadacitinib for at least 1 year and 2 years, respectively.

The main safety analysis sets are the following:

- Placebo-Controlled Induction (PC_IND): Includes all Phase 3 treated subjects randomized to Placebo or UPA 45 mg QD during the 12-week placebo-controlled induction period.

- Extended Treatment Period (EXT_TRT): Includes all Phase 3 treated subjects who received randomized or open-label UPA 45 mg QD during induction and received UPA 30 mg QD during extended treatment.

- Randomized Responders Maintenance (RESP_MAIN): Includes all Phase 3 treated UPA 45 mg induction responders who were re-randomized to receive placebo, UPA 15 mg QD, or UPA 30 mg QD during maintenance. Data from the first dose of maintenance through the last dose of maintenance or long-term-extension prior to rescue administration of OL UPA 30 mg QD are included in this analysis set

- All Treated Responders by Subject (ALL_TRT_RESP[subj]): Includes all Phase 3 treated subjects who received study drug during induction and in maintenance or LTE. Data from the first dose of induction through the end of maintenance or long-term-extension are included. Treatment cohorts for subject are defined as:

  - PBO / PBO – received placebo during induction and maintenance/LTE; data after rescue are excluded from this cohort and reported in the RESC UPA 30 mg cohort;

  - UPA 45 mg / PBO – received 45 mg during induction or extended treatment and randomized to placebo in maintenance; data after rescue are excluded from this cohort and reported in the RESC UPA 30 mg cohort;

  - UPA 45 mg / 15 mg – received 45 mg during induction or extended treatment and randomized to 15 mg in maintenance; data after rescue are excluded from this cohort and reported in the RESC UPA 30 mg cohort;

  - UPA 45 mg / 30 mg – received 45 mg during induction or extended treatment and randomized or assigned 30 mg in maintenance/LTE; data after rescue are not excluded (as the dose did not change);

  - RESC UPA 30 mg – received OL rescue UPA 30 mg after previously receiving placebo or UPA 15 mg; only includes data from the first dose of rescue medication through the end of LTE.

  - Any UPA[Resp] – Any subjects who responded to the induction treatment (placebo or upadacitinib) and received at least one maintenance dose of upadacitinib

Overview of adverse events

During the placebo-controlled 12-week induction period, the frequency of adverse events (AEs) was 62.2% in the placebo group and 65.1% in the UPA group. SAEs occurred in 8.4% in the placebo group and 8.0 % in the UPA group. The frequency of patients with AEs leading to discontinuation was higher in the placebo group (5.5% vs 4.9%). There were no deaths in either group during the induction period. In the extended treatment group, the EAERs of SAEs, severe TEAEs, and TEAEs leading to discontinuation of study drug were higher than the rates observed during the initial 12 weeks of induction treatment with upadacitinib 45 mg. One death, due to Covid infection occurred during the extended treatment phase. In the maintenance period, the EAERs of TEAEs overall, SAEs, and severe TEAEs were higher in the placebo group compared with both upadacitinib treatment groups.

Common adverse events

Common adverse events in the CD studies were in line with previous known AEs. In the induction phase the most frequently reported TEAEs were acne, nasopharyngitis, anaemia, and headache in the upadacitinib 45 mg group. In the maintenance phase, the EAERs of TEAEs reported at ≥ 5 E/100 PY in the placebo group were generally higher than or similar to those in the upadacitinib groups; exceptions included COVID-19 in both upadacitinib groups and upper respiratory tract infection in the upadacitinib 30 mg group.

No new ADRs were suggested for inclusion in the Section 4.8 of the SmPC by the MAH. However, pneumonia were more common (>1%) in both maintenance doses of upadacitinib in the CD studies than previous reported and thus, the MAH proposed to update pneumonia from uncommon to common in the table of adverse reactions in Section 4.8 of the SmPC. The reason for the higher prevalence of pneumonia in the CD studies are not fully clarified but may be related to the COVID-19 pandemic.

In addition, the following statement regarding the frequencies of most commonly AEs was proposed in Section 4.8 of the SmPC (added text in bold):

*"In the placebo-controlled ulcerative colitis and **Crohn's disease** induction and maintenance clinical trials, the most commonly reported adverse reactions (≥3% of patients) with upadacitinib 45 mg, 30 mg or 15 mg were upper respiratory tract infection (19.9%), **pyrexia (8.7%)**, blood CPK increased (7.6%), **anemia (7.4%)**, **headache (6.6%)**, acne (6.3%), neutropaenia (6.0%), rash (5.2%), herpes zoster **(6.1%)**, **blood CPK increased (4.1%)**, **pneumonia (4.1%)**, hypercholesterolemia (4.0%), **bronchitis (3.9%)**, **aspartate transaminase increased (3.9%), fatigue (3.9%), alanine transaminase increased (3.5%)**, folliculitis (3.6%), herpes simplex (3.2%), and influenza (3.2%)."*

The frequencies are the highest frequencies observed in the induction or maintenance phases for the UPA 15 mg, UPA 30 mg or UPA 45 mg dose in the CD studies. Hence, this proposal was acceptable to CHMP.

Upon CHMP request, the MAH included a brief description of selected events, including GI perforation, in the CD population also under the heading "*Description of selected adverse reactions*" in the Section 4.8 of the SmPC (see further discussion below).

Deaths and serious adverse events

Three deaths were reported in the Phase 3 CD clinical program and on additional death was reported in the phase 2 program. Two deaths, one due to septic shock and one due to postoperative complication, also with sepsis, occurred >150 days after discontinuing UPA and it is agreed with the MAH that these events are unlikely to be related to UPA because of the long time to onset from last dose. The other two deaths were related to Covid infection; One treatment-emergent death due to COVID-19 was reported for a subject receiving upadacitinib 30 mg during extended treatment and one treatment-emergent death due to COVID-19 pneumonia was reported for a subject who received rescue with upadacitinib 30 mg during long-term treatment. All 4 fatal events were considered by the investigator as having no reasonable possibility of being related to study drug. However, for the two COVID-19 cases it could not be ruled out that UPA contributed to these events. There is already a statement in the Section 4.4 of the SmPC that serious and sometimes fatal infections have been reported in patients receiving upadacitinib and no additional update is deemed necessary.

SAEs reported in more than 1 subject were worsening of CD (UPA 2.1%, Placebo 4.3%), GI haemorrhage and intestinal obstruction (3 [0.4%] subjects each in the upadacitinib 45 mg group), anal abscess (3 [0.4%] subjects in the upadacitinib 45 mg group and 3 [0.9%] subjects in the placebo group); and abdominal pain, ileus, and nephrolithiasis (2 [0.3%] subjects each in the upadacitinib 45 mg group). In the extended treatment group (patients that did not respond on 45 mg UPA after 12 week treatment and continued to receive 30 mg UPA OL for additional 12 weeks) the EAERs for the most frequently reported TEAEs (≥ 10 E/100 PY) in the upadacitinib 45 mg/30 mg group through Week 24 were generally similar to rates reported during the initial 12 weeks of upadacitinib 45 mg treatment; except higher rates of worsening of CD, influenza and herpes zoster. The EAERs of SAEs, severe TEAEs, and TEAEs leading to discontinuation of study drug were however higher than the rates observed during the initial 12 weeks of induction treatment. The EAER of treatment-emergent SAEs increased with longer duration of exposure to upadacitinib, primarily driven by worsening of CD (64.5 E/100 PY through Week 24 compared with 51.8 E/100 PY during the initial 12 weeks of treatment).

Upon CHMP request, the MAH provided additional information regarding 122 patients (excluding the patient that initially received placebo for 12 weeks) There were no major differences in safety profiles between the 12-week induction with upadacitinib 45 mg and the 24-week treatment with upadacitinib 45 mg/30 mg, with the exception of overall SAEs (primarily driven by worsening of CD in 7 patients). Further, there were no GI perforations during the extended treatment for the 122 subjects receiving extended treatment 30mg QD after 45 mg QD induction treatment. This is reassuring and the proposal for extended induction treatment was considered acceptable. See further discussion in Section 2.4.3.

Adverse events of special interest

During the induction phase, the percentage of subjects with serious infections was similar in subjects receiving upadacitinib 45 mg and placebo (1.9% and 1.7%, respectively). The most commonly reported serious infections were of gastrointestinal infections. The only serious infections by PT reported in ≥ 1 subject in any group was anal abscess reported in 3 patients in both treatment groups. Also in patients who were non responders at week 12 and received extended treatment, the EAER of serious infections (19.4 E/100 PY) was similar to the rate reported during the initial 12 weeks of induction treatment (21.3 E/100 PY). During the maintenance phase, the EAERs of TEAEs of serious infections were higher in the placebo group (7.2 E/100PY) compared with the upadacitinib 15 mg group (4.0 E/100PY) and upadacitinib 30 mg group (5.7 E/100PY). The event rates of serious infections were slightly higher with progression of time for the upadacitinib 30 mg cohorts, but the types of serious infections observed were consistent with those anticipated in patients with moderately to severely active CD (e.g., intra-abdominal abscess), reflective of the COVID-19 pandemic, or expected for upadacitinib. No new safety signals were observed, and serious infection is adequately addressed in Sections 4.3, 4.4 and 4.8 of the SmPC. A paragraph on serious infections occurring during the treatment of CD was included in the Section 4.8 of the SmPC.

No events of active TB were reported in the studies. There is a recommendation in section 4.4 of the SmPC to screen for TB before start of Rinvoq treatment. This is acceptable.

Opportunistic infections (excluding TB and herpes zoster) occurred in three subjects during the induction or extended treatment period and three additional infections occurred during maintenance/LT. Opportunistic infections are an identified risk of upadacitinib treatment and are described in Sections 4.4 and 4.8 of the SmPC.

Herpes zoster was reported in 20 subjects receiving upadacitinib 45 mg as induction treatment, while no event of herpes zoster was reported in subjects receiving placebo. During maintenance treatment, higher rates of herpes zoster were observed with upadacitinib 30 mg compared with upadacitinib 15 mg and placebo. The majority of herpes zoster events were cutaneous (generally 1 dermatome or 2 dermatomes on the same side), with cases involving 3 or more dermatomes reported in 12.9% of subjects in the any upadacitinib treatment cohort. Four subjects experienced events with ophthalmic involvement. Herpes zoster is a well-known common AE regarding UPA treatment and a class effect for JAK inhibitors and adequately described in the SmPC. No updates are deemed necessary.

Gastrointestinal perforation

Anti-interleukin (IL)-6 receptor therapy has been associated with an increased risk of gastrointestinal perforations and given upadacitinib's effects on the IL-6 signalling pathway, GI perforation is considered an AESI and was included in the RMP as an important potential risk. In previous studies of upadacitinib, events of diverticulitis have been reported and included as uncommon in Section 4.8 of the SmPC. In addition, a warning regarding diverticulitis as risk factor for GI perforation is included in Section 4.4 of the SmPC. According to the MAH, based on the long-term data as of 15 August 2021, the incidence rates of GI perforation were ≤ 0.1 E/100 PY in both RA and PsA studies with upadacitinib 15 mg, and 0.2 E/100 PY in RA and 0 E/100 PY in PsA with upadacitinib 30 mg. No events of GI

perforation were reported in the AS and AD clinical programs. In the UC studies of upadacitinib, no events of GI perforation were reported during the induction treatment, but one single event of GI perforation was reported in a subject while on upadacitinib 15 mg during the long-term extension period. In the CD studies, 14 patients experienced GI perforation, which is the highest amount across indications. In almost all cases, the event led to discontinuation of UPA. According to the MAH, the patients had severe active CD, strictures or other signs of severe disease. The event occurred in 4 patients receiving UPA during induction treatment but in none of the placebo patients at induction and in several patients receiving rescue treatment in the maintenance phase. It could be agreed that CD patients have a higher risk of GI perforations than for example UC patients, and the findings may reflect this. Although it could not be ruled out that the GI-perforation events occurred because of lack of efficacy of UPA, there could be an association with UPA treatment. Indeed, all but one event occurred in patients on UPA-treatment, some patients with a higher risk of perforation were excluded from the study and there is a biological plausible reason why this event could be associated with the treatment. Hence, at CHMP's request, the MAH has included GI perforation as an uncommon ADR in Section 4.8 of the SmPC and also included a description of the findings in the clinical studies under the heading "Description of selected adverse reactions" in the same section. In addition, Section 4.4 of the SmPC has been updated to includes a reference to Section 4.8 and information that patients with active Crohn´s disease are at increased risk for developing GI-perforation. Finally, section 5.1 of the SmPC has been updated to include information that patients with symptomatic bowel strictures were excluded from the studies. The Annex II.D Guide for healthcare professionals and patient card have been updated accordingly. GI perforation was changed to an Important identified risks in the RMP (see 2.6.)

Additional information regarding patients with severe disease was requested to further explore this topic and the results showed that there is a clear benefit with UPA treatment also for patients with a high disease activity (CDAI >300) and stricturing/stenosing disease and no new safety problems were seen in these subgroups.

Malignancy

No TEAE of malignancy, malignancy excluding NMSC, NMSC, or lymphoma was reported in the induction phase. During maintenance and long term follow up the EAIR of TEAEs of malignancy excluding NMSC was 0.4 n/100 PY (1 subject with metastatic ovarian cancer) in the upadacitinib 15 mg group, 1.1 n/100 PY (3 subjects: 1 subject with adenocarcinoma of colon, 1 subject with invasive lobular breast carcinoma, 1 subject with pleomorphic malignant fibrous histiocytoma) in the upadacitinib 30 mg group, and 0.7 n/100 PY (1 subject with intraductal proliferative breast lesion reported as breast ductal carcinoma in situ) in the placebo group. As noticed previously for other indications, there is a concern regarding dose-dependent increase in EAIR; however, the numbers of malignancies were few and no specific pattern in type of malignancies are reported in this development program.

MACE

There were no cases of MACE reported in the induction Phase or in the UPA 15 mg group. Two (2) events occurred in the rescue group ((non-fatal stroke and non-fatal MI). Additionally, there were 2 events (acute MI and pneumonia aspiration with abnormal cardiac enzymes) adjudicated as MACE reported in the Phase 2 studies. According to the MAH, all subjects with adjudicated MACE had at least one CV risk factor, such as hypertension, obesity, smoking history, and diabetes. A dose-dependency is observed; however, the total number of cases are few which hampers firm conclusions. The risk of MACE is already adequately addressed in the SmPC; no update was deemed necessary based on the information submitted as part of this application.

<u>VTE</u>

During the induction phase, there were no VTE case reported in the CD studies. However, during the maintenance, adjudicated VTE was reported in the upadacitinib 45 mg/30 mg cohort with an incidence rate of VTE of 0.6 n/100 PY, and none was reported in the upadacitinib 45 mg/15 mg cohort. Two subjects treated with upadacitinib 45 mg/30 mg experienced adjudicated DVT and 1 subject treated with upadacitinib 45 mg/30 mg experienced DVT and PE. Additionally, one adjudicated VTE (DVT, 0.7 n/100 PY) was reported in a subject who received placebo during both the induction and maintenance treatment periods. Based on this information, no update of the SmPC was deemed required.

<u>Laboratory findings</u>

In the CD studies, ALT and AST elevation was one of the most commonly reported AEs, occurring in ≥3% of patients. Hence, it was included in the description of commonly reported events for CD in the Section 4.8 of the SmPC at the CHMP's request. During induction treatment, ≤ 1.0% of subjects receiving upadacitinib 45 mg experienced an ALT or AST ≥ 5 × ULN. During maintenance treatment, ALT or AST ≥ 5 × ULN were uncommon in subjects receiving upadacitinib 15 mg or 30 mg and were slightly higher in the upadacitinib 15 mg group. Treatment-emergent adverse events of hepatic disorder were primarily mild or moderate elevations in transaminases; no events were serious and discontinuation of study drug due to hepatic disorder was uncommon. All biochemical Hy's law cases were identified to have alternate etiologies that accounted for the increased ALT/AST and TBL. Both ALT and AST elevation are included in the Section 4.8 of the SmPC as common AEs. In addition, a monitoring guidance, although not very specific, regarding hepatic transaminases is included in Section 4.2 of the SmPC. No updates are needed necessary in those sections based on the finding in the current studies.

Anaemia is a known AE for upadacitinib, listed as a common adverse reaction in Section 4.8 of the SmPC. Monitoring recommendation and dose interruption recommendations are already included in the Section 4.2 and 4.4 of the SmPC. In the induction phase of the CD studies, the percentage of subjects with TEAEs of anaemia was numerically higher in the upadacitinib 45 mg group (7.4%) compared with the placebo group (5.5%). According to the MAH decreases in haemoglobin from baseline occurred over the first 12 to 24 weeks of upadacitinib treatment but mean changes from baseline were generally stabilized around the baseline level with continued treatment. However, as pointed out by the MAH, anaemia is also a common complication of CD, which occurs more frequently in patients with CD than in patients with UC. Anemia is included in the summary of safety profile in Section 4.8 of the SmPC.

A decrease in neutrophil levels was observed during the first 4 weeks of the study, and subsequently stabilized with fluctuations over the long-term treatment. The percentage of subjects with TEAEs of neutropenia was higher in the upadacitinib 45 mg group (2.1%) compared with the placebo group (0.3%). All TEAEs of neutropenia were mild or moderate in severity and no subjects discontinued study drug due to a TEAE of neutropenia. Neutropenia is a known risk with Rinvoq treatment, and no updates of the SmPC are considered needed.

<u>Fractures</u>

Fractures is included as a potential risk in the RMP of UPA. In the clinical CD studies, numerically more fractures were seen in patients treated with UPA than placebo, but since the information provided only lists the different fractured bone separately, and no information regarding the total amount of fractures are displayed, the analysed data is difficult to interpret. Thus, at the CHMP's request, the MAH performed a comprehensive analysis of fractures reported in the Crohn's disease (CD) program and other indication programs for upadacitinib. The EAER of fractures was 2.9 E/100 PY during the induction phase in the CD program. All cases (6) occurred in the UPA treated group; however, all 6 cases were assessed as having no relation to study drug.

In the maintenance phase, with treatment duration up to 52 weeks, the EAERs of TEAEs of fractures were similar in the upadacitinib 15 mg (0.9 E/100 PY) and 30 mg (0.8 E/100 PY) groups compared with the placebo group (0.7 E/PY.) In the overall population ever treated with UPA, 18 events were seen (1.5 E/100 PY). The overall exposure-adjusted long-term event rates of fracture by indication was highest in patients with RA and lowest in patients with CD. The fracture data from the CD clinical program do not alter the overall assessment of the risk of fracture with upadacitinib. No label update for fracture is warranted but fracture will remain as an important potential risk for upadacitinib. The MAH will continue to gather additional data to characterize fractures in on-going clinical trials, long-term post-authorization safety studies, and post marketing data. This is acceptable to the CHMP.

The MAH has updated the RMP with the long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe. The main objectives of the study are to:

- To describe and compare the incidence of the safety outcome GI perforation, and to describe and compare, where possible, the incidence of fractures and DILI, in adult individuals with UC or CD treated with upadacitinib, relative to those treated with biological drug therapies at a similar line of therapy (primary objectives).

- To describe and, where possible, to compare the incidence of the following safety outcomes in adult individuals with UC or CD treated with upadacitinib, relative to those treated with biological drug therapies at a similar line of therapy for UC and CD in the course of routine clinical care: malignancy (excluding NMSC), NMSC, MACE, VTE, serious infections (defined as all infections that require hospitalization, including opportunistic infections), herpes zoster, active TB, and all-cause mortality (secondary objectives).

- To describe the incidence of the above clinical events by dosing pattern (45 mg induction followed by 15 mg and/or 30 mg maintenance dosing), in very elderly patients (aged ≥ 75 years), in patients with moderate hepatic impairment, in patients with severe renal impairment, and in patients with chronic HBV or HCV infection.

See RMP (2.6.) for complete description.

Special populations

No new safety information occurred in this study. Dose adjustments for older patients and patients with severe kidney disease in the Section 4.2 of the SmPC are in line with the recommended adjustments for UC. This is acceptable to the CHMP.

2.5.2. Conclusions on clinical safety

The safety findings from the CD studies are in general line with the known safety profile of upadacitinib in other indications, including UC.

At CHMP's request, the MAH has included GI perforation as an uncommon ADR in Section 4.8 of the SmPC. In addition, Section 4.4 of the SmPC has been updated to include information that patients with active Crohn´s disease are at increased risk for developing GI-perforation. Finally, section 5.1 of the SmPC has been updated to include information that patients with symptomatic bowel strictures were excluded from the studies. The Annex II.D Guide for healthcare professionals and patient card have been updated accordingly.

The product information and the RMP (see Section 2.6.) have been updated in line with the safety findings from the studies in Crohn's disease. Overall, the new indication is acceptable from a safety perspective.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 13.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 13.3 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	• Serious and opportunistic infections including TB • Herpes zoster • NMSC • GI perforation
Important potential risks	• Malignancies excluding NMSC • MACE • VTEs (deep venous thrombosis and pulmonary embolus) • DILI • Foetal malformation following exposure in utero • Fractures
Missing information	• Use in very elderly (≥ 75 years of age) • Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C • Use in patients with moderate hepatic impairment • Use in patients with severe renal impairment • Long-term safety • Long-term safety in adolescents with AD

Pharmacovigilance plan

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable	--	--	--	--
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable	--	--	--	--
Category 3 – Required additional pharmacovigilance activities				

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P19-150 Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe/Ongoing	To evaluate the safety of upadacitinib among patients with RA receiving routine clinical care.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures Missing Information: use in very elderly (≥ 75 years of age); use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C; use in patients with moderate hepatic impairment; use in patients with severe renal impairment; long-term safety	• Draft protocol • Progress report • Interim report • Targeted submission of interim study report to EMA • Final study report • Targeted submission of final study report to EMA	• Submitted 16 March 2020 • Annually starting in 2022 • Approximately 5 years following market availability (31 March 2025) • 30 June 2025 • Approximately 10 years following market availability (31 March 2030) • 30 June 2030

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P19-141 Long-Term Safety Study of Upadacitinib Use in RA Patients in the US/Ongoing	To compare the incidence of malignancy (excluding NMSC), NMSC, MACE, VTE, and serious infection events in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA. To describe the incidence rates of herpes zoster, opportunistic infections such as TB, GI perforations, evidence of DILI, all-cause mortality, and fractures. To describe the incidence of the above outcomes in very elderly patients (aged ≥ 75 years). To characterize VTE clinical risk factors and baseline biomarkers in a sub-study of new initiators of upadacitinib and comparator biologic therapies.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures Missing information: use in very elderly (≥ 75 years of age); long-term safety	• Draft protocol • Progress report • Update on prevalence of baseline biomarkers and clinical risk factors within PSUR • Interim report • Targeted submission of interim study report to EMA • Final study report • Targeted submission of final study report to EMA	• Submitted 16 March 2020 • Annually starting in 2022 • Annually for the first 2 years and thereafter in accordance with the PSUR reporting schedule • Approximately 3 years post-approval (31 March 2023) • 30 June 2023 • Approximately 10 years post-approval (31 March 2030) • 30 June 2030

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P20-199 Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation/Ongoing	To describe the baseline characteristics of new users of upadacitinib (e.g., demographics, medical history, medical condition associated with upadacitinib use, and concomitant medication use), and in a similar manner, to describe new users of a bDMARD for comparison. To evaluate the effectiveness of the aRMMs, including: • Quantify the occurrence of upadacitinib use among patients who are at high risk for VTEs and among patients who are currently being treated for active TB; • Quantify the number of patients who are pregnant at the time of initiation or become pregnant while taking upadacitinib; and • Describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring.	Important identified risks: serious and opportunistic infections including TB; herpes zoster Important potential risks: MACE; VTEs; and foetal malformation following exposure in utero	• Draft protocol • Progress report • Final study report • Targeted submission of final study report to EMA	• Submitted 16 March 2020) • Annually starting in 2022 • 30 September 2024 • 31 December 2024 (estimated)

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P20-390 Long-Term Safety Study of Upadacitinib Use in AD Patients/Planned	To compare the incidence of the following outcomes, in adolescent and adult patients treated with upadacitinib relative to those treated with other alternative systemic drug therapies for AD, in the course of routine clinical care: Malignancy (excluding NMSC), NMSC, MACE, VTE, serious infections, herpes zoster, opportunistic infections, EH/Kaposi's varicelliform eruption, active TB, GI perforations, evidence of DILI, all-cause mortality, and fractures. To describe the incidence of the above AEs in patients who receive upadacitinib 15 mg and 30 mg. To describe the incidence of the above AEs by age subgroups (adolescents [12 – 17 years], adults aged 18 – 64 years, and elderly patients aged ≥ 65 years). To describe the incidence rates of the above safety outcomes in the following subgroups of interest, with limited or missing information from the clinical development program: Patients with moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies. Patients with evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic drug therapies. Patients with severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTE; DILI; fractures Missing information: use in very elderly (≥ 75 years of age); long-term safety; use in patients with moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies; use in patients with evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic	• Final Study Report	• Estimated Q4 2033

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
		drug therapies; use in patients with severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies; long-term safety in adolescents with AD		
Study P21-825 Effectiveness Evaluation of aRMMs for Upadacitinib in AD/Planned	To evaluate the effectiveness of the aRMMs for upadacitinib in AD. The specific aims are to: • Quantify the occurrence of upadacitinib use among patients who are at high risk for VTEs and among patients who are currently being treated for active TB; • Quantify the number of patients who are pregnant at the time of initiation or become pregnant while taking upadacitinib; • Describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring; and • Additional objectives to evaluate changes to aRMM (EMA procedure under Article 20 of Regulation (EC) 726/2004 [EMEA/H-A20/1517/C/004760/0017]) will be added based on feasibility.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC Important potential risks: MACE; VTEs; malignancies excluding NMSC; and foetal malformation following exposure in utero	• Final Study Report	• Estimated Q2 2026

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones		Due Dates	
Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of RA/ Planned	To evaluate the effectiveness of the aRMMs for upadacitinib in RA. The specific aim is to: • Objectives to evaluate changes to aRMM (EMA procedure under Article 20 of Regulation (EC) 726/2004 [EMEA/H-A20/1517/C/004760/0017]) will be added based on feasibility.	Important identified risk: NMSC Important potential risks: malignancies excluding NMSC	•	TBD	•	TBD
Study P21-824 A Study of Growth in Adolescents with AD Who Receive Upadacitinib/Planned	To evaluate the growth, development, and maturation in adolescents with moderate to severe AD who receive upadacitinib vs. systemic comparators in routine clinical care. The specific objectives are to: • Describe changes in body weight, standing height, height SDS, height velocity, and height velocity SDS in adolescents who received upadacitinib for the treatment of AD from initiation of upadacitinib through adulthood, relative to similar adolescents on other systemic treatments • Describe age at peak height velocity (a somatic maturation milestone) in adolescents who receive upadacitinib for the treatment of AD from initiation of upadacitinib through adulthood (18 years), relative to similar adolescents on other systemic treatments • Describe incidence of fractures in adolescents who receive upadacitinib for the treatment of AD from initiation of upadacitinib through adulthood (18 years), relative to similar adolescents on other systemic treatments	Important potential risk: fractures Missing information: long-term safety in adolescents with AD	•	Final study report	•	Estimated Q4 2030

| Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe /Planned | To describe and compare the incidence of the safety outcome GI perforation, and to describe and compare, where possible, the incidence of fractures and DILI, in adult individuals with UC or CD treated with upadacitinib, relative to those treated with biological drug therapies at a similar line of therapy (primary objectives).

To describe and, where possible, to compare the incidence of the following safety outcomes in adult individuals with UC or CD treated with upadacitinib, relative to those treated with biological drug therapies at a similar line of therapy for UC and CD in the course of routine clinical care: malignancy (excluding NMSC), NMSC, MACE, VTE, serious infections (defined as all infections that require hospitalization, including opportunistic infections), herpes zoster, active TB, and all-cause mortality (secondary objectives). | Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation

Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures

Missing Information: use in very elderly (≥ 75 years of age); long-term safety; use in patients with: moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies; evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic drug therapies; severe renal impairment at the time | • Interim study report

• Final study report | • Estimated Q4 2029

• Estimated Q2 2035 |

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
		of initiation of upadacitinib or other systemic drug therapies.		
	To describe the incidence of the above clinical events by dosing pattern (45 mg induction followed by 15 mg and/or 30 mg maintenance dosing), in very elderly patients (aged ≥ 75 years), in patients with moderate hepatic impairment, in patients with severe renal impairment, and in patients with chronic HBV or HCV infection.			
			•	•
Study P23-479 Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark/Planned	To evaluate the use of upadacitinib in routine clinical care for UC through the following specific objectives: 1. To describe the baseline characteristics of UC patients who are new users of upadacitinib (e.g., demographics, medical history, medical condition associated with upadacitinib use, and concomitant medication use), and in a similar manner, to describe new users of biologic therapies for comparison; 2. To describe the prescribing patterns of upadacitinib 45 mg for induction and 15 mg and/or 30 mg for maintenance in patients with UC; 3. To quantify the occurrence of upadacitinib use among patients who are at high risk for VTEs and among patients who are currently being treated for active TB; 4. To quantify the number of patients who are pregnant at the time of initiation or become pregnant while taking upadacitinib;	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC Important potential risks: MACE; VTEs; malignancies excluding NMSC; and foetal malformation following exposure in utero	• Final study report	• Estimated Q3 2027

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	5. To describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring; and			
	6. Additional objectives to evaluate changes to aRMM (EMA procedure under Article 20 of Regulation (EC) 726/2004 [EMEA/H-A20/1517/C/004760/0017]) will be added based on feasibility.			
Long-Term Extension Portion of Study M13-542/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 02 January 2023 • 02 April 2023

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M13-549/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 17 January 2023 • 17 April 2023

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M14-465/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 30 August 2028 • 30 November 2028

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M15-555/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 17 June 2023 • 17 September 2023

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M13-545/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 7.5 mg QD (for subjects in Japan only), and 15 mg QD in subjects with RA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 22 September 2023 • 22 December 2023

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M15-554/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 31 December 2024 • 30 April 2025

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M15-572/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 30 September 2025 • 31 December 2025

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M16-098/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with AS who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 07 November 2022 • 07 February 2023

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M19-944 (Study 1)/ Ongoing	To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active bDMARD-IR AS (Study 1), who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI, fractures; foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• Q2 2026 • Q3 2026

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M19-944 (Study 2)/ Ongoing	To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active nr-axSpA (Study 2), who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI, fractures, foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• Q2 2026 • Q3 2026

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M16-045/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents with AD	• Final study report	• 26 February 2026

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M16-047/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in combination with TCS in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents with AD	• Final study report	• 04 April 2026

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M18-891/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents with AD	• Final study report	• 21 April 2026

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Study M14-533/ Ongoing	To evaluate the long-term safety and tolerability of upadacitinib 15 mg QD and 30 mg QD in subjects with UC who were nonresponders in Study M14-234 Substudy 1, subjects who lost response during Study M14-234 Substudy 3, and subjects who completed Study M14-234 Substudy 3	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report	• Q1 2025

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M14-430/ Ongoing	To evaluate safety and efficacy of long-term administration of upadacitinib in subjects with moderately to severely active CD who participated in the Phase 3 upadacitinib induction and maintenance studies.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• Q1 2028 • Q2 2028

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious and opportunistic infections including TB	Routine risk minimization measures: • SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk. • SmPC Section 4.4 includes a statement on dose-dependency of upadacitinib on reports of serious infection. • SmPC Section 4.4 specifies a higher incidence of infections in the elderly and diabetic populations. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for serious and opportunistic infections including TB Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• The PL advises that patients do not take Rinvoq if they have active TB and warns that patients with a history of TB, or who have been in close contact with someone with TB should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 outlines lymphocyte and neutrophil counts and when not to initiate upadacitinib dosing. • SmPC Section 4.2 outlines interruption guidelines based on ALC and ANC. • SmPC Section 4.3 indicates that upadacitinib is contraindicated in patients with active TB or active serious infections. • SmPC Section 4.4 states that patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib and that upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. • SmPC Section 4.4 advises to consider the risks and benefits of initiating upadacitinib in patients with chronic or recurrent infections. • A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib should be interrupted if the patient is not responding to therapy. • Screening for TB prior to initiation is advised, and upadacitinib should not be given if active TB is diagnosed. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with untreated latent TB or in patients with risk factors for TB infection.	• P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• SmPC Section 4.4 specifies patient populations for which upadacitinib should be used with caution. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU Other routine risk minimization measures: Prescription only medicine.	
Herpes zoster	Routine risk minimization measures: • SmPC Section 4.4 describes the risk of viral reactivation such as herpes zoster. • SmPC Section 4.8 describes findings from upadacitinib clinical trials. • The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL warns that patients who have had a herpes zoster infection (shingles) should tell their doctor if they get a painful skin rash with blisters as these can be signs of shingles. • SmPC Section 4.4 advises that prior to initiating upadacitinib patients be brought up to date with all immunisations including herpes zoster according to current immunisation guidelines. • SmPC Section 4.4 advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Additional risk minimization measures: • HCP educational guide • Patient card Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for serious infections Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430)
NMSC	Routine risk minimization measures: • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 indicates that NMSCs have been reported in patients treated with upadacitinib and includes a statement on dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 advises on periodic skin examination. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. aRMMs: • HCP educational guide • Patient card • One-time distribution of DHPC in EU Other routine risk minimization measures:	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of RA • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Prescription only medicine	• Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430)
GI perforation	Routine risk minimization measures: • SmPC Section 4.4 informs on reports of diverticulitis and GI perforation in clinical trials and from post-marketing sources. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 advises to use with caution in patients who may be at risk for GI perforation and prompt evaluation if specific signs/symptoms occur. Additional risk minimization measures: • HCP educational guide • Patient card Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for GI perforation Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430)
Malignancies excluding NMSC	Routine risk minimization measures: • SmPC Section 4.4 indicates that malignancies have been reported in patients receiving JAK inhibitors, including upadacitinib, and includes a statement on upadacitinib dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. aRMMs: • HCP educational guide • Patient card • One-time distribution of DHPC in EU Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of RA • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430)
MACE	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined. • SmPC Section 4.4 indicates that events of MACE were observed in clinical trials for upadacitinib. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: • HCP educational guide • Patient card	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for MACE Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• One-time distribution of DHPC in EU Other routine risk minimization measures: Prescription only medicine.	• Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430)
VTEs (deep venous thrombosis and pulmonary embolus)	Routine risk minimization measures: • SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in clinical trials for upadacitinib. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get certain symptoms. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies in patients with VTE risk factors other than cardiovascular or malignancy risk factors, use upadacitinib with caution. Examples of the risk factors which may put a patient at higher risk for VTE are provided. • SmPC Section 4.4 on re-evaluation of VTE risk and to promptly evaluate patients with signs and symptoms of VTE and discontinue upadacitinib in	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including: • Follow-up questionnaire for VTEs • Monitoring of VTE risk and literature review provided within the PSUR Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	patients with suspected VTE, regardless of dose. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU Other routine risk minimization measures: Prescription only medicine.	• Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430)
DILI	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on transaminases. • SmPC Section 4.4 recommends prompt investigation of the cause of liver enzyme elevation to identify potential cases of DILI. • SmPC Section 4.4 advises that if increases in ALT or AST are observed during routine patient management and DILI is suspected, upadacitinib should be interrupted until this diagnosis is excluded. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for DILI Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430)
Foetal malformation following exposure in utero	Routine risk minimization measures: • SmPC Section 4.6 describes the teratogenic effects observed in animals receiving upadacitinib and states that there are no or limited data from use of upadacitinib in pregnant women. • The PL advises that patients do not take Rinvoq if they are pregnant, that Rinvoq must not be used during pregnancy, and that patients who become pregnant while taking Rinvoq must consult their doctor straight away. • SmPC Section 4.3 and Section 4.6 indicate that upadacitinib is contraindicated during pregnancy. • SmPC Section 4.6 and PL advise on use of effective contraception. • SmPC Section 4.6 advises that female paediatric patients and/or their caregivers should be informed about the need to contact the treating physician once the patient experiences menarche. • The PL informs caregivers to let their doctor know if their child has their first menstrual period while using Rinvoq. Additional risk minimization measures: • HCP educational guide • Patient card Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaires for pregnancies Additional pharmacovigilance activities (see Part III.2): • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P23-479: Effectiveness Evaluation of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• Long-term extension portion of Phase 3 CD trial (Study M14-430)
Fractures	Routine risk minimization measures: None Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Follow-up questionnaire for fractures Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-824: A Study of Growth in Adolescents With AD Who Receive Upadacitinib • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430)
Use in very elderly (≥ 75 years of age)	Routine risk minimization measures: • SmPC Section 4.2 states that there are limited data in patients 75 years of age and older.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• SmPC Section 4.4 indicates that there is an increased risk of adverse reactions with upadacitinib 30 mg in patients 65 years of age and older. • SmPC Section 4.4 specifies increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomised study of tofacitinib (another JAK inhibitor). • SmPC Section 4.2 specifies that upadacitinib 15 mg is recommended in patients 65 years of age and older. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe
Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	Routine risk minimization measures: • SmPC Section 4.4 describes the risk of viral reactivation. • The PL warns that patients who have ever had hepatitis B or hepatitis C should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 describes the need for screening and consultation with a hepatologist if HBV DNA is detected. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe
Use in patients with moderate hepatic impairment	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with hepatic impairment. • SmPC Section 4.2 states that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment. • SmPC Section 4.3 indicates that upadacitinib is contraindicated for	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	use in patients with severe hepatic impairment. • The PL advises that patients do not take Rinvoq if they have severe liver problems and warns that patients should consult their doctor or pharmacist before and during treatment with Rinvoq if their liver does not work as well as it should. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	• P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe
Use in patients with severe renal impairment	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with renal impairment. • SmPC Section 4.2 states that upadacitinib should be used with caution in patients with severe renal impairment. • SmPC Section 4.2 specifies that for RA, PsA, AS, nr-axSpA, and AD, the recommended dose is 15 mg QD for patients with severe renal impairment and that for UC and CD, the recommended dose is 30 mg QD for induction treatment and 15 mg QD for maintenance treatment for patients with severe renal impairment. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe
Long-term safety	Routine risk minimization measures: SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies are currently limited and long-term studies are ongoing. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		- P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients - Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe - Long-term extension portion of Phase 3 RA trials (Studies M13-542, M13-549, M14-465, M15-555, and M13-545) - Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) - Long-term extension portion of Phase 2/3 bDMARD-naïve AS trial (Study M16-098) - Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) - Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) - Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) - Long-term extension Phase 3 UC trial (Study M14-533) - Long-term extension portion of Phase 3 CD trial (Study M14-430)
Long-term safety in adolescents with AD	Routine risk minimization measures: None Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Additional pharmacovigilance activities (see Part III.2): - P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients - P21-824: A Study of Growth in Adolescents With AD Who Receive Upadacitinib - Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC have been updated. Particularly, a new warning with regard to gastrointestinal perforation has been added to the product information. The Annex II.D Guide for healthcare professionals and patient card have been updated accordingly. The Package Leaflet has been updated accordingly.

The MAH also took this opportunity to correct some figures in Section 5.3 of the SmPC.

In addition, the MAH will make corrections to some of the translations as part of the linguistic review: the updates are generally either grammatical corrections, QRD alignments or correction to align with the EN text. The Romanian (RO), French(FR), Danish(DA), Italian(IT), Czech(CS), Polish(PL), Norwegian (NO), Portuguese (PT), Latvian(LV) and Bulgarian (BG) translations are affected.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The parent Rinvoq and daughter Rinvoq leaflet are very similar. The additional indication wording in the daughter leaflet impacts sections 1, 2, 3, and 4 in parts, although much of the original text is the same. All of the new text has been written in the same style as the existing indications/strengths in the parent text using simple/plain English. The use of bullets to clearly show there are 6 indications also helps to keep the text clear for the reader and sub-headings to guide the reader to the correct information for them also work to ensure that patient understanding will not be impacted by the new indication. Although in some instances the wording in all sections was changed during the MAA review after the initial user testing was completed, we do not believe that this in any way impacted patient readability. In addition, the layout and design are almost identical between the parent blister / bottle leaflets and the daughter blister / bottle leaflets, with the only changes being intentional to help locate information which is indication specific The additional indication wording is not considered to impact the readability of the leaflet and would not impact the key safety messages being found in the leaflet and therefore no further readability testing is warranted.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Crohn's disease (CD) is a chronic inflammatory disease manifested by focal asymmetric, transmural, inflammation affecting any segment of the gastrointestinal tract that leads to symptoms, often debilitating, of prolonged diarrhoea with or without gross blood, abdominal pain, fatigue, weight loss, fever, anaemia and also extra-intestinal manifestations. Due to transmural inflammation, fistula formation can occur and may cause considerable distress in the form of pain, secretion and incontinence, as well as psychological suffering. Consequently, patients with CD have severely impacted quality of life (QoL), and the disease can affect the patient's ability to sleep and function at work or school. The natural history of moderate to severe CD is often progressive, with development of penetrating disease and stricture formation, ultimately requiring hospitalization and surgery, and lifelong treatment is required.

3.1.2. Available therapies and unmet medical need

The aim of medical treatment in CD has been focused on controlling inflammation and reducing symptoms. In addition to improving symptoms, an emerging goal of therapy is to heal the gut mucosa. Resolution of intestinal ulcers and endoscopic remission have been associated with positive clinical benefits, including higher rates of clinical remission, fewer hospitalizations, and few abdominal surgeries. However, improvement of the appearance of the intestinal mucosa may be more difficult to achieve than symptomatic improvement alone.

Treatment of moderately to severely active CD consists of conventional pharmaceutical therapies such as corticosteroids (for short term use) and immunomodulators [e.g., thiopurines and methotrexate], as well as biologic therapies. Contrary to the case in Ulcerative colitis (UC), aminosalicylates has shown limited efficacy in CD and is not recommended.

The approval of the first biologic infliximab over two decades ago and a few years later adalimumab greatly improved the treatment possibilities in CD. More recently, vedolizumab an anti-integrin and ustekinumab an inhibitor of IL-12 and IL-23 has been approved for use in CD.

Still, a proportion of CD patients have limited efficacy of approved treatments due to failing to respond (primary non-response), losing response over time (secondary non-response) or having contra-indications or intolerance to these medications. Regarding anti-TNF agents, data from clinical trials demonstrate that approximately 40% of patients experience primary non-response and secondary loss of response has occurred in 38% of patients at 6 months and 50% of patients at 1 year.

Therefore, there is an unmet clinical need for new effective treatments in CD.

3.1.3. Main clinical studies

This application concerns the use of upadacitinib in CD. Upadacitinib is an oral selective and reversible inhibitor of Janus kinase (JAK). The JAKs comprise 4 family members: JAK1, 2, 3, and tyrosine kinase 2 (Tyk2). Upadacitinib more potently inhibits JAK1 compared to JAK2 and JAK3. This is the first application for a JAK inhibitor for the use in treatment of CD in EU and it is supported by data from two replicate phase 3 induction studies (M14-431 and M14-433) and one phase 3 maintenance study (M14-430) which were all double-blind, randomised, placebo-controlled multi-centre studies.

These studies have been performed in both the US and EU as there are different expectances on the clinical outcomes where CDAI is used for the FDA analyses and PRO 2 is used for EU analyses.

The two Phase 3 induction studies (Study M14-431 and Study M14-433) were multicenter studies conducted in adult subjects $\geq$ 18 and $\leq$ 75 years of age with a confirmed diagnosis of CD for at least 3 months and moderately to severely active CD, with average daily very soft stool frequency (SF) score $\geq$ 4 or average daily abdominal pain score (APS) $\geq$ 2.0, and a centrally-read SES-CD $\geq$ 6 (or $\geq$ 4 for subjects with isolated ileal disease), excluding the narrowing component.

In Study M14-431, subjects should have had an inadequate response or intolerance to one or more biologic agents (Bio-IR) for CD (adalimumab, certolizumab, infliximab, ustekinumab, vedolizumab, and/or natalizumab). To be considered Bio-IR, subjects were required to meet criteria for types, doses, and durations of prior CD treatment as defined in the protocol.

In Study M14-433, subjects should have had an inadequate response or intolerance to conventional therapies but had not failed biologic therapy (Non-Bio-IR population) and/or one or more biologic agents for CD (Bio-IR population).

In Study M14-433, 45.4% of enrolled subjects were Bio-IR and 54.6% were Non-Bio-IR. Study M14-431, by design, only enrolled subjects with prior inadequate response and intolerance to biologics, with 60.8% of subjects having failed at least 2 biologics.

A total of 1150 subjects were enrolled (1021 subjects randomized into the DB portion and 129 subjects enrolled in the OL portion) in the two global Phase 3 induction studies. At the end of the induction studies, 674 subjects achieved clinical response to 12-week induction treatment with upadacitinib 45 mg QD and were re-randomized into the Study M14-430 substudy 1 maintenance period (Cohort 1; of whom 673 received at least one dose of study drug). The maintenance primary efficacy analysis was performed among the first 502 subjects who were re-randomized and dosed in Study M14-430 substudy 1 Cohort 1 (Study M14-430 substudy 1. Out of the 1150 subjects randomized in the two global phase 3 induction studies, 249 subjects did not achieve clinical response at the end of the induction period (Week 12) and were enrolled in the Extended Treatment Period.

For the maintenance study M14-430 (Cohort 1),502 subjects who received the 12-week induction treatment with upadacitinib 45 mg (including those who did not achieve clinical response with placebo and then received upadacitinib 45 mg for 12 weeks) and achieved clinical response in Studies M14-431 or M14-433 were re-randomized to either upadacitinib 30 mg QD, upadacitinib 15 mg QD, or matching placebo in a 1:1:1 ratio. Clinical response was defined as SF/APS $\geq$ 30% decrease in average daily very soft or liquid SF and/or $\geq$ 30% decrease in average daily APS and both not worse than baseline. The randomization was stratified by Bio-IR and Non-Bio-IR status in the induction studies, as well as the clinical remission (per PROs) and endoscopic response status at the entry of Study M14-430 substudy 1.

Dose selection was informed by the analysis of the 16-week safety, efficacy, pharmacokinetic, and exposure-response data from Phase 2 CD Study M13-740, which evaluated 5 induction doses of upadacitinib using the immediate-release (IR) formulation (3, 6, 12, or 24 mg twice daily [BID] or 24 mg QD) versus placebo. The results from Study M13-740 demonstrated the clinical and endoscopic efficacy of upadacitinib compared to placebo across several endpoints with doses of 6 mg BID and higher. Pharmacokinetic analyses have shown that the 12 mg BID and 24 mg BID doses of the IR formulation provided similar daily exposures to the 30 mg QD and 60 mg QD dose of the extended-release (ER) formulation, respectively. Simulations based on the exposure-response analyses showed that doses higher than 45 mg QD (e.g., 60 mg QD) were predicted to provide minimal additional efficacy (2% to 5% increase), while a dose lower than 45 mg QD (e.g., 30 mg QD) predicted 5% to 7% lower efficacy for the endoscopic endpoints compared to the 45 mg QD dose. Based on pathophysiology and data from other targeted immunomodulatory therapies, a lower dose for maintenance was expected to be effective once the initial high disease burden is reduced. Therefore, after induction treatment with 45 mg QD, 15 mg and 30 mg QD doses were chosen for maintenance treatment.

In the EMA Guideline (CPMP/EWP/2284/99 Rev. 2 Guideline on the development of new medicinal products for the treatment of Crohn's disease) "*to fulfil a claim for the treatment of Crohn's disease, it is expected that at least two confirmatory trials are provided*". This is considered as fulfilled. The MAH has received Scientific Advice from the CHMP (EMEA/H/SA/3190/5/2017/II and clarification letter EMA/660515/2018) The clinical development plan was discussed and mainly endorsed and being in line with the EMA CD GL. Most of the CHMP advice were followed with some minor deviation as discussed below. This is one of the first applications using the recommended PROs for efficacy assessment recommended in the updated CD guideline. However, for FDA analyses the CDAI score was the clinical co-primary endpoint and was analysed in a separate SAP. CDAI was used as a highly ranked secondary endpoint in the EU SAP. As the CDAI score has been used for all approved biologics in the treatment in

CD this could bring further validity to the PRO results in this study as CDAI is measured as primary endpoint in the same patients.

The co primary endpoints was the proportion of subjects with clinical remission per SF/APS (average daily very soft or liquid SF ≤ 2.8 and not worse than baseline and average daily APS ≤ 1 and not worse than baseline)) AND proportion of subjects with endoscopic response (decrease in SES-CD > 50% from baseline) assessed at week 12 for the induction studies and at week 52 for the maintenance study. Key secondary endpoints included clinical remission per CDAI (CDAI< 150), Endoscopic remission (SES-CD < 4), steroid-free clinical remission, change in FACIT-Fatigue score and change in IBDQ.

The chosen patient populations and endpoints are accepted although a more stringent endoscopic-primary endpoint would have been preferred (see further discussion in 2.4.3.). The sample size, randomisations procedures and conduct of the studies are acceptable.

3.2. Favourable effects

Induction

Study M14-431 included patients with incomplete response to biologic therapies. At week 12 the results for the clinical remission co-primary endpoint showed that 39.8% of subjects treated with 45mg upa QD achieved clinical remission per PROs compared to 14% of the placebo. In the endoscopic co primary endpoint endoscopic response, 34.6% of patients in active treatment responded compared to 3.5% in the placebo group. For the US/FDA clinical co primary endpoint CDAI remission the corresponding figures were 38.9 % for active treatment and 21,1% for placebo. All these analyses had high statistical significance with p<0.0001.

Induction study M14-433 included patients with inadequate response or intolerance to conventional therapies but had not failed biologic therapy (Non-Bio-IR population) and/or one or more biologic agents for CD (Bio-IR population). At week 12 the results for the co primary clinical endpoints showed that 50.7% of patients in active treatment responded with clinical remission per PROs compared to placebo 22.2%. For the co primary endpoint endoscopic response 45.5% responded in active treatment arm compared to 13.1% in placebo group. The corresponding figures for CDAI was 49.5% in active treatment with 29.1% in the placebo group.

In both induction studies all the key secondary clinical endpoints such as corticosteroid free clinical remission and QoL showed highly statistically significance and clinically relevant results.

Concerning the important endpoint key secondary endoscopic remission 19,1% reached this endpoint in study M14-431 compared to 2.3% in the placebo group. In study M14-433 the corresponding results were 28.9% and 7.4% respectively. In addition, the more stringent endoscopic remission endpoint (SES-CD ulcerated surface subscore-mucosal healing) showed beneficial results for active treatment where 17% reached this endpoint in study M13-431 compared to 0 patients in placebo group. In study M14-433 the corresponding figures were 25%& and 55 respectively p<0.0001.

Maintenance

Maintenance treatment with upadacitinib 15 mg or 30 mg was superior to placebo in achieving clinical remission per SF/APS (35.5%, 46.4% and 14.4% respectively) and endoscopic response (40.1%, 27.6% and 7.3% respectively) at Week 52.

Most key secondary endpoints under the pre-defined strategy for overall Type-I error control were achieved with upadacitinib 15 mg and 30 mg treatment compared with placebo. Superiority was observed for endoscopic remission and the more stringent endpoint of deep remission (combined

clinical and endoscopic remission), as well as for steroid-free clinical remission irrespective of steroid use at baseline. The result for the higher dose was overall more robust but clinically relevant results were found also for the lower maintenance dose.

However, the definition of endoscopic co-primary endpoint at week 52 is not the most relevant as it is preferred to aim at endoscopic remission because it is assumed that is important to achieve healing of the mucosa to prevent structural complications in the bowel. However, as the totality of data especially including the more strictly defined endoscopic endpoints clinical remission SES-SD <4 and also SES-CD 0-2 met statistically significance that was deemed as clinically relevant and therefore it is considered that the efficacy on intestinal mucosa is shown.

Most key secondary endpoints under the pre-defined strategy for overall Type-I error control were achieved with upadacitinib 15 mg and 30 mg treatment compared with placebo. Superiority was observed for endoscopic remission and the more stringent endpoint of deep remission (combined clinical and endoscopic remission), as well as for steroid-free clinical remission irrespective of steroid use at Baseline. Maintenance of clinical remission was achieved among subjects in clinical remission at Week 0. Improvements from Baseline for FACIT-Fatigue and resolution of EIMs continued with upadacitinib 30 mg maintenance therapy. Results of stringent endoscopic assessments (absence of ulcers by endoscopy [US]/mucosal healing [EU], SES-CD 0-2) and mean changes in markers FCP and hs-CRP support continued improvement of inflammation up to Week 52 on upadacitinib 15 mg or 30 mg QD. This is adequately reflected in the dosing recommendations in Section 4.2 of the SmPC.

Altogether the clinical study programme in Crohn´s disease shows a robust clinical efficacy in nearly all chosen endpoint an aspect of Crohn's disease.

3.3. Uncertainties and limitations about favourable effects

The PROs stool frequency and abdominal pain are often the most bothersome symptoms for the patients suffering from CD. The earlier CDAI score used in clinical trials for CD treatment includes these symptoms as well but also general wellbeing, the presence of extraintestinal symptoms, the presence of a palpable abdominal mass and has several limitations including a complex calculation and high score has been shown even for patient with irritable bowel syndrome (IBS). Therefore, with any of these symptoms score it is crucial to combine the clinical score with an endoscopic assessment as a co-primary endpoint which is the case in these studies. The CDAI score was included as a ranked secondary endpoint in the EU and the co primary endpoint it the separate SAP for US/FDA. This makes it possible to a certain limit to compare the results for SF/APS and CDAI considering that CDAI has been used as an endpoint in previous applications for treatments of Crohn's disease in EU as well.

In the study programme for CD the MAH has chosen the co-primary endpoint endoscopic response although endoscopic remission is the preferred endpoint in the updated EMA GL and also suggested in the CHMP advice. However, as several stringent endoscopic assessments including endoscopic remission (SES-CD $\leq$ 4 and at least a 2-point reduction versus baseline and no subscore > 1 in any individual variable) and mucosal healing (SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore $\geq$ 1 at baseline) showed statistically significant and clinically relevant results this has been considered acceptable by the CHMP.

Further, CD is a disease that is difficult to treat and even if about 45% of patients achieve clinical remission after induction treatment and approximately the same proportion of patients (46%) achieves clinical remission with maintenance dosing of 30 mg QD and 35% of patients with 15mg QD maintenance dosing. Therefore, it is evident that there is still unmet need for treatments in Crohn

disease. Moreover, no data is available for any potential effect on fistulas which is a very bothersome complication to CD.

The primary suggestion for the wording of the indication was "*Upadacitinib is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent, or for whom such therapies are not advisable*". However, the last section of the proposed indication "*or for whom such therapies are not advisable*" was not accepted by the CHMP as it is not in line with the population included. In response to the 1st Request for Supplementary Information (RSI), the MAH submitted a revised wording for the claimed indication in which this claim has been removed as requested by the CHMP.

3.4. Unfavourable effects

During the placebo-controlled 12-week induction period, the frequency of AEs was 62.2% in the placebo group and 65.1% in the UPA group. SAEs occurred in 8.4% in the placebo group and 8.0 % in the UPA group. The frequency of patients with AEs leading to discontinuation was higher in the placebo group (5.5% vs 4.9%). In the maintenance period, the EAERs of TEAEs overall, SAEs, and severe TEAEs were higher in the placebo group compared with both upadacitinib treatment groups.

Common adverse events in the CD studies were in line with previously known AEs. In the induction phase, the most frequently reported TEAEs in the UPA 45 mg group were acne, nasopharyngitis, anaemia, and headache. These are all listed in section 4.8 of the SmPC and do not constitute any new safety signals. In the maintenance phase, the EAERs of TEAEs reported at $\geq$ 5 E/100 PY in the placebo group were generally higher than or similar to those in the upadacitinib groups; exceptions included COVID-19 in both upadacitinib groups and upper respiratory tract infection in the upadacitinib 30 mg group.

Three deaths were reported in the Phase 3 CD clinical program and one additional death was reported in the phase 2 program. Two deaths, one due to septic shock and one due to postoperative complication, also with sepsis, occurred >150 days after discontinuing UPA and are unlikely to be caused by UPA. The other two deaths were related to COVID-19 infection; one treatment-emergent death due to COVID-19 was reported for a subject receiving upadacitinib 30 mg during extended treatment and one treatment-emergent death due to COVID-19 pneumonia was reported for a subject who received rescue with upadacitinib 30 mg during long-term treatment. It could not be ruled out that UPA contributed to these events. There is already a statement in the Section 4.4 of the SmPC that serious and sometimes fatal infections have been reported in patients receiving upadacitinib and no additional update is necessary.

SAEs reported in more than 1 subject during induction treatment were worsening of CD (UPA 2.1%, Placebo 4.3%), GI haemorrhage and intestinal obstruction (3 [0.4%] subjects each in the upadacitinib 45 mg group), anal abscess (3 [0.4%] subjects in the upadacitinib 45 mg group and 3 [0.9%] subjects in the placebo group); and abdominal pain, ileus, and nephrolithiasis (2 [0.3%] subjects each in the upadacitinib 45 mg group). In the maintenance phase, the EAER of treatment-emergent SAEs was higher in the placebo group (31.8 E/100 PY) compared with the upadacitinib 15 mg (16.9 E/100 PY) and 30 mg (18.0 E/100 PY) groups. Most SAEs were reported no more than once in each group, except for worsening of CD (11 subjects in the placebo group, 8 subjects in the upadacitinib 15 mg group).

During the induction phase, the percentage of subjects with serious infections was similar in subjects receiving upadacitinib 45 mg and placebo (1.9% and 1.7%, respectively). The most commonly

reported serious infections were of gastrointestinal infections. Also, in patients who were non responders at week 12 and received extended treatment, the EAER of serious infections (19.4 E/100 PY) was similar to the rate reported during the initial 12 weeks of induction treatment (21.3 E/100 PY). During the maintenance phase, the EAERs of TEAEs of serious infections were higher in the placebo group (7.2 E/100PY) compared with the upadacitinib 15 mg group (4.0 E/100PY) and upadacitinib 30 mg group (5.7 E/100PY). The event rates of serious infections were however slightly higher with progression of time for the upadacitinib 30 mg cohorts, but the types of serious infections observed were consistent with those anticipated. No new safety signals were observed, and serious infection is adequately addressed in the Sections 4.3, 4.4 and 4.8 of the SmPC.

No events of active TB were reported in the studies. Opportunistic infections (excluding TB and herpes zoster) were uncommon. Herpes zoster was reported in 20 subjects receiving upadacitinib 45 mg as induction treatment, while no event of herpes zoster was reported in subjects receiving placebo. During maintenance treatment, higher rates of herpes zoster were observed with upadacitinib 30 mg compared with upadacitinib 15 mg and placebo. The majority of herpes zoster events were cutaneous, with cases involving 3 or more dermatomes reported in 12.9% of subjects in the any upadacitinib treatment cohort. Four subjects experienced events with ophthalmic involvement. Herpes zoster is a well-known common AE regarding UPA treatment, a class effect for JAK inhibitors, and is adequately described in the SmPC. No updates are deemed required.

No TEAE of malignancy, malignancy excluding NMSC, NMSC, or lymphoma was reported in the induction phase. During maintenance and long term follow up the EAIR of TEAEs of malignancy excluding NMSC was 0.4 n/100 PY in the upadacitinib 15 mg group, 1.1 n/100 PY and 0.7 n/100 PY in the placebo group. As noted previously, for other indications, a dose-dependent increase in EAIR for malignancy was seen; however, the numbers of malignancies were few and no specific pattern in type of malignancies are reported.

There were no cases of MACE reported in the induction Phase or in the UPA 15 mg group. Two (2) events occurred in the rescue group (non-fatal stroke and non-fatal MI). Additionally, there were 2 events (acute MI and pneumonia aspiration with abnormal cardiac enzymes) adjudicated as MACE reported in the Phase 2 studies. A dose-dependency is observed; however, the total number of cases are few hampering firm conclusions. The risk of MACE is already adequately addressed in the SmPC; no update was deemed necessary based on the information submitted as part of this application.

During the induction phase, there were no VTE case reported in the CD studies. However, during the maintenance, adjudicated VTE was reported in the upadacitinib 45 mg/30 mg cohort with an incidence rate of VTE of 0.6 n/100 PY, and none was reported in the upadacitinib 45 mg/15 mg cohort.

ALT and AST elevation was one of the most commonly reported AEs, occurring in ≥3% of patients and thus included in the description of commonly reported events for CD in the SmPC 4.8. During induction treatment, ≤ 1.0% of subjects receiving upadacitinib 45 mg experienced an ALT or AST ≥ 5 × ULN. Treatment-emergent adverse events of hepatic disorder were primarily mild or moderate elevations in transaminases; no events were serious and discontinuation of study drug due to hepatic disorder was uncommon. Two biochemical Hy's law cases were identified but had alternate aetiologies that accounted for the increased ALT/AST and TBL.

3.5. Uncertainties and limitations about unfavourable effects

In the extended treatment group (patients that did not respond on 45 mg UPA after 12 week treatment and continued to receive 30 mg UPA OL for additional 12 weeks) the EAERs for the most frequently reported TEAEs (≥ 10 E/100 PY) in the upadacitinib 45 mg/30 mg group through Week 24

were generally similar to rates reported during the initial 12 weeks of upadacitinib 45 mg treatment; except higher rates of worsening of CD, influenza and herpes zoster. The EAERs of SAEs, severe TEAEs, and TEAEs leading to discontinuation of study drug were however higher than the rates observed during the initial 12 weeks of induction treatment. The EAER of treatment-emergent SAEs increased with longer duration of exposure to upadacitinib, primarily driven by worsening of CD (64.5 E/100 PY through Week 24 compared with 51.8 E/100 PY during the initial 12 weeks of treatment). Upon request, the MAH provided additional information regarding 122 patients (excluding the patient that initially received placebo for 12 weeks) There were no major differences in safety profiles between the 12-week induction with upadacitinib 45 mg and the 24-week treatment with upadacitinib 45 mg/30 mg, with the exception of overall SAEs (primarily driven by worsening of CD in 7 patients). Further, there were no GI perforations during the extended treatment for the 122 subjects receiving extended treatment 30mg QD after 45 mg QD induction treatment. This is reassuring and the extended treatment dosing recommendations in Section 4.2 of the SmPC are considered acceptable by the CHMP.

In line with the existing warning and dose reduction recommendations in patients at higher risk of VTE, MACE and malignancy implemented as part of the Art 20 JAKi referral (see 2.1.2.), the dosing recommendations in Section 4.2 of the SmPC have been adjusted for CD patients to state that a maintenance dose of 15 mg is recommended for patients at higher risk of VTE, MACE and malignancy.

In addition, 10 patients experienced GI perforation in the pivotal studies, and 3 additional patients in the phase 2 studies, which is the highest amount across indications. In almost all cases, the event led to discontinuation of UPA. The event occurred in one patient receiving UPA during induction treatment and 3 patients during the extended treatment period and in several patients receiving rescue treatment with UPA 30 mg in the maintenance phase. Although it is acknowledged that several patients had severe active CD, strictures or other signs of severe disease, reflecting a patient group with a higher risk of GI perforations, there is a concern regarding the safety of treatment with UPA in these patients. Anti-interleukin (IL)-6 receptor therapy has been associated with an increased risk of gastrointestinal perforations and given UPAs effects on the IL-6 signalling pathway, GI- perforation is considered an AESI and was included in the RMP as an important potential risk. Upon CHMP's request, the MAH provided additional information regarding the patients that experienced a GI-perforation event. In the majority of the GI-perforation cases, there were signs of active, progressing CD at the time of the event and thus, worsening of the underlying disease could be a possibly explanation for the events as suggested by the MAH. However, all but one event occurred in patients on UPA-treatment. In addition, some patients with a higher risk of perforation were excluded from the study and there is a biological plausible reason why this event could be associated with the treatment. Hence, at CHMP's request, the MAH included GI perforation as an uncommon ADR in Section 4.8 of the SmPC. In addition, the Section 4.4 of the SmPC has been updated to include information that patients with active Crohn´s disease are at increased risk for developing GI-perforation and that patients should be evaluated promptly if presenting with new onset of related abdominal signs and symptoms. GI perforation was changed to an Important identified risks in the RMP (see 2.6.) and the MAH has updated the RMP with a long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe. As part of the main objectives of the study, the monitoring of GI perforation is included. This is acceptable.

In the clinical CD studies, numerically more fractures were seen in patients treated with UPA than placebo, but since the information provided only lists the different fractured bone separately, and no information regarding the total amount of fractures are displayed, the analysed data is difficult to interpret. At the CHMP's request, the MAH performed a comprehensive analysis of fractures reported in the Crohn's disease (CD) program and other indication programs for upadacitinib. The EAER of

fractures was 2.9 E/100 PY during the induction phase in the CD program. All cases (6) occurred in the UPA treated group; however, all 6 cases were assessed as having no relation to study drug.

In the maintenance phase, with treatment duration up to 52 weeks, the EAERs of TEAEs of fractures were similar in the upadacitinib 15 mg (0.9 E/100 PY) and 30 mg (0.8 E/100 PY) groups compared with the placebo group (0.7 E/PY.) In the overall population ever treated with UPA, 18 events were seen (1.5 E/100 PY). The overall exposure-adjusted long-term event rates of fracture by indication was highest in patients with RA and lowest in patients with CD.

In conclusion, the update of the product information with new information on fracture is not warranted at this stage. However, fracture will remain as an important potential risk in the RMP for upadacitinib. The MAH will continue to gather additional data to characterize fractures in ongoing clinical trials, in long-term post-authorization safety studies, and from post marketing data. The MAH has updated the RMP with a long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe. As part of the main objectives of the study, the monitoring of fractures is included. This is acceptable.

Overall, long-term data for upadacitinib are still limited, since upadacitinib was first approved in 2019. Regarding unusual events such as malignancies and MACE, no updates are deemed required based on the findings from the current study.

3.6. Effects Table

Table 68 **Effects Table for Upadacitinib for moderate to severe Crohn's disease**

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Clinical remission per PROs at Week 12 Co-primary	Average daily very soft or liquid SF ≤ 2.8 and not worse than baseline and average daily APS ≤ 1 and not worse than baseline	N (%)	UPA 45mg 324 (39.8%)	171 (14.0%)	p< 0.0001	M14-431
Endoscopic response at Week 12 Co-primary	Decrease in SES-CD > 50% from baseline	N (%)	324 (39.8%)	171 (14.0%)	p< 0.0001	M14-431
Clinical remission per CDAI at Week 12-Key secondary	CDAI<150	N (%)	324 (38.9%)	171 (21.1%)	p< 0.0001	M14-431
Clinical remission per PROs at Week 4	See above	N (%)	324 (32.4%)	171 (9.4%)	p< 0.0001	M14-431
Endoscopic remission at	(SES-CD ≤ 4 and at least	N (%)	324 (19.1%)	171 (2.3%)	p< 0.0001	M14-431

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Week 12 -Key secondary	a 2-point reduction versus baseline and no subscore > 1					
Steroid-free and clinical remission per PROs at Week 12	See above	N (%)	108 (37.0%)	60 (6.7%)	p< 0.0001	M14-431
Change from baseline in FACIT-Fatigue at Week 12			11.4 [10.1, 12.8]	3.9 [2.0, 5.8]	p< 0.0001	M14-431
Change from baseline in IBDQ at Week 12			46.0 [41.7, 50.2]	21.6 [15.7, 27.6]	p< 0.0001	M14-431
Clinical remission per PROs at Week 12 Co-primary	Average daily very soft or liquid SF ≤ 2.8 and not worse than baseline and average daily APS ≤ 1 and not worse than baseline	N (%)	350 (50.7%)	176 (22.2%)	p< 0.0001	M14-433
Endoscopic response at Week 12 Co-primary	Decrease in SES-CD > 50% from baseline	N (%)	350 (45.5%)	176 (13.1%)	p< 0.0001	M14-433
Clinical remission per CDAI at Week 12-Key secondary	CDAI<150	N (%)	350 (49.5%)	176 (29.1%)	p< 0.0001	M14-433
Clinical remission per PROs at Week 4	See above	N (%)	350 (35.7%)	176 (14.8%)	p< 0.0001	M14-433
Endoscopic remission at Week 12 -Key secondary	(SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no subscore > 1	N (%)	350 (28.9%)	176 (7.4%)	p< 0.0001	M14-433
Steroid-free and clinical	See above	N (%)	126 (44.4%)	64 (12.5%)	p< 0.0001	M14-433

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
remission per PROs at Week 12						
Change from baseline in FACIT-Fatigue at Week 12			11.3 [10.0, 12.5]	5.0 [3.2, 6.8]	p< 0.0001	M14-433
Change from baseline in IBDQ at Week 12			46.3 [42.5, 50.0]	24.4 [19.0, 29.8]	p< 0.0001	M14-433
Clinical remission per PROs at Week 52		N (%)	UPA 30 mg 168 (46.4%) UPA 15 mg 169 (35.5%)	165 (14.4%)	p< 0.0001 both doses	M14-430
Endoscopic response at Week 52		N (%)	30mg 168 (40.1%) 15mg 169 (27.6%)	165 (7.3%)	p< 0.0001 both doses	M14-430
Clinical remission per CDAI at Week 52			30mg 168 (47.6%) 15mg 169 (37.3%)	165 (15.1%)	p< 0.0001 both doses	M14-430
Endoscopic remission at Week 52		N (%)	30mg 168 (28.6%) 15mg 169 (19.1%)	165 (5.5%)	p< 0.0001 both doses	M14-430
Change from induction baseline in IBDQ at Week 52]	[95% CI]	N (%)	30 mg 64.5 [58.3, 70.7] 15 mg 59.3 [52.9, 65.6]	46.4 [38.5, 54.3]	30mg p< 0.0001 15mg P<0.0033	M14-430
CR-100 at Week 52		N (%)	30mg 168 (51.2%) 15mg 169 (41.4%)	165 (15.2%)	p< 0.0001 both doses	M14-430
Steroid-free and clinical remission per PROs at Week 52		N (%)	30mg 168 (44.6%) 15mg 169 (34.9%)	165 (14.4%)	p< 0.0001 both doses 1	M14-430
Steroid-free		N (%)	30mg	61 (4.9%)	p< 0.0001	M14-430

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
and clinical remission per PROs at Week 52 among subjects taking corticosteroids for CD at Induction Baseline,			63 (38.1%) 15mg 63 (38.1%)		both doses	
Clinical remission per PROs at Week 52 among subjects with clinical remission per PROs at Week 0,		N (%)	30mg 105 (60.0%) 15mg 105 (50.5%)	101 (19.6%)	p< 0.0001 both doses	M14-430
Change from baseline in FACIT-Fatigue at Week 52 [95% CI]	[95% CI]		30mg 16.1 [14.1, 18.1] 15mg 14.3 [12.2, 16.4]	12.0 [9.4, 14.7]	30mg P=0.0039 15 mg ns	M14-430
Clinical remission per PROs and endoscopic remission at Week 52,		N (%)	30mg 168 (22.6%) 15mg 169 (13.7%)	165 (4.3%)	30mg p< 0.0001 15mg p=0.0011	M14-430
Occurrence of CD-related hospitalization through Week 52 (AO), n/100PY		(AO)n/100 PY	30mg 7.8 15mg 11.2	12.0	ns	M14-430
Resolution of EIMs at Week 52 among subjects with any EIMs at induction baseline)		N (%)	30mg 73 (35.6%) 15mg 61 (24.6%)	66 (15.2%)	30mg 0.0007 15mg ns	M14-430
SES-CD 0-2, week 52		N (%)	30mg N=168 (21.4%) 15mg	N=169 (3.0%)		M14-430

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			169 (11.2%			
Unfavourable Effects						
Adverse event	AEs during 12-week induction	N (%)	UPA 45mg 439/674 (65.1)	216/347 (62.2)		
Serious adverse event	SAEs during 12-week induction	N (%)	UPA 45 mg 54/674 (8.0)	29/347 (8.4)		
Adverse event	AEs during maintenance	N (E/100 PYs)	UPA 15 mg 723/221 (320.9) UPA 30 mg 767/229 (293.5)	554/223 (400.5)		
Serious adverse event	SAEs during maintenance	N (E/100 PYs)	UPA 15 mg 38/221 (16.9) UPA 30 mg 47/229 (18.0)	44/223 (31.8)		
Serious infections	Serious infections during maintenance	N (E/100 PYs)	UPA 15 mg 9/221 (4.0) UPA 30 mg 15/229 (5.7)	10/223 (7.2)		
Herpes zoster	HZ during maintenance	N (E/100 PYs)	UPA 15mg 9/221 (4.0) UPA 30 mg 14/229 (5.4)	5/223 (3.6)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The two pivotal induction studies demonstrated a clinically relevant and statistically significant superiority of Upadacitinib 45 mg compared to placebo in inducing the co-primary endpoint, clinical remission in patients with moderate to severe Crohn´s disease. A superior efficacy was seen in symptomatic relieve already at week 2 (CR-100) and week 4 (SF/APS), and after 12 weeks of induction treatment with 45 mg upadacitinib QD, 45.5% of patients achieved clinical SF/APS remission with active treatment compared to 18.2% in the placebo group in the integrated analyses. Further, important clinical key secondary endpoints such as steroid free clinical remission and QoL showed highly statistically significant and clinically relevant result at week 12.

The co-primary endpoint endoscopic response has well demonstrated a significant difference between active treatment and placebo in the integrated induction analyses with 40.3% responders in active treatment compared to 8.4% in placebo group. For endoscopic remission the corresponding figures were 24.4% and 4.9% for active treatment and placebo. In addition, Upadacitinib provided a beneficial effect compared to placebo regarding the strictest endpoint, mucosal healing (SES-CD) at week 12 with a treatment difference of 17% and 20% respectively for study M14-431 and M14-433 compared to placebo.

In the maintenance study statistically significant ($p<0.0001$) and clinically relevant treatment differences between both Upadacitinib doses (15 mg and 30 mg) and placebo were observed for the co-primary and all key secondary endpoints with the exception of CD hospitalisation and effect on extraintestinal manifestations (EIM) for the 15 mg. There was a clear dose response showing more robust effect with the higher maintenance dosing. For example, clinical remission per SF/APS score was reached by 46.4% of patients treated with 30 mg maintenance dosing compared to 35.5% treated with 15 mg. The corresponding figure for placebo was 15.1%. Especially in patients with a high disease burden and in patients in need of a prolonged induction regimen, the 30 mg dose seemed to provide a more pronounced beneficial effect over the 15 mg dose. The proposal to be able to choose maintenance (15 mg or 30 mg) dose after the individual patient's characteristics is therefore endorsed and reflected in Section 4.2 of the SmPC. However, in line with the conclusion of the JAKi referral (see 2.1.2.), it is stated in Section 4.2 of the SmPC that a dose of 30 mg once daily may be appropriate for CD patients with high disease burden who are not at higher risk of VTE, MACE and malignancy.

The safety profile of Rinvoq has been well characterised through studies in the currently approved indications. The induction (45 mg) and maintain doses (15 mg and 30 mg) are similar as the doses in the recently approved UC indication. The safety profile is similar to the already known safety profile with respect to common AEs. There are concerns regarding a higher amount of gastrointestinal perforation in the CD studies. As a consequence, new warning with regard to gastrointestinal perforation has been added to the Section 4.4 and Sections 4.8 and 5.1 of SmPC have been updated accordingly. The Annex II.D Guide for healthcare professionals and patient card have been updated accordingly. This risk will be monitored as part of a post authorisation safety study (See RMP 2.6.).

3.7.2. Balance of benefits and risks

Upadacitinib is an oral treatment which can be a valuable additional treatment option for Crohn´s Disease as it has shown efficacy especially in patients that have not responded or lost response to biologic therapy. In the phase 3 study programme, the treatment with updacitinib has shown a robust beneficial effect both on primary and important secondary clinical and endoscopic endpoints in patients who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent. The overall safety profile observed in patients with CD is generally consistent with that observed in patients with other approved indications. A new warning with regard to gastrointestinal perforation has been added to the product information.

3.8. Conclusions

The overall B/R of Rinvoq is positive in the indication "*RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent*".

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of moderately to severely active Crohn's disease in adult patients for RINVOQ, based on final results from three Phase III studies, two confirmatory placebo-controlled induction studies (Study M14 431/U-EXCEED/CD-1) and Study M14 433/U-EXCEL/CD-2) and a placebo-controlled maintenance/long-term extension study (Study M14-430/U-ENDURE/CD-3).

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC and the Annex II.D are updated. The Package Leaflet is updated in accordance. Version 13.3 of the RMP has been adopted.

The MAH also took this opportunity to correct some figures in Section 5.3 of the SmPC.

In addition, the MAH will make corrections to some of the translations as part of the linguistic review: the updates are generally either grammatical corrections, QRD alignments or correction to align with the EN text. The Romanian (RO), French(FR), Danish(DA), Italian(IT), Czech(CS), Polish(PL), Norwegian (NO), Portuguese (PT), Latvian(LV) and Bulgarian (BG) translations are affected.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Rinvoq EMEA/H/C/004760/II/0027'

Attachments

1. SmPC, Annex II, Package Leaflet (changes highlighted) as a relevant example with changes highlighted as adopted by the CHMP on 23/02/2023.