19 May 2022
EMA/575056/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RINVOQ

International non-proprietary name: upadacitinib

Procedure No. EMEA/H/C/004760/X/0012/G

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact Telephone +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

6-MP	6-mercaptopurine
AD	atopic dermatitis
AE	adverse event
AESI	adverse events of special interest
axSpA	axial spondylarthritis
AZA	azathioprine
Bio-IR	Subjects who had an inadequate response, loss of response, or intolerance to biologic therapy
CD	Crohn's disease
COA	Clinical Outcome Assessment
CPK	creatine phosphokinase
CPP	Critical Process Parameters
CQAs	Critical Quality Attributes
CV	cardiovascular
DVT	deep vein thrombosis
ER	extended-release
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
GCA	giant cell arteritis
GI	gastrointestinal
HPLC	High performance liquid chromatography
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
IPC	in process controls
JAK	Janus kinase
LTE	long-term extension
MACE	major adverse cardiovascular
MI	myocardial infarction
MTX	methotrexate
NMSC	non-melanoma skin cancer
non-Bio-IR	Subjects who did not have an inadequate response, loss of response, or intolerance to biologic therapy
pcJIA	polyarticular course juvenile idiopathic arthritis
PE	pulmonary embolism
PGA	physician global assessment
Ph. Eur.	European Pharmacopoeia
QD	once daily
RA	rheumatoid arthritis
RBS	rectal bleeding subscore
SAE	serious adverse event
SFS	stool frequency subscore
TB	tuberculosis
TNF	tumor necrosis factor
UC	ulcerative colitis

VTE	venous thromboembolic event

1. Background information on the procedure

1.1. Submission of the dossier

AbbVie Deutschland GmbH & Co. KG submitted on 11 September 2021 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation:

Variation(s) requested		Type
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	II

Extension application to add a new strength (45 mg) of the prolonged-release tablets, grouped with a type II variation (C.I.6.a) to include the treatment of adults with moderately to severely active ulcerative colitis who had an inadequate response, lost response or were intolerant to either conventional therapy or a Biologic agent; as a consequence of the EoI sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. The RMP (version 6.0) has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0068/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001741-PIP02-16-M01 was not yet completed as some measures were deferred. In addition, the PIP EMEA-001741-PIP01-14-M05 (P/0510/2021) was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The MAH received Scientific advice from the CHMP on 2016-05-26 (EMEA/H/SA/3190/2/2016/II). The Scientific advice pertained to clinical aspects.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

The application was received by the EMA on	11 September 2021
The procedure started on	30 September 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 December 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 December 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 January 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	27 January 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	17 February 2022
The CHMP Rapporteur circulated the Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	22 March 2022
The PRAC Rapporteur circulated the Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	25 March 2022
The PRAC Rapporteur circulated the updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	31 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 April 2022
The CHMP Rapporteur circulated the updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	13 April 2022
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the MAH on	22 April 2022
The MAH submitted the responses to the CHMP List of Outstanding Issues on	26 April 2022
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	05 May 2022
The CHMP Rapporteur circulated the updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	12 May 2022
The PRAC Rapporteur circulated the Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	12 May 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	19 May 2022

a marketing authorisation to RINVOQ on	

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Ulcerative colitis is one of the two primary forms of idiopathic inflammatory bowel disease (IBD) along with Crohn's Disease (CD). It is postulated that UC is caused by unregulated and exaggerated local immune response to environmental triggers in genetically susceptible individuals.

2.1.2. Epidemiology

Studies conducted in various geographic regions have found an increasing trend in the prevalence of UC over time, with the highest prevalence (cases per 100,000 persons) of 505.0 in Europe, 286.3 in North America, and 106.2 in Asia and the Middle East. In a 2017 report, the annual incidence of UC (cases per 100,000 person-years) was 57.9 in Europe, 23.1 in North America, and 6.5 in Asia and the Middle East.

2.1.3. Clinical presentation, diagnosis and prognosis

UC is a chronic, relapsing inflammatory disease of the large intestine characterized by inflammation and ulceration of mainly the mucosal and occasionally submucosal intestinal layers. The hallmark clinical symptoms include bloody diarrhea associated with rectal urgency and tenesmus. The diagnosis of UC is suspected on clinical grounds and supported by diagnostic testing, and elimination of infectious causes.

Ulcerative colitis is a serious disease that, in some cases, may cause life-threatening complications that can be fatal. The most severe intestinal manifestations of UC are toxic megacolon and perforation. Extra-intestinal complications include arthritis, dermatological conditions, uveitis, and primary sclerosing cholangitis. Subjects with UC are at an increased risk for colon cancer, and the risk increases with the duration of disease as well as extent of colon affected by the disease.

2.1.4. Management

The aim of medical treatment in UC is to control inflammation, reduce symptoms and heal the mucosa. Available pharmaceutical therapies are limited, do not always completely abate the inflammatory process, and may not heal the mucosa.

Conventional therapies include oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide) and corticosteroids. These therapies are recommended for mild to moderate active UC. Corticosteroids are used in subjects with more severe symptoms but are not recommended for longer term therapy due to their side effects. The frequency and severity of corticosteroid toxicities are significant, including infections, emotional and psychiatric disturbances, skin injury, and metabolic bone disease. Corticosteroids are not effective for the maintenance of remission, and the UC practice guidelines from the American College of Gastroenterology state that the optimal goal of management is a sustained and durable period of steroid-free remission. Similarly, the European Medicines Agency

(EMA) guideline for Development of new medicinal products for the treatment of Ulcerative Colitis recommend against chronic steroid treatment.

Subjects with moderate to severe symptoms may derive some benefits from conventional therapy with immunomodulatory agents (azathioprine [AZA], 6 mercaptopurine [6-MP], or methotrexate [MTX]); however, the use of these agents is limited as induction treatment due to a slow onset of action (3 to 6 months) and as maintenance therapy due to adverse events (AEs), including bone marrow suppression, infections, hepatotoxicity, pancreatitis, and malignancies.

Biologics agents targeting specific immunological pathways have demonstrated efficacy in treating subjects with UC. Anti tumor necrosis factor (TNF) agents (infliximab, adalimumab, and golimumab) were the first biologics to be used for IBD, followed by vedolizumab, an integrin receptor antagonist, and ustekinumab, an interleukin-12 and -23 antagonist.

Only 17% to 45% of subjects who receive biologics achieve clinical remission. For some biologics the onset of efficacy can be slow and take over 3 months to achieve maximal efficacy, with response rate to induction treatment of only about 50%. In addition, anti drug antibodies can lead to loss of response and hypersensitivity reactions.

Even with availability of these therapies, up to 25% of subjects with UC may require hospitalization and approximately 15% of subjects develop acute severe ulcerative colitis (ASUC), a life-threating condition where hospitalization and inpatient treatment is advised and where a fast onset of response is crucial. Over a decade, approximately 10% to 15% of UC subjects experience an aggressive clinical course leading to high rates of relapse, and 10% to 15% of UC subjects require removal of the colon/rectum, to eliminate the source of the inflammatory process, although colectomy is accompanied by significant morbidity. Thus, there remains a clear medical need for additional therapeutic options in UC for subjects with inadequate response to or intolerance to conventional therapies and biologic therapies.

The Janus kinases or JAKs are a family of intracellular tyrosine kinases that function as dimers in the signaling process of many cytokine receptors. The JAKs play a critical role in both innate and adaptive immunity, making them attractive targets for the treatment of inflammatory diseases. Targeting the JAK signaling pathway for autoimmune diseases is supported by the involvement of various proinflammatory cytokines that signal via JAK pathways in the pathogenesis of these immune-mediated inflammatory disorders.

Pro-inflammatory cytokines (primarily IL-6, IL-7, IL-15, and IFN-γ) transduce signals via the JAK1 pathway and are involved in ulcerative colitis pathogenesis.

Tofacitinib, the first drug studied in this class, is an oral JAK inhibitor that inhibits JAK1, JAK2, and JAK3 with high in vitro functional specificity for kinases 1 and 3. Tofacitinib has been approved in the United States, Europe, and in other countries for treating moderately to severely active RA and subsequently for the treatment of PsA and UC. Filgotinib is an oral JAK1 inhibitor with high in vitro functional specificity for kinases 1 over 2 and is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.

2.2. About the product

Upadacitinib is a selective and reversible Janus kinase (JAK) inhibitor that is being developed for the treatment of moderately to severely active ulcerative colitis (UC) in adults. Upadacitinib was approved for treatment of rheumatoid arthritis (RA) in the US in August 2019 and in EU in December 2019. It

was approved for treatment of psoriatic arthritis and ankylosing spondylitis in the EU in January 2021, and for atopic dermatitis (AD) in August 2021.

This proposed new indication is:

Ulcerative colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

EMA's safety committee, PRAC, has started a review of the safety of Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis).

The review was prompted by the final results from a clinical trial (study A3921133) of the JAK inhibitor Xeljanz (tofacitinib). The results showed that patients taking Xeljanz for rheumatoid arthritis and who were at risk of heart disease were more likely to experience a major cardiovascular problem (such as heart attack, stroke or death due to cardiovascular disease) and had a higher risk of developing cancer than those treated with medicines belonging to the class of TNF-alpha inhibitors. The study also showed that compared with TNF-alpha inhibitors, Xeljanz was associated with a higher risk of death due to any cause, serious infections, and blood clots in the lungs and in deep veins (venous thromboembolism, VTE).

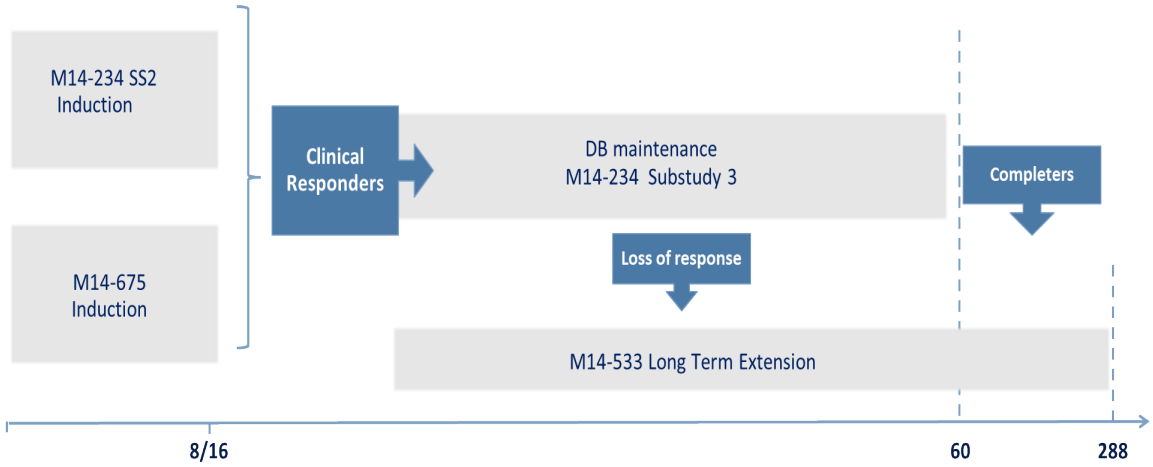
In addition, preliminary findings from an observational study involving another JAK inhibitor, Olumiant (baricitinib), also suggest an increased risk of major cardiovascular problems and VTE in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.

In the treatment of inflammatory disorders, Olumiant and other JAK inhibitors work in a similar way to Xeljanz. PRAC is therefore carrying out a review to determine whether these risks are associated with all JAK inhibitors authorised in the EU for the treatment of inflammatory disorders and whether the marketing authorisations for these medicines should be amended.

The review of JAK inhibitors in the treatment of inflammatory disorders has been initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004 and is currently on-going.

2.3. Type of Application and aspects on development

The Phase 3 program includes two replicate Phase 3 induction studies (Study M14-234 Substudy 2 and Study M14-675), a Phase 3 maintenance study (Study M14-234 Substudy 3), and a Phase 3 long-term extension (LTE) study (Study M14-533) (Figure 1). In addition, a Phase 2b placebo-controlled, dose-ranging induction study (Study M14-234 Substudy 1) was conducted.



DB = double-blind; SS2 = Substudy 2; UC = ulcerative colitis

Note: Subjects received Upadacitinib 30 mg QD or 45 mg QD in Study M14-234 SS1 who achieved clinical response at the end of induction study can also enter Study M14-234 SS3. Subjects who did not achieve clinical response at the end of the induction study from the Phase 2 Study M14-234 SS1, or achieved clinical response per Partial Adapted Mayo Score but with missing endoscopy at Week 8/16 of Study M14-234 SS1 or Study M14-675 due to COVID 19 can also enter Study M14-533.

Figure 1 Overview of the Upadacitinib UC Phase 3 Program

The MAH received Scientific Advice at the CHMP (EMA/CHMP/SAWP/336739/2016 EMEA/H/SA/3190/2/2016/II), where the rather complex study design of study M14-234 (a three part study with a seamless design including one dose finding part (substudy 1), one induction study (substudy 2) and a maintenance study (substudy 3) was discussed and approved. Most of the CHMP advices were followed with some minor deviation that are discussed in relevant sections.

2.4. Quality aspects

2.4.1. Introduction

The scope of this line extension grouped application is to introduce a higher dose strength of 45 mg to the currently approved strengths 15 mg and 30 mg, in order to support a new indication (treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy of a biologic agent).

The finished product is presented as prolonged-release film-coated tablet containing upadacitinib hemihydrate as active substance, equivalent to 45 mg upadacitinib.

Other ingredients are:

-in tablet core: hypromellose, microcrystalline cellulose, mannitol, tartaric acid, silica colloidal anhydrous, magnesium stearate;

-in the film-coating: poly(vinyl alcohol), macrogol, talc, titanium dioxide, iron oxide yellow, iron oxide red.

The product is available in HDPE bottles with desiccant and propylene cap or in polyvinyl chloride/ polyethylene/polychlorotrifluoroethene-aluminium blisters.

2.4.2. Active Substance

The active substance (AS) upadacitinib has already been assessed in the centralised procedure during the initial Marketing Authorisation Application and subsequent variation applications. No new information relating to the active substance has been presented in the application for the new 45 mg tablet strength; this is acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product (FP) is presented as an oblong, biconvex film-coated prolonged-release tablet containing 45 mg of upadacitinib. The tablet has a yellow colour, and the dimensions are 14.0 mm x 8.0 mm. The tablet is plain on one side and has “a45” debossed on the other side.

The description and composition of the finished product is satisfactory. The pharmaceutical development of the 45 mg prolonged-release tablet was based on the extensive knowledge gained during development of the lower strengths (15 mg and 30 mg). The 15 mg and 30 mg prolonged-release film-coated tablets were co-developed with the 7.5 mg (not marketed in Europe). Development information was provided in Module 3 about all the strengths of upadacitinib prolonged-release tablets in the original market application EMEA/H/C/004760.

The release rate of upadacitinib tablets is controlled through the use of hypromellose (hydroxypropyl methylcellulose, HPMC). Tablets are made using a granulation process where the AS is granulated with microcrystalline cellulose (MCC) and HPMC. The granules are dried, milled and then blended with the extragranular excipients prior to compression into tablets.

Upadacitinib prolonged release 45 mg tablet were developed with the same upadacitinib granules and the same extragranular excipients as used in the already assessed 7.5 mg (not marketed in Europe), and already authorised 15 and 30 mg tablets. The same granulate blend is used for all tablet strengths. All dose strengths of upadacitinib tablets have identical tablet core weight, size and shape (15 mg, 30 mg, 45 mg). HPMC is used as a binder and release controlling polymer. The granulate blend contains HPMC, where it also serves as a binder. The remaining portion of the HPMC is added during preparation of tablet blends. Tablets of various strengths differ in the amount of AS and the corresponding amount of filler (MCC) and cosmetic film coating used in the tablets.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The quality and function of each excipient, their quality and quantity have been sufficiently discussed.

The formulation used during clinical studies is the same as that intended for marketing bar a change in the film-coating colour and debossment of the tablets. Since the new strength subject of this application has been developed for a new indication no bioequivalence study was performed.

There were two major goals for developing an appropriate Upadacitinib 45 mg Prolonged Release Tablet dissolution method: (1) clinically relevant discrimination between the 30 mg formulations used to establish IVIVC for the upadacitinib lower strengths, and (2) complete release from the 45 mg Upadacitinib Tablet. The dissolution method for 7.5, 15 and 30 mg is not appropriate for the 45 mg tablet because it does not provide clinically relevant results and it does not enable complete in vitro release. The development of the proposed dissolution method waError! Reference source not

found.s described in detail in the dossier and the proposed dissolution conditions were scientifically justified.

The discriminatory power of the proposed 45 mg dissolution method was primarily based on the Level A Linear IVIVC established across the 15, 30 and 45 mg tablets. The discriminatory power of the dissolution method was demonstrated using 30 mg tablet dissolution data (generated using the proposed 45 mg method). It is agreed that these data also can be representative for the 45 mg tablet because it was sufficiently demonstrated that the method can distinguish non-bioequivalent batches from the commercial formulation. The use of the 30 mg tablets to demonstrate the discriminatory properties of the proposed 45 mg dissolution method is further justified based on the similarity in the formulation design and the release mechanism for all dosage strengths. In addition, this dissolution method was used to establish a Level A IVIVC including the 45 mg strength. The Level A IVIVC has been acceptably established and further justify the discriminatory properties of the 45 mg method.

The Level A IVIVC is acceptably designed and validated across 15, 30 and 45 mg dosage strengths and supports the future use of a biowaiver for the 45 mg strength.

Dissolution results demonstrating that there is no risk for dose dumping in the presence of alcohol had been presented for the 30 mg tablets; it is agreed that these data also are applicable for the 45 mg tablet strength.

A summary of the manufacturing process development history is included in the dossier. Pharmaceutical development of the finished product contains QbD elements. A summary of the systematic quality risk management (QRM) process utilised during development was presented in the dossier. The quality target product (QTPP) of this higher strength is identical to that of the already assessed 7.5 mg and already authorised, 15 mg and 30 mg strengths.

The process covers definition of the quality target product profile (QTPP), identification of critical quality attributes (CQAs) risk assessment and evaluation of risk factors on the drug product CQAs. The critical quality attributes identified are: assay, uniformity of dosage units, degradation products, dissolution, microbiological quality, water content, and appearance.The risk factors evaluated were found to be related to formulation, process and packaging. For the initial risk assessment, an overall risk rating was given for the impact of each risk factor on each CQA based on early development, clinical manufacturing, scientific rationale, mathematical modeling, previous experience with similar products and/or literature sources.

Based on the initial risk assessment, areas for development were identified and development work was carried out. All of the risk factors were mitigated to low in the final risk assessment. A discussion of the risks associated with each CQA was presented in the dossier.

Overall, the manufacturing process development has been described in sufficient details. Critical Process Parameters (CPPs) were discussed in relation to Critical Quality Attributes (CQAs) identified during formulation development. The acceptable ranges applied for CPPs and in process controls (IPCs) are justified.

Design spaces covering granulation and coating of the finish product were evaluated and found acceptable in the initial MAA application (EMEA/H/C/004760). For the current procedure, the same granules are utilised as for 15 mg and 30 mg tablets, and an identical design space covering the granulation process is suggested. As the new strength uses a different coating in a slightly different amount, the design space covering the coating process has been slightly modified compared to the design space already approved for 15 mg and 30 mg tablets.

The design space granulation parameters have been sufficiently justified in the dossier. The coating parameters design space is also accepted based on the finished product manufacturers extensive

knowledge regarding the manufacturing process and acceptable batch data. As mentioned above, the coating is for cosmetic purpose only and that it has no function in the prolonged-release mechanism of the formulation. Furthermore, none of the process parameters associated with coating is found to be critical. Therefore, the proposed design spaces covering the granulation and the coating steps are found to be acceptable for the new strength too.

The product is available in HDPE bottles with desiccant and a child resistant polypropylene (PP) cap or in polyvinyl chloride/ polyethylene/ polychlorotrifluoroethene polymer blisters with push through aluminium foil.

This is the same packaging material used for the authorised strengths. Specifications were provided for all packaging materials and compliance with relevant EU legislation has been confirmed for the blister packaging materials and the bottle pack. At the time of initial approval, it has also been confirmed that the bottle with child resistant closure complies with ISO8317.

The critical attributes of the container closure have been discussed in relation to product CQAs and it has been concluded that the packaging should protect the product from moisture. Moisture uptake modelling studies were presented, the selected packaging configurations have been evaluated in stability studies and confirmed suitable. The information provided is assessed as sufficient to support the use of the selected container closures.

2.4.3.1. Manufacture of the product and process controls

The manufacturing process consists of six unit operations: granulation, milling, blending, tableting, cosmetic coating and packaging. An acceptable process description has been provided.

A summary of the full finished product control strategy has been presented. The in-process controls (IPCs) and their applied limits have been justified and acceptable ranges have been set. The blending unit operation was identified as the only critical step in the process and is controlled by an appropriate IPC (total number of revolutions in the blending unit operation). No other critical process parameters have been identified.

Design spaces were developed and proposed for the granulation and coating steps of the manufacturing process of the medicinal product at commercial scale; these steps of the process are common for all the strengths as they are produced from a common blend.

Process hold times were already established at the time of initial approval for the milled granulate, final blend, uncoated and coated tablets based on relevant stability studies.

The process would be considered a non-standard process as per the process validation guideline because it concerns a modified release formulation. However, as with the authorised strength, it has been claimed that the manufacturing site has previous experience with similar types of products and in the meantime with the authorised RINVOQ tablets as well (150 batches). It is therefore, accepted that the applicant has sufficiently justified that the product process can be considered standard for the proposed particular manufacturer in line with the relevant guideline.

Process validation will be conducted on three consecutive production-scale batches of the 45 mg tablets following a traditional approach at the commercial manufacturing facilities before commercialisation of the product. A validation plan including the additional sampling proposed is provided in the dossier; this is acceptable.

2.4.3.2. Product specification

The finished product release and shelf-life specifications include appropriate tests and limits for description (visual), identification (UV, HPLC), assay (HPLC), degradation products (HPLC), water content (loss on drying - in-house), dissolution (Ph. Eur.) and uniformity of dosage units (Ph. Eur.).

The specifications are outlined in accordance with ICH Q6A. Limits for degradation products are in line with ICH Q3B. The proposed dissolution a three-point specification limits are in line with the requirements stated in “Guideline on quality of oral modified release products” and the Level A IVIVC further justify the proposed limits.

It is noted that the specifications cover the same tests as the approved 15 mg and 30 mg tablets. The exclusion of tests for microbiological quality, residual solvents, elemental impurities and mutagenic impurities have been acceptably justified based on the previously assessed information on the already approved strength.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data covering 11 batches of the 45 mg prolonged-release tablet was presented, 3 of them using the commercial formulation manufactured by the commercial site. All batches including those for clinical use meet the commercial specification acceptance criteria.

2.4.3.3. Stability of the product

Stability data on three representative batches of Rinvoq 45 mg tablets stored in the proposed blisters and bottles packaging for up to 12 months under long-term conditions (25 ± 2 °C / 60% ± 5% RH) and at intermediate (30 ± 2 °C / 75% ± 5% RH), and under accelerated conditions (40 ± 2 °C / 75% ± 5% RH) for six months has been presented according to ICH guideline. One batch is at approximately 80% of the commercial launch batch size and two batches are at 180% of commercial launch batch size. If the batch size was scaled up to the maximum commercial batch size, these batches would be at 20 and 45% of maximum batch size, respectively.

Samples were tested for description, assay, degradation products, water content, and dissolution. At selected intervals, the tablets were also tested for water activity, total aerobic microbial count (TAMC) and total combined yeasts and molds count (TYMC) as per Ph. Eur. methods.

No significant change in any of the quality attributes monitored were seen at either long term, intermediate or accelerated conditions. Some out of trend (and out of specification) results were recorded for dissolution in both bottle and blister presentations at the 3-month timepoint only, which was not observed at later timepoints. The observed higher results was caused by insufficient

preparation of the dissolution medium. After update of the method (more vigorously mixed dissolution medium) all subsequent time points have met the dissolution acceptance criteria.

Tablets stored in the bulk package configuration of a single polyethylene bag inside a heat-sealed laminate foil bag at -20°C and 50°C/75% RH for 2 weeks, 30°C/75% RH for up to 12 months (2 batches) and 40°C/75% RH for up to 1 month showed no change in description, assay, degradation products and dissolution data compared to initial values. No change was observed for TAMC and TYMC at 30°C/75% RH for up to 12 months.

A photostability study as per ICH Q1B for 3 batches was performed. No meaningful changes were observed for assay, degradation products, description and dissolution in tablets exposed without the primary packaging (3 batches). Based on these stability data, no restrictions will be used to control light exposure.

In-use studies were performed for the bottle packaging by removing one tablet at a time over a 60-day period after 9 months of storage at 30 °C/ 75% RH (2 batches). The 60-day in-use studies equal to twice the expected in-use period and was performed without desiccant representing a worst case scenario. No meaningful changes were observed for description, degradation products, assay and dissolution. As expected, water content increased as a result of opening and closing the bottle repeatedly in the 75% RH environment. Water content values up to 7.6% were observed in the in-use studies performed without desiccant. All the other parameters remained within the specification acceptance criteria. Therefore, it is concluded that no in-use shelf life is warranted to be defined in line with the authorised strengths.

Forced degradation studies were performed on the 7.5 mg strength because they represent the worst case in terms of drug loading. Samples were exposed to heat, heat/humidity, light, hydrolysis (exposure to acid and base in conjunction with heat) and oxidation (exposure to hydrogen peroxide and Iron (III)). Following exposure to each stress condition, the samples were analysed for assay and impurities. At each stress condition, the degradation products were separated from the upadacitinib peak. The forced degradation data indicate that the method is stability indicating.

In a temperature cycling study no meaningful changes were observed for description, degradation products, assay, and dissolution data during the 35 day temperature cycling period (2 batches stored in blister and bottle). Based on the stability data, temperature cycling of -20°C for 15 days, and 50°C for 15 days is justified for Rinvoq tablets stored in blisters and bottles with desiccant.

Based on the overall data presented, a shelf life of 2 years for tablets stored in blisters and bottles with desiccant without any special temperature storage conditions but with the precaution “Store in the original blister or bottle in order to protect from moisture. Keep the bottle tightly closed.” as per SmPC sections 6.3 and 6.4, are acceptable.

2.4.3.4. Adventitious agents

No excipient or materials of animal or human origin are used. Magnesium stearate are derived from vegetable source.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance information was assessed and found acceptable in the initial MAA application for Rinvoq 15 mg prolonged-release tablets (EMEA/H/C/004760). No new information is provided for the current application.

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The new strength of 45 mg prolonged-release film-coated tablets is introduced to support a new indication. The new strength was developed based upon the already approved 15 mg and 30 mg tablets (and the lower not marketed strength of 7.5 mg). Extensive development information was provided about all three strengths (7.5 mg 15 mg and 30 mg) of Rinvoq prolonged-release tablets. The information specific for the 45 mg tablets has been assessed in the current procedure and found satisfactory. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant has applied QbD principles in the development of the finished product and their manufacturing process. Design spaces have been proposed for two steps in the manufacture of the finished product (granulation and coating). The design spaces have been adequately verified.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way

2.4.6. Recommendations for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical studies were submitted which was considered acceptable to the CHMP.

2.5.2. Ecotoxicity/environmental risk assessment

The MAH has provided an ERA, but 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, ankylosing spondylitis and atopic dermatitis.

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.

Phase I

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

A $PEC_{SW-TOTAL}$ was calculated (0.6 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 five 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	0.6 µg/L	63 µg/L	0.01 (<1)
Groundwater	0.15 µg/L	160 µg/L	0.00094 (<1)
Microorganism	0.6 µg/L	100000 µg/L	0.000006 (<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	0.68 mg/kg	15.6 mg/kg	0.044 (<1)

Conclusion

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

2.5.3. Discussion and conclusion on non-clinical aspects

The non-clinical aspects of upadacitinib were thoroughly evaluated during the original approval procedure for Rinvoq. No new non-clinical studies were submitted in support of the present application which was considered acceptable to the CHMP.

Section 5.3 of the SmPC was updated in line with the SmPC guideline to limit the information to the findings.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

	M14-234			M14-675 (Phase 3 Induction)	M14-533 (Long-Term Extension)
	Substudy 1 (Phase 2b Induction)	Substudy 2 (Phase 3 Induction)	Substudy 3 (Phase 3 Maintenance)		
Duration of Treatment	8 weeks	Up to 16 weeks (Weeks 1 – 8: Induction; Weeks 9 – 16: Extended Induction)	Up to 52 weeks	Up to 16 weeks	Up to 288 weeks
Number of subjects enrolled/exposed to at least 1 dose of upadacitinib	382/336	474/404	1046/659	522/460	913/877
Study Blind	Double-blind	Double-blind to Week 8; open-label from Week 8 to Week 16 in extended treatment period	Double-blind to Week 52	Double-blind to Week 8; open-label from Week 8 to Week 16 in extended treatment period	Open label in Cohort 1[e] and blinded in Cohort 2[f]
Primary Efficacy Endpoint[c]	Clinical remission at Week 8 per Adapted Mayo score[b]	Clinical remission at Week 8 per Adapted Mayo score[c]	Clinical remission at Week 52 per Adapted Mayo score[c]	Clinical remission at Week 8 per Adapted Mayo score[c]	NA
Status	Completed	Completed	Ongoing[d]	Completed	Ongoing

Bio-IR = subject who had demonstrated inadequate response to, loss of response to, or intolerance to biologic therapy (biologic inadequate responders); COVID-19 = coronavirus disease 2019; NA = not applicable; Non-bio-IR = subject who had received a prior biologic for up to 1 year but discontinued the biologic for reasons other than inadequate response or intolerance (e.g., change of insurance, well controlled disease) or met the criteria for inadequate response, loss of response or intolerance to aminosalicylates, corticosteroids and/or immunosuppressants as defined in the protocol.; PBO = placebo; QD = once daily; RBS = rectal bleeding subscore; SFS = stool frequency subscore; SS1 = Substudy 1; SS2 = Substudy 2; SS3 = Substudy 3; UC = ulcerative colitis

a. Subject was a clinical responder per Partial Adapted Mayo at Week 8/16 but missed having endoscopy performed at Week 8 or 16 due to the COVID-19 pandemic.
b. SFS ≤ 1, RBS of 0, and endoscopic subscore ≤ 1.
c. SFS ≤ 1 and not greater than baseline, rectal bleeding subscore (RBS) of 0, and endoscopic subscore ≤ 1. Evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2.
d. The primary efficacy analysis was planned to be based on the first 450 randomized subjects with 8-week upadacitinib 45 mg QD induction treatment in Study M14-234 SS3 Cohort 1 under the protocol for 52-week maintenance treatment, SS3 study is ongoing.
e. Subjects who had not responded at the end of the induction period in Study M14-234 SS1 or who had loss of response during the maintenance period of Study M14-234 SS3.
f. Subjects who complete Study M14-234 SS3 through Week 52.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The characterization of upadacitinib pharmacokinetics after single and multiple doses, absorption, distribution, metabolism, excretion (ADME) characteristics, drug-drug interaction potential, and pharmacokinetics in special populations were included in the regulatory submission dossier for the use of upadacitinib in the treatment of RA. To support the PK information in this application the MAH has provided a BA-study and a cocktail DDI study using multiple doses of 45 mg upadacitinib. Further a level A IVIVC has been submitted. Data from the Phase 2b and 3 studies (Studies M14-234 and M14-675) were utilized to characterize upadacitinib pharmacokinetics (popPK) and exposure-response relationships in subjects with UC.

Population pharmacokinetic analysis

Population pharmacokinetic analysis was performed using data from Studies M14-234 SS1, M14-234 SS2, and M14-675 for Induction. The model was developed using nonlinear mixed effects modeling approach in NONMEM 7.4.4. A total of 525 of these records (3.6%) were below the LLOQ. Given the small fraction of concentrations below the LLOQ, the M5 imputation method was used by imputing BLQ concentrations with LLOQ/2. The first LLOQ/2 after last dose was included in the analysis, while the rest were excluded. Additional 4.5% of data were excluded after applying the pre-decided exclusion rules. All concentrations greater than the computed upper limit or below the computed lower limit were flagged as outlier concentrations and thus excluded from the analysis dataset (4.3%).

Statistically significant covariates identified in the previous model (subject population [HV versus AD/UC/CD and RA versus AD/CD/UC], creatinine clearance, and sex on apparent oral clearance (CL/F), and sex and body weight on apparent volume of distribution of central compartment (Vc/F) were retained as the basis for the current model development. The effect of additional covariates on upadacitinib pharmacokinetics was evaluated using the stepwise forward inclusion backward elimination approach. All model parameters, including covariate effects, from the original model were re-estimated based on the data included in the current analysis. Standard model evaluation and qualification methods were used, i.e. graphical and numerical methods to assess model goodness of-fit.

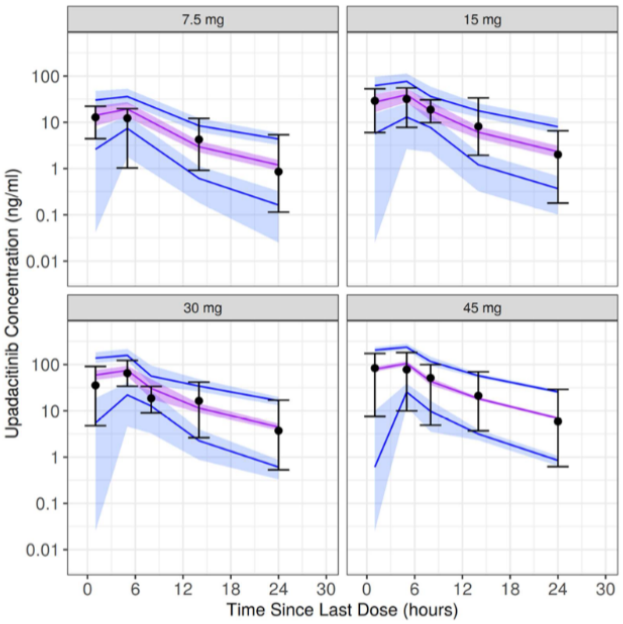
The final model was a two-compartment model with first-order absorption with lag time for the IR formulation, mixed zero- and first-order absorption with lag time for the ER formulation and linear elimination adequately described upadacitinib plasma concentration-time profiles. The final parameter estimates are presented in Table 1. The inter-subject variability for upadacitinib CL/F and apparent volume of distribution of the central compartment (Vc/F) were 35% and 27% respectively. Shrinkage on CL/F, Vc/F, Extended-Release KA and Immediate-Release KA were 16%, 43%, 59% and 62%, respectively. Statistically significant covariates that were included in the final model were creatinine clearance, RA, HV, sex and AST on CL/F; and sex and body weight on Vc/F. Baseline UC disease severity and UC-specific concomitant medications demonstrated negligible impact on upadacitinib pharmacokinetics. Upadacitinib plasma exposures were comparable between Japanese and non-Japanese subjects with UC. The Visual Predictive Checks (VPCs) of Upadacitinib Concentration in Subjects with UC (Studies M14-234 and M14-675) Stratified by Dose Group is shown in Figure 2.

To evaluate the consistency of upadacitinib pharmacokinetics between induction and maintenance treatment in UC the developed model was used to describe observed upadacitinib plasma concentrations from Phase 3 Study M14-234 SS3 using a post hoc approach (Figure 3). Population parameter estimates of the fixed effects and estimates for the random effects (inter-individual variability) of this previously established population pharmacokinetic model were used to generate individual post hoc estimates for subjects from the Phase 3 Study M14-234 SS3. Model parameters were not re-estimated.

Table 1 Comparison of PK parameter estimates for population PK final model with and without excluding outliers

COMPARISON OF PK PARAMETER ESTIMATES FOR POPULATION PK FINAL MODEL WITH AND WITHOUT EXCLUDING OUTLIERS

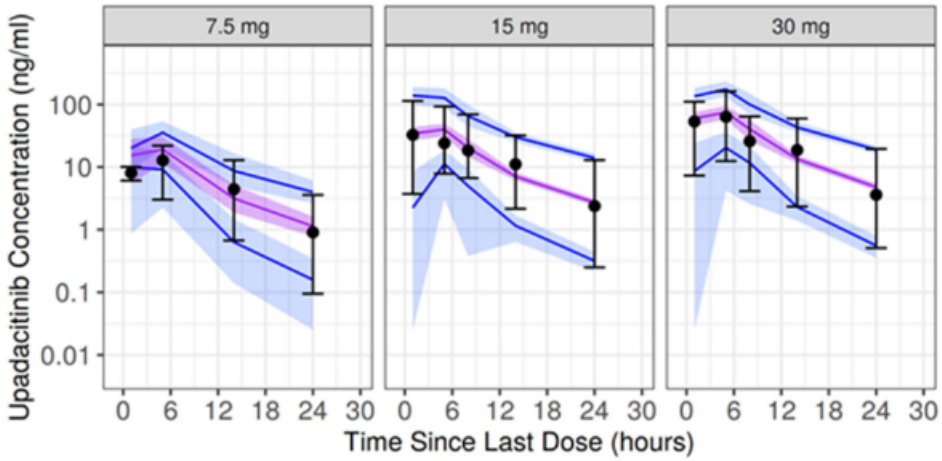
Parameter	Model excluding outliers: Population Estimate	Model excluding outliers: 95% Confidence Interval	Model without excluding outliers: Population Estimate	Model without excluding outliers: 95% Confidence Interval
CL/F (L/h)	37.0	35.8 - 38.2	37.7	36.1 - 39.4
Vc/F (L)	169	162 - 177	183	173 - 194
Extended-Release KA (1/h)	0.114	0.102 - 0.128	0.0765	0.0683 - 0.0858
Immediate-Release KA (1/h)	1.85	1.66 - 2.06	2.11	1.87 - 2.38
Extended-Release Absorption Lag Time (h)	0.159	0.150 - 0.169	0.157	0.148 - 0.167
Immediate-Release Absorption Lag Time (h)	0.237	0.233 - 0.240	0.239	0.237 - 0.242
Fraction of Extended-Release Dose Absorbed through Zero-Order Process (%)	72.5	71.8 - 73.2	72.6	71.9 - 73.4
Zero-Order Absorption Duration (h)	3.39	3.32 - 3.45	3.32	3.26 - 3.39
Bioavailability of the Extended-Release Formulation Relative to the Immediate-Release Formulation (%)	79.8	78.6 - 80.9	79.3	78.1 - 80.5
Q/F (L/h)	3.86	3.69 - 4.03	3.67	3.54 - 3.80
Vp/F (L)	61.6	60.4 - 62.7	70.8	69.6 - 72.1
Covariate Exponent of Creatinine Clearance on CL/F	0.213	0.158 - 0.268	0.297	0.215 - 0.379
CL/F Ratio of RA Subjects Compared to Subjects with AD,UC or CD	0.929	0.888 - 0.972	0.865	0.805 - 0.930
CL/F Ratio of Females Compared to Males	0.874	0.837 - 0.913	0.865	0.820 - 0.913
Vc/F Ratio of Females Compared to Males	0.811	0.766 - 0.858	0.856	0.797 - 0.918
Covariate Exponent of Body Weight on Vc/F	0.493	0.379 - 0.607	0.616	0.455 - 0.777
CL/F Ratio of Healthy Subjects Compared to Subjects with AD,UC or CD	1.22	1.13 - 1.32	1.08	0.930 - 1.25
Covariate Exponent of Aspartate Amino Transferase on CL/F	-0.0810	-0.122 - -0.0402	-0.0950	-0.159 - -0.0307
Scaling Factor on Residual Error	1.68	1.62 - 1.74	1.56	1.51 - 1.61
ISV on CL/F (%)	34.5	32.9 - 36.0	45.4	43.1 - 47.6
ISV on Vc/F (%)	27.0	24.0 - 29.6	33.3	29.6 - 36.7
ISV on Extended-Release KA (%)	94.3	82.0 - 105	86.7	76.4 - 95.8
ISV on Immediate-Release KA (%)	71.4	62.9 - 79.0	80.5	70.2 - 89.7
Proportional Error (Phase 1) SD	0.261	0.258 - 0.264	0.271	0.268 - 0.275
Proportional Error (Phase 2/3) SD	0.456	0.447 - 0.465	0.564	0.553 - 0.575
Additive Error SD (ng/mL)	0.115	0.110 - 0.120	0.120	0.114 - 0.125



The blue lines represent the 90% prediction interval of the model, the shaded blue areas the associated 90% confidence intervals of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median, the purple shaded area its 90% confidence interval. The dots and errorbars are the median and 90% inter-percentile range (5th to 95th percentile) of the observed data.

Note: Time bins were chosen at 1, 5, 8, 14 and 24 hrs after last dose for the 15, 30, 45 mg and at 1, 5, 14 and 24 hrs after last dose for the 7.5mg group as there are no observed records at 8 hrs after last dose.

Figure 2 Visual Predictive Checks of Upadacitinib Concentration in Subjects with UC (Studies M14-234 and M14-675) Stratified by Dose Group



The blue lines represent the 90% prediction interval of the model, the shaded blue areas the associated 90% confidence intervals of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median, the purple shaded area its 90% confidence interval. The dots and error bars are the median and 90% inter-percentile range (5th to 95th percentile) of the observed data.

Note: Time bins were chosen at 1, 5, 8, 14 and 24 hours after last dose for the 15 mg and 30 mg, and at 1, 5, 14 and 24 hours after last dose for the 7.5mg group as there are no observed records at 8 hours after last dose.

Figure 3 Visual Predictive Checks of Upadacitinib Concentration in Subjects with UC (Phase 3 Study M14-234 SS3) Stratified by Dose Group

Absorption

IVIVC

A linear IVIVC model was established using in vivo and in vitro data for the 15 mg, 30 mg, and 45 mg tablet formulations as well as variants of the 30 mg tablet formulations with different in vitro release rate. The model showed acceptable predictability and predicted the plasma concentration-time curves well. Furthermore, internal and external validation resulted in prediction errors within the acceptance criteria defined in the EMA guideline. The developed IVIVC was used to predict upadacitinib plasma exposures following the administration of the planned 45 mg strength commercial and the phase 3 formulations. There are issues raised regarding the IVIVC from a quality perspective.

Bioequivalence

Study M19-376 was a Phase 1 single-dose, open-label, randomized, four-period, four-sequence, crossover design to assess the bioavailability of upadacitinib 45 mg commercial formulation (ER19) relative to the reference 45 mg Phase 3 formulation (ER19P). The study also characterized the effect of a high-fat/high-calorie meal on upadacitinib 45 mg commercial formulation.

65 subjects completed the study. Three subjects had upadacitinib plasma concentrations that were below or close to the LLOQ at all time points during one or more study periods. Thorough investigation was conducted for the records for Study M19-376 related to clinical operation, drug supply, drug dispensing, monitoring, adverse events, sample collection, sample analysis but no recording could explain the aberrant concentrations in these individuals. Results from both excluding and including outlier observations from the three subjects are presented. Primary results driving the conclusion are based on the analyses excluding the outlier observations.

Table 2 Excluding outlier data from three subjects: bioavailability of upadacitinib 45 mg market-image formulation compared to the phase 3 formulation under fasting conditions, after a high-fat/high-calorie meal

Regimens Test vs. Reference	Pharmacokinetic Parameter(units)	Point Estimate	CI90 Lower	CI90 Upper
Regimen B Market-Image vs. Regimen A Phase 3 Formulation **(Both under Fasting Conditions)**	C_{max} (ng/mL)	0.975	0.918	1.036
	AUC_t (ng•h/mL)	0.992	0.954	1.030
	AUC_{inf} (ng•h/mL)	0.987	0.950	1.026
Regimen D Market-Image vs. Regimen C Phase 3 Formulation **(Both after High-Fat/High-Calorie Meal)**	C_{max} (ng/mL)	1.019	0.971	1.070
	AUC_t (ng•h/mL)	0.989	0.962	1.017
	AUC_{inf} (ng•h/mL)	0.985	0.958	1.012

Table 3 Comparison of IVIVC Model-Predicted Plasma Exposures for Upadacitinib 45 mg Strength Commercial and Phase 3 Formulations

Parameter	Geometric Mean		Percent Difference
	45 mg Commercial Formulation (Test)	45 mg Phase 3 Formulation (Reference)	
AUC_{inf}	689	696	1%
C_{max}	76.9	75.5	2%

Influence of food

Study M19-376 also evaluated the effect of food on the commercial formulation of the 45 mg strength. The outliers discussed above are excluded in the data presented below.

Table 4 Excluding outlier data from three subjects: bioavailability of upadacitinib 45 mg market-image formulation under fasting or fed conditions

Regimens Test vs. Reference	Pharmacokinetic Parameter(units)	Point Estimate	CI90 Lower	CI90 Upper
Regimen D Market-Image (High-Fat/High-Calorie Meal) vs. Regimen B Market-Image (Fasting) **(Food Effect Assessment)**	C_{max} (ng/mL)	1.596	1.511	1.685
	AUC_t (ng•h/mL)	1.272	1.225	1.321
	AUC_{inf} (ng•h/mL)	1.258	1.212	1.307

The effect of food on other strengths of the ER-formulation has been investigated previously. Coadministration of upadacitinib with a high-fat/high-calorie meal increased upadacitinib AUCinf by approximately 30% and Cmax by 18% to 60% across the different studies and strengths. Upadacitinib 15 mg, 30 mg, and 45 mg strength tablets were administered in UC Phase 3 studies without regard to food.

Pharmacokinetic interaction studies

Study M19-139 evaluated the effect of repeated doses of upadacitinib 45 mg QD ER on the pharmacokinetics of sensitive probe substrates of different CYP enzymes. This was a cocktail drug interaction study similar in design as the cocktail study performed for the initial MAA in RA. 20 healthy adults were enrolled and 19 subjects completed the study.

Overall, administration of upadacitinib 45 mg QD doses resulted in only a limited effect on midazolam, a sensitive CYP3A substrate, exposures (approximately 25% decrease in Cmax and AUC) and dextromethorphan, a sensitive CYP2D6 substrate, exposures (35% increase in AUC and 30% increase in Cmax). Upadacitinib 45 mg QD had no relevant effects on the sensitive probe substrates/markers for CYP1A2, CYP2C9 and CYP2C19. These results are in line with those obtained for 30 mg Upadacitinib in the original application, only for CYP2D6 are the point estimates higher for 45 mg. However, the magnitude of the observed effect is within the typical range of intra-subject variability in CYP2D6 drug substrates (~40%).

2.6.2.2. Pharmacodynamics

Pharmacodynamics and Pharmacokinetics-Pharmacodynamics (PK/PD)

Upadacitinib exposure-response relationships for efficacy and safety parameters were evaluated using quartile plots and logistic regression analyses. Upadacitinib doses of 7.5, 15, 30 and 45 mg were included in the analyses for the induction phase and 7.5, 15 and 30 mg for the maintenance phase. Non-linear and linear logistic regression analyses for the efficacy and safety parameters were evaluated to characterize the relationship between upadacitinib Cavg (the predicted average concentration in subject i, based on the population pharmacokinetic model) as a predictor variable and the different endpoints as binary variables. The covariates were investigated in the exposure-response analyses in an exploratory fashion by adding each covariate to the primary model and evaluating the impact on the coefficient estimate for upadacitinib effect in the model.

Relationship between exposure and efficacy

The week 8 efficacy endpoints were clinical remission per Adapted Mayo score, clinical Response per Adapted Mayo score, endoscopic improvement, endoscopic remission. There was an incremental increase in efficacy with increasing upadacitinib plasma exposures up to Cavg of ~40 ng/mL. Maximal upadacitinib efficacy appeared to be approached at approximately Cavg of 40 ng/mL, which is approximately equivalent to the median Cavg for 45 mg QD. Biologic therapy-intolerant or inadequate responder (Bio-IR) status, baseline corticosteroid use, baseline Adapted Mayo Score and study effect were accounted for in the models. Statistically significant exposure-response relationships with upadacitinib Cavg were observed for all evaluated efficacy endpoints. Based on the exposure-response models, upadacitinib 45 mg QD is predicted to result in 3% to 5% greater percentage of subjects achieving the different evaluated efficacy endpoints compared to a 30 mg QD regimen using the extended-release formulation; the higher efficacy of 45 mg QD compared to lower doses (e.g., 30 mg QD) was consistent across both bio-IR and non-bio-IR populations.

Week 52 exposure-response models were developed to describe the observed increase in percentage of subjects achieving clinical remission, endoscopic improvement, histo-endoscopic mucosal improvement, or steroid-free clinical remission with increasing upadacitinib concentrations. Across these efficacy endpoints, model-predicted response rates demonstrated 8% to 10% greater efficacy with the upadacitinib 30 mg dose compared to 15 mg. No exposure-response relationship beyond treatment effect was identified for endoscopic remission.

Clinical remission status per Adapted Mayo score at Week 0 was a statistically significant factor for all endpoints and age was a statistically significant covariate for clinical remission per Adapted Mayo score and steroid-free clinical remission. However, neither of the two covariates (Bio-IR and Corticosteroid Use at Week 0) had a statistically significant interaction with the upadacitinib exposure effect in any of the evaluated endpoints, indicating consistency of upadacitinib efficacy exposure-response relationships at Week 52 across the different patient subgroups.

Relationship between exposure and safety

No events occurred for lymphopenia ≥ Grade 4 and neutropenia ≥ Grade 4 at Week 8 (LOCF), therefore no analysis was performed. For lymphopenia ≥ Grade 3 (Week 8; LOCF), neutropenia ≥ Grade 3 (Week 8; LOCF), hemoglobin < 8 g/dL (Week 8; LOCF), Herpes Zoster infections (anytime up to Week 8) and pneumonia (anytime up to Week 8), there were no more than 10 events, therefore no further analysis beyond quartile plots was performed. The exposure-response quartile plots for the percentage of subjects who experienced the different safety endpoints versus maximum upadacitinib concentration showed no trend.

Week 8 exposure safety models were developed for the endpoints hemoglobin (2 g/dL decrease from baseline, 2 g/dL decrease from baseline and less LLN, < 8 g/dL) and serious infections. No trend for exposure-response relationships was observed between upadacitinib average concentrations and any of the evaluated safety endpoints at Week 8, indicating that increasing upadacitinib plasma exposures (within the 7.5 mg to 45 mg extended-release exposure range) is not associated with a significant increase in any of the evaluated safety endpoints the first 8 weeks. The exposure-response quartile plots for the percentage of subjects who experienced the different safety endpoints versus maximum upadacitinib concentration showed no trend.

At week 52, no events had occurred for neutropenia ≥ Grade 3, lymphopenia ≥ Grade 4 and neutropenia ≥ Grade 4, therefore no analysis was performed for these endpoints. The incidence of the evaluated safety endpoints (> 2 g/dL Decrease in Hemoglobin, herpes zoster infections, serious infections) was generally low and none of the endpoints showed trends for exposure-dependent increases with increasing upadacitinib average concentrations.

Relationship between exposure and effects on QT Interval

The relationship between QT interval prolongation for upadacitinib was investigated through exposure-response analyses of data from single (1-48 mg) and multiple ascending (3-24 mg) dose Phase 1 studies, previously submitted in the original regulatory application for upadacitinib in RA (R&D/17/1139).

The range of upadacitinib exposures evaluated in the QT exposure-response analyses were compared to the model-estimated Cmax for the highest proposed dose in UC (45 mg QD for induction) under therapeutic and the worst-case supratherapeutic scenario (if co-administered with strong CYP3A inhibitors, Table 5).

Table 5 Multiples of Exposures Covered by the Range of Upadacitinib Concentrations Included in the Analyses Relative to the Highest Proposed Dose in UC (45 mg QD for Induction)

Scenario	Highest Individual Concentration in QTc Analysis (ng/mL)	Highest Upadacitinib Extended-Release Dose in UC (mg)	Mean C_{max} (ng/mL)	Multiples of Exposure Covered by Highest Individual Concentration
Therapeutic Exposures in UC Patients	442 ng/mL	45 mg QD	126	3.5
Exposures in UC Patients under Worst Case Scenario (with strong CYP3A inhibition)			214[a]	2.1

UC = Ulcerative Colitis

a. Calculated from therapeutic exposures in subjects with UC assuming 70% increase with CPY3A inhibition

2.6.3. Discussion on clinical pharmacology

Population PK analysis

The MAH has conducted population pharmacokinetic (popPK) and pharmacokinetic-pharmacodynamic (PKPD) analyses of Upadacitinib in subjects with RA, CD, UC or AD. The popPK analysis dataset included data from the UC studies M14-234 and M14-675, and data from other studies (RA, CD, AD studies and studies in healthy subjects).

A total of 525 of these records (3.6%) were below the LLOQ. Given the small fraction of concentrations below the LLOQ, the M5 imputation method was used by imputing BLQ concentrations with LLOQ/2. The first LLOQ/2 after last dose was included in the analysis, while the rest were excluded. This is acceptable. All concentrations greater than the computed upper limit or below the computed lower limit were flagged as outlier concentrations and thus excluded from the analysis dataset (4.3%). At total of 3.1% and 5.7% of the concentrations below and above the upper limit, respectively, were excluded for the UC population within the population PK analysis dataset. The UC population constituted 50.8% of the total dataset including all populations (HV 9.2%, RA 24.1%, CD 9.3%, and AD 6.5%), whereof 78.8% (40% of total dataset) received 45 mg induction dose. Based on the high number of subjects with UC included in the dataset, and that the percentage of excluded data is similar between the populations, while the exclusion is not agreed with the issue is not pursued further. In addition, the final parameters did not change drastically when the final model was rerun on the full dataset including the outliers.

The MAH has used popPK analysis to support the dose selection and to simulate exposures (Caverage) to be used in PKPD analysis. Standard model evaluation and qualification methods were used, i.e., graphical and numerical methods to assess model goodness of-fit. Presented prediction corrected VPCs were stratified on induction dose group, maintenance dose group and indication and formula. The figures demonstrate that the model can describe all data adequately.

The final model was a two-compartment model with first-order absorption with lag time for the IR formulation, mixed zero- and first-order absorption with lag time for the ER formulation and linear elimination. The model adequately described upadacitinib plasma concentration-time profiles. The inter-subject variability for upadacitinib CL/F and apparent volume of distribution of the central compartment (Vc/F) were 35% and 27% respectively. The shrinkage was high for Vc/F, ER-KA and IR-KA (43%, 59% and 62%, respectively). Statistically significant covariates that were included in the final model were CrCL, RA, HV, sex and AST on CL/F; and sex and body weight on Vc/F. Upadacitinib plasma exposures were comparable between Japanese and non-Japanese subjects with UC. The goodness-of-fit plots of the final population pharmacokinetic model for subjects with moderate to severely active UC indicate some trends in the individual predicted versus observed concentration. At the CHMP's request, the Visual Predictive Checks (VPCs) of Upadacitinib Concentration in Subjects with UC (Studies M14-234 and M14-675) were provided and the CHMP considered that they were acceptable.

The pharmacokinetic model was used to describe observed upadacitinib plasma concentrations from Phase 3 Study M14-234 SS3 (maintenance phase) using a post hoc approach. Trendlines are missing in the GOF plots. There appears to be a small trend in observed vs predicted concentrations. Figures of dose normalised observed concentrations in subjects with UC (including SS3 data) vs other indications, and a table of predicted Cmin, Cmax and Caverage across the different indications and doses indicates that the exposure in the UC population is similar to the exposure in other populations.

Absorption

The study M19-376 design is appropriate, given a half-life of 9-14 hours the washout is sufficient. Upadacitinib does not accumulate significantly, and it has in previous applications (see initial marketing authorisation application for discussion) been concluded that no multiple dose BE-study is necessary.

Three (3) subjects had upadacitinib plasma concentrations close to zero at all timepoints in one or several different periods of the study. The MAH has thoroughly investigated the cause of this, but no recording could explain the aberrant results. According to the Guideline on investigation of bioequivalence exclusion of data could be allowed for a subject with lack of any measurable concentrations or only very low plasma concentrations for reference medicinal product. In this case there is no approved reference product; however, the phase-3 formulation is supported by clinical data and hence the reference product in this setting. However, there are results close to zero for both formulations and the MAH has omitted all these data from the main statistical analysis. In the main analysis, results are within BE criteria. With all subjects included, results are not within BE criteria. No analysis has been presented where only subjects with low concentrations of the phase 3 formulation are excluded. However, the phase-3 and commercial formulation differ only in colour, the core composition is the same. Thus, there is no obvious reason why the two formulations would not be bioequivalent. In this particular case the cause of the very low concentrations in three subjects is no concern needed to pursue further and the commercial formulation is considered to achieve similar exposure of upadacitinib as the phase-3 formulation. This is further supported by the IVIVC predicted exposures.

The effect of food on the commercial 45 mg strength has been investigated. The effect on AUC was in line with previous results for other formulations and strength while the effect on Cmax was higher than previous results. Also this analysis is affected by the exclusion of outlier-data. The analysis including all data reveals a lesser effect of food on both Cmax and AUC. Section 5.2 of the SmPC has been updated with the results from the analysis with excluded data, which is the “worst” scenario. Even with this larger effect of food, especially on Cmax, it is agreed that no food restriction is necessary.

DDI

The interaction potential of the 45 mg dose has been appropriately evaluated. A clinical cocktail DDI study has been performed with substrates for the main CYPs and other relevant interactions has been adequately discussed in the provided documentation.

Compared to the 30 mg dose evaluated for DDI potential in the original MAA, the only difference is that the 45 mg dose is a mild inhibitor of CYP2D6.

Section 4.5 of the SmPC has been updated as follows: “*Administration of multiple 45 mg once daily doses of upadacitinib to healthy subjects led to a limited increase in AUC and C_{max} of dextromethorphan (sensitive CYP2D6 substrate) by 30% and 35%, respectively, indicating that upadacitinib 45 mg once daily has a weak inhibitory effect on CYP2D6. No dose adjustment is recommended for CYP3A substrates, CYP2D6 substrates, rosuvastatin or atorvastatin when coadministered with upadacitinib*.”

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, posaconazole, voriconazole, and clarithromycin). Sections 4.2 and 4.5 of the SmPC have been updated to reflect that for patients with ulcerative colitis using strong CYP3A4 inhibitors, the recommended induction dose is 30 mg once daily (for up to 16 weeks) and the recommended maintenance dose is 15 mg once daily.

PK / PD

The exposure-response relationships for upadacitinib efficacy and safety following 8 and 52 weeks of treatment were evaluated in subjects with moderately to severely active UC using data from the Phase 2b Study M14-234 SS1, the Phase 3 Study M14-234 SS2, Phase 3 Study M14-675 and Study M14-234 SS3. Upadacitinib doses of 7.5, 15, 30 and 45 mg were included in the analyses for the induction phase and 7.5, 15 and 30 mg for the maintenance phase.

For both week 8 and week 52 exposure-efficacy analyses, the predicted percentage of subjects achieving clinical endpoints (improvement and remission) increased with increasing upadacitinib plasma exposures while no clear trend was observed for exposure-safety relationships, indicating that safety events did not increase with increasing upadacitinib plasma exposures. Overall results indicate that upadacitinib plasma exposures associated with the 45 mg QD regimen achieves therapeutic benefit at Week 8 without a clear trend for increase in safety events.

This support the dosing recommendation in Section 4.2 of the SmPC: The recommended induction dose of upadacitinib is 45 mg once daily for 8 weeks. See also discussions in 2.6.6.

Relationship between exposure and effects on QT Interval

The exposure-QTcF analysis submitted in the original regulatory application for upadacitinib in RA (R&D/17/1139) was based on data form SAD and MAD studies where doses up to 48 mg Upadacitinib IR tablet was given. The mean Cmax with a 48 mg IR tablet was 314 ng/mL, which is approximately 2.5-fold higher compared to the mean Cmax,ss in UC patients receiving 45 mg ER QD (126 ng/mL). In the concentration-QTc analysis, the upper bound of the 2-sided 90% confidence interval of the predicted ΔΔQTcF was below 3.33 msec for the highest exposure level which is below the upper cut-off of 10 msec. Subsequently it is concluded that upatacitinib has no clinically relevant effect on the QT interval at exposures reached with 45 mg QD ER-tablet treatment. However, subjects with moderate HI are expected to have a on average 43% higher Cmax, limiting the concentration-QTc analysis with regards to the covered exposure range, prohibiting a conclusion based on only this analysis for this subpopulation (see Clinical Safety section).

2.6.4. Conclusions on clinical pharmacology

Relevant PK-studies have been provided in support of this submission. The pharmacokinetics of upadacitinib in subjects with UC is adequately described by the population PK model and indicates that the exposure in the UC population is similar to the exposure in other populations.

The CHMP concluded that the clinical pharmacology data was adequate to support the new strength of 45mg and the new indication in the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent. The SmPC has been updated with the new pharmacology information.

2.6.5. Clinical efficacy

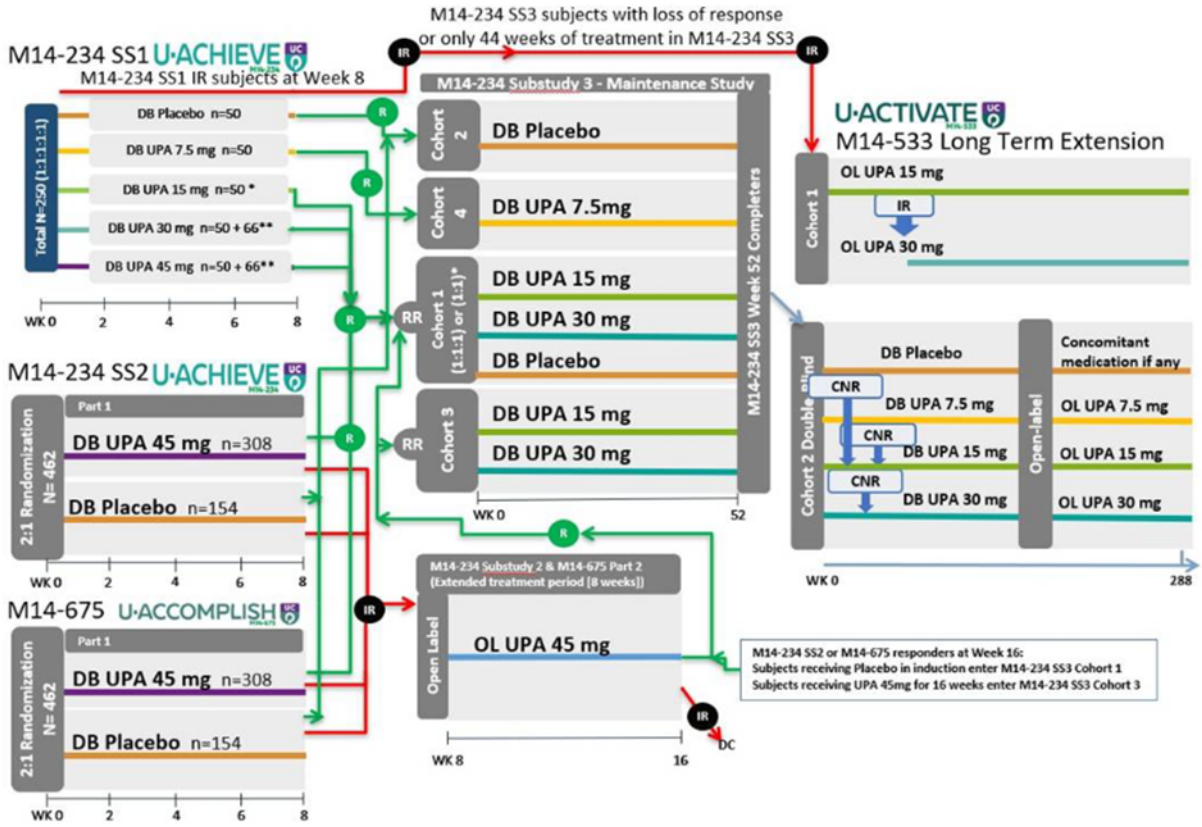
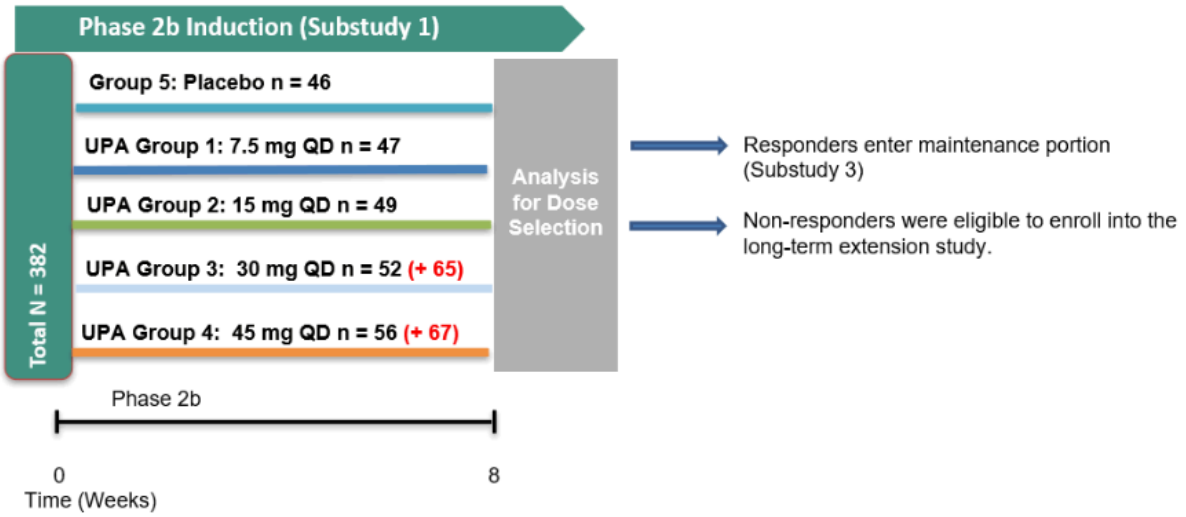


Figure 4 Process Flow of Upadacitinib UC Global Phase 2b and 3 Studies

2.6.5.1. Dose response study

M14-234 Substudy 1 A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis



QD = once daily; UPA = upadacitinib

Note: Planned numbers were 50 subjects each in Groups 1 – 5 (250 total) + 50 additional subjects in each of Groups 3 (upadacitinib 30 mg) and 4 (upadacitinib 45 mg) for the overall planned total of 350 subjects.

Figure 5 Substudy 1 Design Schematic – Actual Numbers Enrolled and Dosed

Approximately 250 subjects were planned to be randomized 1:1:1:1:1 to the placebo group and 4 upadacitinib doses. Randomization was stratified by previous biologic therapy use (yes/no), Baseline corticosteroid use (yes/no), and Baseline Adapted Mayo score (≤ 7 or > 7). Approximately 75% of subjects enrolled in Substudy 1 were bio-IR and 25% of subjects were non-bio-IR. Bio-IR is defined as subjects who had inadequate response, loss of response, or intolerance to biologic therapy. Non-bio-IR is defined as subjects who had inadequate response, loss of response, or intolerance to conventional therapy but had not failed biologic therapy. The study duration included a Screening Period of up to 5 weeks and an 8-week double-blind (DB) Induction Period.

During the analysis period, when the first 250 randomized subjects completed the study, 132 additional subjects were randomized into Groups 3 and 4 of Substudy 1 (upadacitinib 30 mg and 45 mg dose groups; approximately 66 subjects per dose group). The objectives of enrolling these additional subjects were to avoid interrupting the study activities during the analysis period and to support a sufficient number of subjects with clinical response to be re-randomized into the maintenance portion in Substudy 3.

Study participants

Subjects enrolled in this study were between 16 and 75 years old who have been inadequate responders or intolerant to immunosuppressants, corticosteroids, and/or biologic therapies. Subjects enrolled had a diagnosis of UC for 90 days prior to Baseline, confirmed by colonoscopy during the Screening Period, with exclusion of current infection, colonic dysplasia and/or malignancy. Eligible study subjects must have had an Adapted Mayo score of 5 to 9 points and endoscopy subscore of 2 to 3. During the time that subjects were enrolled in Substudy 1, the eligibility criteria included subjects age 18 to 75 years.

Treatments:

Subjects were assigned to 1 of 5 groups and received 2 tablets of blinded study drug daily: 2 placebo tablets; or 1 upadacitinib 7.5, 15, or 30 mg tablet + placebo

tablet; or 1 upadacitinib 30 mg tablet + 15 mg tablet (subjects in the upadacitinib 45 mg group).

Objectives and endpoints

The primary endpoint was the proportion of subjects who achieved clinical remission per Adapted Mayo score (defined as SFS ≤ 1, RBS of 0, and endoscopic subscore ≤ 1) at Week 8.

Ranked secondary efficacy variables were:

1. Proportion of subjects with endoscopic improvement (defined as an endoscopic subscore ≤ 1) at Week 8
2. Proportion of subjects achieving clinical remission per Full Mayo score (defined as a Full Mayo score ≤ 2 with no subscore > 1) at Week 8
3. Proportion of subjects achieving clinical response per Adapted Mayo score (defined as decrease from Baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from Baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1) at Week 8
4. Proportion of subjects achieving clinical response per Partial Mayo score (using the Mayo Scoring System for Assessment of Ulcerative Colitis Activity, excluding endoscopic subscore; clinical response defined as decrease from Baseline in the Partial Mayo score ≥ 2 points and ≥ 30% from Baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1) at Week 2
5. Change in Full Mayo score from Baseline to Week 8
6. Proportion of subjects with endoscopic remission (defined as an endoscopic subscore of 0) at Week 8
7. Proportion of subjects who achieved histologic improvement (defined as decrease from Baseline in Geboes score) at Week 8

Participant flow

Disposition of Subjects

Substudy 1 main subjects (intent-to-treat [ITT] 1A Population) are defined as those first randomized 250 subjects who completed the 8-week induction. Substudy 1 additional subjects (ITT1B Population) are defined as any subject who was randomized after the main subjects.

250 subjects were planned to be randomized 1:1:1:1:1 to the placebo and upadacitinib groups in the main subject group; 250 subjects were actually randomized, with approximately 50 subjects per group. Totals for the upadacitinib 30 and 45 mg groups in the main subject group included 12 subjects who were randomized with only 2 options (upadacitinib 30 mg or 45 mg) due to an error.

One hundred additional subjects were planned (50 subjects each in the upadacitinib 30 [Group 3] and 45 mg [Group 4] groups), and 132 additional subjects were actually randomized to receive upadacitinib 30 or 45 mg after the original 250 subjects were enrolled.

Table 6 Substudy 1 – Subject Accountability (All Randomized Subjects)

			Study Drug	
Treatment	Randomized n	Treated n	Completed n	Discontinued n
Placebo	46	46	41	5
UPA 7.5 mg (main)	47	47	45	2
UPA 15 mg (main)	49	49	45	4
UPA 30 mg (main)	52	52	46	6
UPA 45 mg (main)	56	56	50	6
UPA 30 mg (additional)	65	65	62	3
UPA 45 mg (additional)	67	67	63	4
Main total	250	250	227	23
Additional total	132	132	125	7

UPA = upadacitinib

Table 7 Substudy 1 – Summary of Study Drug Discontinuation Due to Primary Reason for Discontinuation– Main Subjects (ITT1A Population)

		Upadacitinib				
	Placebo (N = 46) n (%)	7.5 mg (N = 47) n (%)	15 mg (N = 49) n (%)	30 mg (N = 52) n (%)	45 mg (N = 56) n (%)	Total (N = 204) n (%)
Discontinuation due to primary reasons	5 (10.9)	2 (4.3)	4 (8.2)	6 (11.5)	6 (10.7)	18 (8.8)
Adverse event	3 (6.5)	1 (2.1)	2 (4.1)	4 (7.7)	4 (7.1)	11 (5.4)
Withdraw consent	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0
Lack of efficacy	2 (4.3)	1 (2.1)	1 (2.0)	1 (1.9)	2 (3.6)	5 (2.5)
Other	0	0	1 (2.0)	1 (1.9)	0	2 (1.0)

ITT1A = intent-to-treat population for main subject group; UPA = upadacitinib

Note: 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.

Recruitment

A total of 382 subjects were randomized at 142 sites in the following countries: Australia, Austria, Belgium, Canada, Croatia, Czech Republic, Estonia, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Korea (Republic of), Latvia, Malaysia, Netherlands, Norway, Poland, Portugal, Slovakia, South Africa, Switzerland, Taiwan, United Kingdom, United States.

First Subject First Visit: 03 September 2016

Last Subject Last Visit 14 June 2018

Results

Table 8 Substudy 1 – Demographic and disease Characteristics –(ITT1A Population)

Variable	Placebo (N = 46) n (%)	Upadacitinib 7.5 mg (N = 47) n (%)	Upadacitinib 15 mg (N = 49) n (%)	Upadacitinib 30 mg (N = 52) n (%)	Upadacitinib 45 mg (N = 56) n (%)	Total (N = 204) n (%)
Sex						
Female	17 (37.0)	24 (51.1)	19 (38.8)	21 (40.4)	19 (33.9)	83 (40.7)
Male	29 (63.0)	23 (48.9)	30 (61.2)	31 (59.6)	37 (66.1)	121 (59.3)
Race						
White	37 (80.4)	36 (76.6)	38 (77.6)	37 (71.2)	38 (67.9)	149 (73.0)
Black or African American	0	3 (6.4)	1 (2.0)	2 (3.8)	1 (1.8)	7 (3.4)
Asian	8 (17.4)	7 (14.9)	10 (20.4)	11 (21.2)	16 (28.6)	44 (21.6)
American Indian or Alaska Native	0	0	0	1 (1.9)	0	1 (0.5)
Multiple	1 (2.2)	1 (2.1)	0	1 (1.9)	1 (1.8)	3 (1.5)
Ethnicity						
Hispanic or Latino	2 (4.3)	0	2 (4.1)	5 (9.6)	3 (5.4)	10 (4.9)
Not Hispanic or Latino	44 (95.7)	47 (100)	47 (95.9)	47 (90.4)	53 (94.6)	194 (95.1)

ITT1A = intent-to-treat population for main subject group

Variable Treatment	N	Mean	SD	Median	Min	Max
Age (years)						
Placebo	46	42.3	13.29	40.0	21	67
UPA 7.5 mg	47	41.7	14.58	41.0	18	75
UPA 15 mg	49	46.0	13.58	47.0	22	71
UPA 30 mg	52	42.0	14.89	42.0	20	72
UPA 45 mg	56	39.8	14.20	37.0	19	74
UPA total	204	42.3	14.40	41.0	18	75
Body Mass Index (kg/m^2)						
Placebo	46	25.0	5.54	24.2	15.2	43.1
UPA 7.5 mg	47	25.1	6.28	23.8	16.6	45.8
UPA 15 mg	47	25.9	6.14	24.3	15.5	41.7
UPA 30 mg	52	24.8	5.06	23.7	17.3	39.5
UPA 45 mg	54	24.2	5.85	22.8	15.7	43.6
UPA total	200	24.9	5.82	23.5	15.5	45.8

ITT1A = intent-to-treat population for main subject group; SD = standard deviation; UPA = upadacitinib

Variable	Placebo (N = 46) n (%)	Upadacitinib 7.5 mg (N = 47) n (%)	Upadacitinib 15 mg (N = 49) n (%)	Upadacitinib 30 mg (N = 52) n (%)	Upadacitinib 45 mg (N = 56) n (%)	Total (N = 204) n (%)
Bio-IR						
Yes	34 (73.9)	34 (72.3)	36 (73.5)	40 (76.9)	42 (75.0)	152 (74.5)
No	12 (26.1)	13 (27.7)	13 (26.5)	12 (23.1)	14 (25.0)	52 (25.5)
Adapted Mayo score						
≤ 7	27 (58.7)	29 (61.7)	31 (63.3)	33 (63.5)	38 (67.9)	131 (64.2)
> 7	19 (41.3)	18 (38.3)	18 (36.7)	19 (36.5)	17 (30.4)	72 (35.3)
Missing	0	0	0	0	1 (1.8)	1 (0.5)
Baseline corticosteroid use						
Yes	26 (56.5)	24 (51.1)	27 (55.1)	25 (48.1)	29 (51.8)	105 (51.5)
No	20 (43.5)	23 (48.9)	22 (44.9)	27 (51.9)	27 (48.2)	99 (48.5)
Baseline biologics use						
Yes	0	0	0	0	0	0
No	46 (100)	47 (100)	49 (100)	52 (100)	56 (100)	204 (100)
Baseline immunosuppressant use						
Yes	1 (2.2)	2 (4.3)	2 (4.1)	2 (3.8)	3 (5.4)	9 (4.4)
No	45 (97.8)	45 (95.7)	47 (95.9)	50 (96.2)	53 (94.6)	195 (95.6)
Baseline aminosalicylates use						
Yes	26 (56.5)	27 (57.4)	25 (51.0)	28 (53.8)	25 (44.6)	105 (51.5)
No	20 (43.5)	20 (42.6)	24 (49.0)	24 (46.2)	31 (55.4)	99 (48.5)
Baseline hsCRP						
≤ 5 mg/L	21 (45.7)	24 (51.1)	11 (22.4)	18 (34.6)	24 (42.9)	77 (37.7)
> 5 mg/L	25 (54.3)	23 (48.9)	38 (77.6)	34 (65.4)	32 (57.1)	127 (62.3)
Disease duration						
≤ 3 years	15 (32.6)	10 (21.3)	13 (26.5)	12 (23.1)	18 (32.1)	53 (26.0)
> 3 years	31 (67.4)	37 (78.7)	36 (73.5)	40 (76.9)	38 (67.9)	151 (74.0)

bio-IR = subjects with inadequate response, loss or response, or intolerance to biologic therapy; hsCRP = high-sensitivity C-reactive protein; ITT1A = intent-to-treat population for main subject group

Note: Percentages calculated on non-missing values.

Table 9 Substudy 1 – Primary Endpoint: Clinical Remission per Adapted Mayo Score at Induction Week 8 (NRI) (ITT1A Population)

		Upadacitinib			
	Placebo n (%)	**7.5 mg n (%)**	**15 mg n (%)**	**30 mg n (%)**	**45 mg n (%)**
Clinical remission per Adapted Mayo score at Week 8	(N = 46)	(N = 47)	(N = 49)	(N = 52)	(N = 56)
Yes	0	4 (8.5)	7 (14.3)	7 (13.5)	12 (21.4)
Adjusted risk difference[a,b] (95% confidence interval[b])		8.4 (0.0, 16.8)	13.5 (3.3, 23.8)	13.8 (3.8, 23.9)	21.1 (8.6, 33.6)
P-value[b]		0.049	0.010	0.007	< 0.001

ITT1A = intent-to-treat population for main subject group; NRI = non-responder imputation

a. Risk difference = (upadacitinib – placebo).

b. Based on Cochran-Mantel-Haenszel (CMH) test stratified by previous biologic use, Baseline corticosteroid use, and Baseline Adapted Mayo score (≤ 7 and > 7).

Table 10 Substudy 1 – Secondary Endpoints (NRI/LOCF) (ITT1A Population)

		Upadacitinib			
	Placebo	**7.5 mg**	**15 mg**	**30 mg**	**45 mg**
Endoscopic improvement at Week 8 (NRI)					
	N = 46 n (%)	N = 47 n (%)	N = 49 n (%)	N = 52 n (%)	N = 56 n (%)
Yes	1 (2.2)	7 (14.9)	15 (30.6)	14 (26.9)	20 (35.7)
Adj. risk difference[a,b]		13.1	27.6	26.6	35.4
P value[b]		0.030	< 0.001	< 0.001	< 0.001
95% CI[b]		(1.2, 25.0)	(13.1, 42.1)	(12.3, 40.8)	(19.2, 51.7)

		Upadacitinib			
	Placebo	**7.5 mg**	**15 mg**	**30 mg**	**45 mg**
Clinical remission per Full Mayo score at Week 8 (NRI)					
	N = 46 n (%)	N = 47 n (%)	N = 49 n (%)	N = 52 n (%)	N = 56 n (%)
Yes	0	5 (10.6)	5 (10.2)	6 (11.5)	11 (19.6)
Adj. risk difference[a,b]		11.0	9.6	12.2	20.1
P value[b]		0.021	0.024	0.015	0.001
95% CI[b]		(1.7, 20.4)	(1.3, 18.0)	(2.3, 22.0)	(8.0, 32.1)
Clinical response per Adapted Mayo score at Week 8 (NRI)					
	N = 46 n (%)	N = 47 n (%)	N = 49 n (%)	N = 52 n (%)	N = 56 n (%)
Yes	6 (13.0)	14 (29.8)	24 (49.0)	24 (46.2)	31 (55.4)
Adj. risk difference[a,b]		16.7	35.2	33.6	45.1
P value[b]		0.038	< 0.001	< 0.001	< 0.001
95% CI[b]		(0.9, 32.5)	(17.5, 52.8)	(16.3, 50.8)	(26.2, 63.9)
Clinical response per Partial Mayo score at Week 2 (NRI)					
	N = 46 n (%)	N = 47 n (%)	N = 49 n (%)	N = 52 n (%)	N = 56 n (%)
Yes	8 (17.4)	11 (23.4)	17 (34.7)	19 (36.5)	31 (55.4)
Adj. risk difference[a,b]		5.9	15.9	19.2	40.1
P value[b]		0.495	0.074	0.033	< 0.001
95% CI[b]		(−11.1, 22.9)	(−1.6, 33.4)	(1.6, 36.9)	(20.5, 59.7)
Change from Baseline in Full Mayo score to Week 8 (LOCF)					
	N = 41	N = 43	N = 44	N = 44	N = 48
Within Group Mean	−0.741	−2.870	−3.589	−4.211	−4.606
LS mean – Between Group Comparison		−2.142	−2.938	−3.736	−4.061
95% CI		(−3.2323, −1.0520)	(−4.0284, −1.8478)	(−4.8247, −2.6470)	(−5.1252, −2.9974)
P value[c]		< 0.001	< 0.001	< 0.001	< 0.001

		Upadacitinib			
	Placebo	**7.5 mg**	**15 mg**	**30 mg**	**45 mg**
Endoscopic remission at Week 8 (NRI)					
	N = 46 n (%)	N = 47 n (%)	N = 49 n (%)	N = 52 n (%)	N = 56 n (%)
Yes	0	3 (6.4)	2 (4.1)	5 (9.6)	10 (17.9)
Adj. risk difference[a,b]		6.6	3.8	11.1	17.8
P value[b]		0.075	0.199	0.015	0.004
95% CI[b]		(–0.7, 13.9)	(–2.0, 9.6)	(2.2, 20.0)	(5.8, 29.9)
Histologic improvement at Week 8 (NRI)					
	N = 46 n (%)	N = 47 n (%)	N = 49 n (%)	N = 52 n (%)	N = 56 n (%)
Yes	3 (6.5)	15 (31.9)	25 (51.0)	23 (44.2)	27 (48.2)
Adj. risk difference[a,b]		25.6	43.6	39.4	43.1
P value[b]		0.003	< 0.001	< 0.001	< 0.001
95% CI[b]		(8.9, 42.3)	(25.4, 61.8)	(21.3, 57.5)	(24.4, 61.9)

Adj. = adjusted; CI = confidence interval; ITT1A = intent-to-treat population for main subject group; LOCF = last observation carried forward; LOCF = last observation carried forward; LS = least square; NRI = non-responder imputation; SD = standard deviation

a. Risk difference = (Upadacitinib - placebo).

b. Based on Cochran-Mantel-Haenszel (CMH) test stratified by previous biologic use, Baseline corticosteroid use, and Baseline Adapted Mayo score (≤ 7 and > 7).

c. *P*-value for test of difference between each upadacitinib dose group and placebo for mean change from Baseline using analysis of covariance with treatment, randomization stratification factors (previous biologic use, Baseline corticosteroid use and Baseline Adapted Mayo score [≤ 7 and > 7]) and Baseline value as covariate.

After all randomized subjects completed the 8-week induction, a dose-selection analysis of efficacy and safety (selected laboratory parameters) of upadacitinib versus placebo was performed. Based on this dose-selection analysis, one induction dose (upadacitinib 45 mg) was identified for further evaluation in Substudy 2 and a second Phase 3 induction study, Study M14-675. The results of this analysis were reviewed and discussed with regulatory authorities, as applicable, prior to initiation of enrollment of subjects in Substudy 2 and/or Study M14-675.

2.6.5.2. Main studies

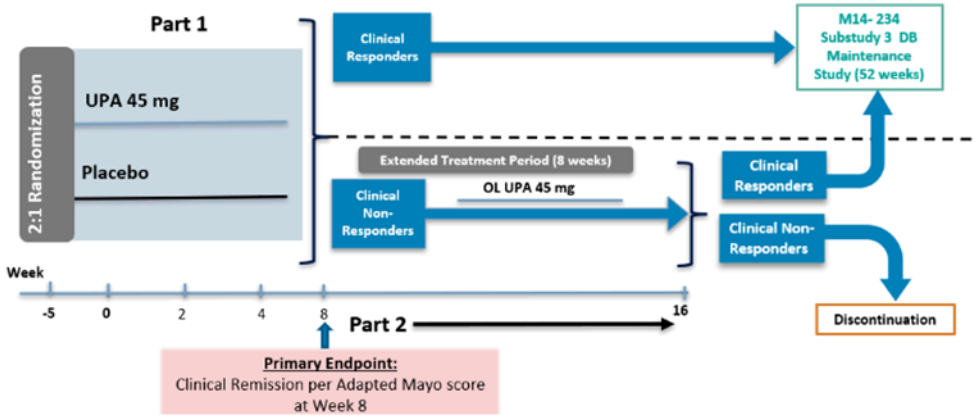
M14-234 substudy 2 A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) for Induction Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis

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

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

Methods

Induction Studies M14-234 substudy 2 and M14-675:



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

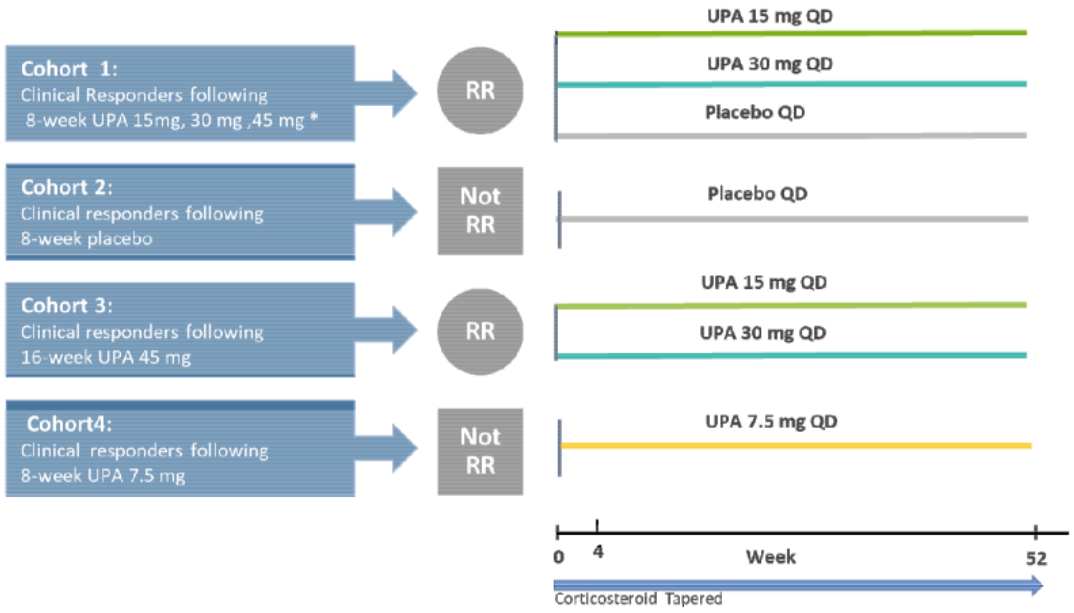
Notes: Study M14-234 Substudy 2, N = 474 randomized and treated (UPA 45 mg, n = 319; placebo, n = 155)
Study M14-675, N = 522 randomized, 521 treated (UPA 45 mg, n = 344; placebo, n = 177).
In each study, eligible subjects were randomized in a 2:1 ratio to one of the two treatment groups (double-blind upadacitinib 45 mg or matching placebo) for 8 weeks.

Figure 6 Induction Studies M14-234 Substudy 2 and Study M14-675 Design Schematic

M14-234 Substudy 2 and Study M14-675 was a two-part Phase 3 dose-confirming studies designed to evaluate the efficacy and safety of oral administration of upadacitinib 45 mg compared to placebo as induction therapy for up to 16 weeks in subjects with moderately to severely active UC. The study included a Screening Period of up to 5 weeks, Part 1, and Part 2. In Part 1 subjects were randomized 2:1 to double-blind (DB) upadacitinib or matching placebo for an 8-week induction period. Randomization was stratified by bio-IR status (bio-IR vs non-bio-IR), corticosteroid use (yes or no), and Adapted Mayo score (≤ 7 or > 7) at Baseline. Within bio-IR, the randomization was further stratified by number of prior biologic treatments (≤ 1 or > 1). Within non-bio-IR, the randomization was further stratified by previous biologic use (yes or no).

Subjects who did not achieve clinical response per Adapted Mayo score at Week 8 in Part 1 could continue in Part 2. Part 2 was an open-label, 8-week extended treatment period for clinical non-responders from Part 1.

Maintenance study M14-234 substudy 3



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

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

Figure 7 Maintenance Study M14-234 Substudy 3 Design Schematic

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

The only eligibility check required for a subject to enter Study M14-234 Substudy 3 was to have achieved clinical response at Week 8 or 16 of Induction Study and not to meet any study discontinuation criteria. Clinical response per Adapted Mayo score is defined as a decrease from baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1. The Baseline Visit of Substudy 3 was to be completed on the same day as the final visit in the Induction Phase (either at Week 8 or Week 16) for subjects who were eligible.

The treatment assignment in Substudy 3 depended on the treatment received in Substudy 1, Substudy 2, or Study M14-675, as detailed below.

Cohort 1: 847 subjects who achieved clinical response in Study M14-234 Substudy1, Substudy 2, or Study M14-675 at either Week 8 or Week 16, and received 1 of the following treatments were re-randomized in a 1:1:1 ratio to one of the treatment groups in Cohort 1:

- Upadacitinib 30 mg QD or 45 mg QD in Study M14-234 Substudy 1
- Upadacitinib 45 mg QD in Study M14-234 Substudy 2 Part 1
- Upadacitinib 45 mg QD in Study M14-675 Part 1
- Placebo QD in Study M14-234 Substudy 2 Part 1 followed by upadacitinib 45 mg QD in Study M14-234 Substudy 2 Part 2
- Placebo QD in Study M14-675 Part 1 followed by upadacitinib 45 mg QD in Part 2

Treatment groups in Cohort 1:

- Group 1: upadacitinib 15 mg QD
- Group 2: upadacitinib 30 mg QD
- Group 3: placebo QD

Subjects who achieved clinical response and received upadacitinib 15 mg QD in Study M14-234 Substudy 1 were re-randomized 1:1 to only receive upadacitinib 15 mg QD or placebo QD (treatment Group 1 or 3).

Cohort 2: 104 subjects who received double-blind placebo QD treatment for 8 weeks during Study M14-234 Substudy 1, Substudy 2 Part 1 or Study M14-675 Part 1 and achieved clinical response at Week 8 continued to receive blinded placebo QD in Substudy 3.

Cohort 3: 75 subjects who received upadacitinib 45 mg QD in induction phase and did not achieve clinical response - and received upadacitinib 45 mg in Extended Treatment in Study M14-234 Substudy 2, Part 2, or Study M14-675, Part 2, and achieved clinical response at Week 16 were re-randomized 1:1 and received blinded upadacitinib 30 mg QD or upadacitinib 15 mg QD in Study M14-234 (Substudy3).

Cohort 4: 20 subjects who received double-blinded treatment of upadacitinib 7.5 mg for 8 weeks during Study M14-234 (Substudy 1) and achieved clinical response at Week 8 continued to receive blinded treatment of upadacitinib 7.5 mg QD in Substudy3.

Study Participants

The following Inclusion/Exclusion criteria are for subjects enrolled in both Study M14-234 Substudies 1 and 2 and M14-675 including both double-blind and open-label induction periods.

Main Inclusion:

1. Male or female between 16 and 75 years of age at Baseline.
2. Diagnosis of UC for 90 days or greater prior to Baseline, confirmed by colonoscopy during the Screening Period, with exclusion of current infection, colonic dysplasia and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the investigator, must be available.
3. Active UC with an Adapted Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3 (confirmed by central reader).
4. Demonstrated an inadequate response, loss of response, or intolerance to at least one of the following treatments including, oral aminosalicylates, corticosteroids, immunosuppressants and/or biologic therapies, in the opinion of the investigator, as defined below:
    - Oral aminosalicylates (e.g., mesalamine, sulfasalazine, olsalazine, balsalazide)
      o Signs and symptoms of persistently active disease, in the opinion of the investigator, during a current or prior course of at least 4 weeks of treatment with 2.4 g/day mesalamine, 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide.
    - Corticosteroids
      Signs and symptoms of persistently active disease despite a history of at least one induction regimen that included a dose equivalent to prednisone ≥ 40 mg/day orally for at least 3 weeks or intravenously for 1 week, OR Unable to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally without recurrent active disease, OR 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 Unable to taper oral budesonide to at or below 6 mg/day without recurrent active disease, OR History of intolerance to corticosteroids (including, but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection).

- Immunosuppressants
  Signs and symptoms of persistently active disease despite a history of at least one 90 day regimen of oral azathioprine (≥ 1.5 mg/kg/day; for subjects in Japan, China, and Taiwan only: ≥ 1.0 mg/kg/day), 6-mercaptopurine (6-MP) (≥ 1 mg/kg/day; [for subjects in Japan, China, and Taiwan only: ≥ 0.6 mg/kg/day, rounded to the nearest available tablet of half tablet formulation] or a documented 6-thioguanine nucleotide [6-TGN] level of 230 –450 pmol/8 × 108 red blood cell count [RBC] or higher on the current dosing regimen), injectable MTX (≥ 15 mg/week subcutaneous [SC] or intramuscular), or tacrolimus (for subjects in Japan, Taiwan, and mainland China only: documented trough level of 5 –10 ng/mL) OR History of intolerance to at least one immunosuppressant (including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver enzyme abnormalities, lymphopenia,
  infection)
  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 unless these subjects were previously treated with aminosalicylates, corticosteroids or immunosuppressants (azathioprine or 6-MP) and have inadequate response to, loss of response to or intolerance to the therapy as defined above.

- Biologic Agents for UC
  Signs and symptoms of persistently active disease despite a history of any of the following: at least one 6-week induction regimen of infliximab (≥ 5 mg/kg intravenous [IV] at 0, 2, and 6 weeks), at least one 4-week induction regimen of adalimumab (one 160 mg subcutaenous [SC] dose followed by one 80 mg SC dose [or one 80 mg SC dose in countries where this dosing regimen is allowed] followed by one 40 mg SC dose at least 2 weeks apart), at least one 2-week induction regimen of golimumab (one 200 mg SC dose followed by one 100 mg SC dose at least 2 weeks apart), at least one 6-week induction regimen of vedolizumab (300 mg IV at 0, 2, and 6 weeks), at least one induction regimen of ustekinumab, a single IV dose using weight-based dosing (260 mg for subjects with body weight ≤ 55 kg; 390 mg for subjects with body weight > 55 kg to ≤ 85 kg; 520 mg for subjects with body weight > 85 kg *OR*
  Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify), *OR*
  History of intolerance to at least one biologic agent (including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection)
  Note: Non-bio-IR subjects who have received a prior biologic for up to 1 year 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 inadequate response, loss of response or intolerance to aminosalicylates, corticorsteroids and/or immunosuppressants as defined above.

5. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Baseline Visit prior to study drug dosing.

6. If female, subject must meet the contraception criteria as stated in Section 5.2.4 of this protocol.

Main Exclusion:

1. Subject with current diagnosis of Crohn's disease (CD) or diagnosis of indeterminate colitis (IC).
2. Current diagnosis of fulminant colitis and/or toxic megacolon.
3. Subject with disease limited to the rectum (ulcerative proctitis) during the Screening endoscopy.
4. Received cyclosporine, tacrolimus, mycophenolate mofetil, or thalidomide within 30 days prior to Baseline.
5. Subject who received azathioprine or 6-mercaptopurine within 10 days of Baseline.
6. Received intravenous corticosteroids within 14 days prior to Screening or during the Screening Period.
7. Subject with previous exposure to JAK inhibitor (e.g., tofacitinib, baricitinib, filgotinib, upadacitinib).
8. Screening laboratory and other analyses show any of the following abnormal results:

- Serum Aspartate Transaminase (AST) or Alanine Transaminase (ALT) > 2 × upper limit of normal (ULN); Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 30 mL/min/1.73 m2; Total White Blood Cell (WBC) count < 2500/µL; Absolute neutrophil count (ANC) < 1,200/µL; Platelet count < 100,000/µL; Absolute lymphocytes count < 750/µL; Hemoglobin < 9 g/dL

Treatments

Induction studies:

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

In Part 1, subjects received 1 tablet of upadacitinib 45 mg or matching placebo; treatment assignment was blinded.

In Part 2, subjects received 1 tablet open-label upadacitinib 45 mg beginning on Day 1 (Entry of Part 2)

Allowed concomitant UC-related medication Oral Corticosteroids, Antibiotics, Aminosalicylates, and/or Methotrexate

In maintenance study patients received Upadacitinib 15 mg, 30 mg or placebo. A small number of patients continued on 7.5 mg, but these patients were not included in the main analysis.

Rescue therapy and steroid tapering

At or after Week 4 in Substudy 3 maintenance period, subjects who demonstrate loss of response and require medical treatment but have not yet met the criteria to enter Study M14-533 Cohort 1, may receive rescue therapy. Rescue therapy may be provided in the form of initiation or increased dosage, at the investigator's discretion, of any allowed UC-related medications to treat new or worsening UC symptoms. The allowed UC-related medications are locally acting, oral, or intravenous corticosteroids, aminosalicylates, MTX or UC-related antibiotics. Azathioprine (AZA), 6-mercaptopurine (6-MP), cyclosporine, tacrolimus, and thalidomide are prohibited medications during the study and could not be used as rescue treatment

At baseline, (week 8 or week 16 of Substudy 1, 2, or Study M14-675) subjects who are taking corticosteroid had their corticosteroid dose tapered had their corticosteroid dose

tapered according to the following proposed schedule or based on investigators' discretion:

Table 11 Corticosteroid Dose Taper

	Dose	Rate
Oral Prednisone (or equivalent)	> 10 mg/day ≤ 10 mg/day	5 mg/day/week 2.5 mg/day/week
Oral Budesonide	≤ 9 mg/day	3 mg/day/week
Oral budesonide-MMX (e.g., Cortiment, eUceris)		Discontinue
Oral beclomethasone		Discontinue

If a subject should experience worsening of disease during the corticosteroid taper, the subject may have their corticosteroid dose increased, per the investigator's discretion during the study. Subjects in whom the maximum steroid dose equivalent exceeds the dose used at Baseline will be considered non-responders and will be censored for efficacy assessments from that point forward through the end of the study. These subjects will continue to be evaluated in the safety analysis set.

Objectives

M14-234 Substudy 2

Evaluate the efficacy and safety of upadacitinib 45 mg QD compared to placebo in inducing clinical remission (per Adapted Mayo score) in subjects with moderately to severely active UC who have had inadequate response, loss of response or intolerance to aminosalicylates, immunosuppressants, corticosteroids, or biologic therapies.

M14-675

Evaluate the efficacy and safety of upadacitinib 45 mg QD compared to placebo in inducing clinical remission (per Adapted Mayo score) in subjects with moderately to severely active ulcerative colitis (UC) who have had inadequate response, loss of response or intolerance to aminosalicylates, immunosuppressants, corticosteroids, or biologic therapies

M14-234 Substudy 3

Evaluate the efficacy and safety of upadacitinib 30 mg and 15 mg once daily compared to placebo in achieving clinical remission (per Adapted Mayo score) in subjects with moderately to severely active ulcerative colitis (UC) who achieved clinical response (per Adapted Mayo score) following induction therapy from Study M14-234 Substudy 1, Substudy 2, or Study M14-675.

Outcomes/endpoints

Induction study M14-675

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

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

- Proportion of subjects with endoscopic improvement (defined as an endoscopic subscore ≤ 1) at week 8
- Proportion of subjects with endoscopic remission (defined as an endoscopic subscore of 0) at week 8
  Proportion of subjects achieving clinical response per Adapted Mayo score (defined as decrease from baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease
  in RBS ≥ 1 or an absolute RBS ≤ 1) at week 8
- Proportion of subjects achieving clinical response per Partial Adapted Mayo score (defined as decrease from Baseline ≥ 1 points and ≥ 30% from Baseline, PLUS a decrease in RBS ≥ 1 or an
  absolute RBS ≤ 1) at week 2
- Proportion of subjects achieving histologic-endoscopic mucosal improvement (endoscopic subscore ≤ 1 and Geboes score ≤ 3.1) at week 8
- Proportion of subjects who reported no bowel urgency at week 8
- Proportion of subjects who reported no abdominal pain at week 8
- Proportion of subjects who achieved histologic improvement at week 8

Induction study Substudy 2:

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

Ranked secondary endpoints used the same definitions as in Substudy 1 and were evaluated at Week 8 or Week 2 (only clinical response per Partial Mayo score):

- Proportion of subjects with endoscopic improvement
- Proportion of subjects with endoscopic remission
- Proportion of subjects achieving clinical response per Adapted Mayo score
- Proportion of subjects achieving clinical response per Partial Adapted Mayo
- Proportion of subjects achieving clinical remission per Full Mayo score (defined as a Full Mayo score ≤ 2 with no subscore > 1)
- Proportion of subjects achieving histologic-endoscopic mucosal improvement
- Proportion of subjects who reported no bowel urgency
- Proportion of subjects who reported no abdominal pain
- Proportion of subjects who achieved histologic improvement
- Change from Baseline in The Inflammatory Bowel Disease Questionnaire (IBDQ)
    - Proportion of subjects with mucosal healing

- Change from Baseline in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)

Maintenance study

The primary endpoint for Phase 3 maintenance (Substudy 3) was the proportion of subjects who achieved clinical remission per Adapted Mayo score (defined as stool frequency subscore [SFS] ≤ 1, rectal bleeding subscore [RBS] of 0, and endoscopic subscore ≤ 1) at Week 52.

Ranked secondary endpoints were:
1. Proportion of subjects with endoscopic improvement at Week 52
2. Proportion of subjects who maintained clinical remission per Adapted Mayo score at Week 52 among subjects who achieved clinical remission per Adapted Mayo score in Study M14-234 (Substudy 1 or 2) or Study M14-675
3. Proportion of subjects who achieved clinical remission at Week 52 per Adapted Mayo score and were corticosteroid free for ≥ 90 days among subjects in clinical remission at the end of the induction treatment in Study M14-234 (Substudy 1 or 2) or Study M14-675
4. Proportion of subjects with endoscopic improvement at Week 52 among subjects with endoscopic improvement in Study M14-234 (Substudy 1 or 2) or Study M14-675
5. Proportion of subjects with endoscopic remission at Week 52
6. Proportion of subjects who maintained clinical response per Adapted Mayo score at Week 52
7. Proportion of subjects with histologic-endoscopic mucosal improvement at Week 52
8. Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total score at Week 52
9. Proportion of subjects with mucosal healing at Week 52
10. Proportion of subjects who reported no bowel urgency at Week 52
11. Proportion of subjects who reported no abdominal pain at Week 52
12. Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score at Week 52

Definition of endpoints:

Clinical remission and clinical response were defined by the following endpoints:

	RBS (0 – 3)	SFS (0 – 3)	PGA (0 – 3)	Endoscopy (0 – 3)	Score Range
Mayo Score	X	X	X	X	0 – 12
Adapted Mayo Score	X	X		X	0 – 9
Partial Adapted Mayo Score	X	X			0 – 6
Partial Mayo Score	X	X	X		0 – 9

PGA = Physician's Global Assessment; RBS = rectal bleeding score; SFS = stool frequency score

Clinical Remission:

Per Adapted Mayo score: SFS ≤ 1 and not greater than baseline, RBS of 0,
and endoscopic subscore ≤ 1 (note: evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity conferred an endoscopic subscore of 2)

Per Full Mayo score: Full Mayo score of ≤ 2 with no subscore > 1

Per Partial Mayo score: Partial Mayo score of ≤ 2 with no subscore > 1

Clinical Response:
Per Adapted Mayo score: decrease from baseline in Adapted Mayo score ≥ 2 points and ≥ 30%, accompanied by a decrease in RBS of ≥ 1 or an absolute RBS of 0 or 1

Per Full Mayo score: decrease from baseline in Full Mayo score ≥ 3 points and ≥ 30%, accompanied by a decrease in RBS of ≥ 1 or an absolute RBS of 0 or 1

Per Partial Adapted Mayo score: decrease from Baseline ≥ 1 points and ≥ 30% from Baseline, plus a decrease in RBS ≥ 1 or an absolute RBS ≤ 1

Endoscopic and histologic assessments were centrally read by external physicians who were not study investigators

Geboes Index: A common histologic index for UC composed of 7 categories. Qualitative UC histological assessment of acute inflammation and chronicity was performed using Geboes histologic activity score (Geboes 2000). Grade 0 indicates structural change only; Grade 1 indicates chronic inflammation; Grade 2 indicates a finding of lamina propria neutrophils; Grade 3 indicates finding of neutrophils in epithelium; Grade 4 indicates crypt destruction; and Grade 5 indicates erosions or ulcers.

Endoscopy: Based on Mayo endoscopic subscore of 0-3 where 0 = normal or inactive disease; 1 = mild disease (erythema, decreased vascular pattern); 2 = moderate disease (marked erythema, lack of vascular pattern, any friability, erosions); 3 = severe disease (spontaneous bleeding, ulceration). Evidence of friability during endoscopy in subjects with otherwise "mild" endoscopic activity conferred an endoscopic subscore of 2. The endoscopic and histologic endpoint definitions for these efficacy variables were:

Endoscopic remission: Endoscopic subscore of 0
Endoscopic improvement: Endoscopic subscore ≤ 1
Histologic improvement: Decrease from Baseline in Geboes score
Histologic-endoscopic mucosal improvement: Endoscopic subscore ≤ 1 and Geboes score ≤ 3.1
Mucosal healing: Endoscopic score = 0 and Geboes score < 2.

Symptoms
Abdominal Pain: Abdominal pain is a scale of measures with response options: 0 = no abdominal pain, 1 = mild (aware but tolerable), 2 = moderate (interferes with usual activity), 3 = severe (intolerable) and a recall period of 24 hours.
Bowel Urgency: Bowel urgency is an item with response option of Yes or No for feeling the need for a bowel movement and having to rush to the toilet to avoid an accident, and a recall period of 24 hours.

Sample size

Induction study M14-675 and M14-234 substudy 2

For each of the Induction Studies, approximately 462 subjects are expected to be randomized to upadacitinib 45 mg QD or placebo in a randomization ratio of 2:1. The sample size for this study is based on the expected proportion of subjects who achieve clinical remission per Adapted Mayo score at Week 8. Based on the results from Phase 2b upadacitinib Study M14-234 (Substudy 1), clinical remission rate is assumed to be 5% in the placebo group and 18% in the upadacitinib 45 mg QD treatment group. Based on these assumptions, a sample size of 154 subjects in placebo and 308 subjects in upadacitinib dose will have > 95% power to detect the 13% treatment difference in the

primary endpoint between upadacitinib 45 mg QD group and placebo group using two-sided Fisher's exact test at a 0.05 significant level.

Maintenance study M14-234 substudy 3

The sample size for the Maintenance Study is based on the expected proportion of subjects who achieve clinical remission per Adapted Mayo score at Week 52. The assumptions of clinical remission rates were based on the historical data from other compounds with similar or different MOAs. In vedolizumab Phase 3 UC study, the clinical remission rate was 16% in placebo group and 42% in treatment group. In tofacitinib Phase 3 UC study, the clinical remission rate was 11.1% in placebo group and 40.6% in 10 mg BID treatment group. Considering the factors that may influence the clinical remission rate (e.g., differences in MOAs, patient population, and clinical remission definition), clinical remission rates are assumed to be 12% in the placebo group and 40% in the upadacitinib treatment group at Week 52.

Assuming clinical remission rate of 12% in the placebo group and 40% in one of the upadacitinib QD treatment groups at Week 52, a sample size of 150 subjects in placebo and 150 subjects in each of the upadacitinib 15 mg QD and 30 mg QD treatment groups will have > 95% power to detect the 28% treatment difference in the primary endpoint between an upadacitinib dose and placebo using two-sided Fisher's exact test at a 0.025 significant level with multiplicity adjustment. Under the assumption that average response rate in upadacitinib doses at the end of induction treatment in the Induction Studies is 50%, a total of approximately 450 subjects will be re-randomized to upadacitinib 15 mg QD or 30 mg QD treatment groups or placebo in a randomization ratio of 1:1:1 if they achieved clinical response from upadacitinib 45 mg QD in the Induction Studies. The assumption of an average response rate of 50% in upadacitinib doses after induction is based on the Phase 2b results.

Randomisation and blinding (masking)

Induction study M14-675 and M14-234 substudy 2

Approximately 462 subjects per induction study will be randomized in a 2:1 ratio to double-blind upadacitinib 45 mg QD or matching placebo for 8 weeks. The randomization will be stratified by bio-IR status (bio-IR vs. non-bio-IR), corticosteroid use (yes vs. no) and Adapted Mayo score (≤ 7 vs. > 7) at Baseline. Within bio-IR, the randomization will be further stratified by number of prior biologic treatments (≤ 1 vs. > 1). Within non-bio-IR, the randomization will be further stratified by previous biologic use (yes vs. no). All eligible subjects entering Part 2 will receive open label upadacitinib 45 mg QD for an additional 8 weeks (until Week 16).

Treatment assignments of induction will be unblinded to AbbVie for statistical analyses when all subjects have completed the induction study. The study sites and subjects will remain blinded to the double-blind induction treatment assignments until all subjects have completed the Maintenance Study.

Maintenance study M14-234 substudy 3

Cohort 1: Subjects will be re-randomized to one of the three treatment groups in Cohort 1 (upadacitinib 15 mg QD, upadacitinib 30 mg QD, or placebo). For subjects who are from Study M14-234 SS2 or Study M14-675 the randomization will be stratified by Bio-IR status (Bio-IR or Non-Bio-IR) at the Baseline of Study M14-234 SS2 or Study M14-675, clinical remission status at Week 0 (yes or no) and corticosteroid use at Week 0 (yes or no). For subjects who are from Study M14-234 SS1 the randomization will be stratified by previous biologic use (yes or no) at the Baseline of Study M14-234 SS1 and induction dose received. Approximately 25 subjects who achieved clinical response and received double-blind induction treatment of upadacitinib 15 mg QD in Study M14-234 Substudy 1 will

be enrolled in this cohort. These subjects will be re-randomized in a 1:1 ratio to receive upadacitinib15 mg QD or placebo QD (Treatment Group 1 or 3). The randomization will be stratified by previous biologic use (yes or no) at the Baseline of Study M14-234 Substudy 1.

Cohort 3: Subjects will be re-randomized to 1 of the 2 treatment groups in Cohort 3 (upadacitinib 15 mg QD and upadacitinib 30 mg QD). Randomization will be stratified by Bio-IR status (Bio-IR or Non-Bio-IR) at the Baseline of Study M14-234 SS2 or Study M14-675, clinical remission status at Week 0 (yes or no) and corticosteroid use at Week 0 (yes or no).

Cohort 2 and cohort 4 are non-randomized.

The primary analysis will be performed after the first 450 subjects in the Maintenance Study Cohort 1 who were upadacitinib 45 mg QD induction responders have completed the Maintenance Study activities (i.e., completed Week 52 or prematurely discontinued prior to Week 52) and the database has been locked, for the purpose of regulatory submission. This is the only and final analysis for the 52-week efficacy analyses. Treatment assignments for the Maintenance Study will be unblinded to AbbVie for statistical analyses. Additional subjects in any cohort who have not completed the Maintenance Study at the time of database lock will be kept on the same blinded treatment until study completion. The study sites and subjects will remain blinded to the maintenance treatment assignments until all subjects have completed the Maintenance Study. Once all subjects have completed the Maintenance Study, the data collected from these subjects will be used to update the safety analysis only.

Statistical methods

Induction study M14-675 and M14-234 substudy 2

All efficacy summaries presented for study M14-675 were based on analyses conducted on primary efficacy data (version K; interim database lock; 09 February 2021). All efficacy summaries presented for Study M14-234 SS2 were based on analyses conducted on primary efficacy data (version S: database lock; 25 November 2020). The statistical methods were documented in separate SAPs for each of the induction studies, dated 19 January 2021 and 13 November 2020 respectively.

All tests will be at the α level of 0.05 (2-sided). The primary analysis will be performed after all ongoing subjects have completed the induction study activities and the database has been locked.

Analysis Populations

Significant non-compliance was identified at a site (Investigator ID 527969). As a result of this finding, efficacy data for the subjects enrolled at this investigational site will be excluded from the statistical analyses. There were 6 subjects enrolled at this site in study M14-675 and 1 subject in study M14-234 SS2.

The ITT population for the 8-week double-blind induction period (Part 1) (denoted by ITT1) includes all randomized subjects who received at least one dose of double-blinded study drug in Part 1. The ITT1 population will be used for all efficacy and baseline analyses for Part 1. For ITT1 population, subjects will be included in the analysis according to the treatment groups that they are randomized to. The ITT population for the 8-week open label extended treatment period (Part 2) (denoted by ITT2) includes all subjects who received at least one dose of upadacitinib 45 mg QD in Part 2.

Estimands

The estimand corresponding to the primary efficacy objective is defined as follows:

Difference in the percentage of subjects achieving clinical remission per Adapted Mayo score at Week 8 regardless of premature discontinuation of study drug and without initiation or dose escalation of UC-related corticosteroids in the upadacitinib 45 mg QD and placebo groups in the ITT population.

The estimands corresponding to the secondary efficacy objectives are defined for each of the binary ranked secondary endpoints as follows:

Difference in the percentage of subjects achieving binary endpoints regardless of premature discontinuation of study drug and without initiation or dose escalation of UC-related corticosteroids in the upadacitinib 45 mg QD and placebo groups in the ITT population.

The estimands corresponding to the secondary efficacy objectives are defined for each of the continuous ranked secondary endpoints as follows:

Difference in the mean change from baseline regardless of premature discontinuation of study drug and if subjects would not initiate or escalate dose of UC-related corticosteroids in the upadacitinib 45 mg QD and placebo groups in the ITT population.

Intercurrent events

Potential intercurrent events include 1) premature discontinuation of study drug and 2) initiation or dose escalation of UC-related corticosteroids. Intercurrent events will be handled using the following methods for the efficacy analysis:

Premature Discontinuation of Study Drug: Data collected will be used regardless of premature discontinuation of study drug.

Initiation or dose escalation of UC-related corticosteroids: Subjects will be considered as "non-responder" for binary endpoints at or after the occurrence of the UC-related corticosteroids intercurrent event through the end of the Induction Study. For continuous endpoints, all measurements at or after the occurrence of the UC-related corticosteroids intercurrent event through the end of the Induction Study will not be used in the analysis.

Missing Data

For binary efficacy endpoints, missing data will be handled using the following approaches:

The primary approach for handling missing data in the analysis of binary endpoints will use Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 (NRI-C). This includes non-responder imputation at or after the occurrence of UC-related corticosteroids intercurrent event.

A sensitivity analysis for categorical endpoints will use NRI with No special data handling for missing due to COVID-19 (NRI-NC).

A Sensitivity analysis will be performed using hybrid multiple imputation method (HMI) for the primary endpoint. Subjects who discontinue study drug prior to Week 8 due to lack of efficacy or AEs and have no available measurements will be considered as "non-responder" for clinical remission. Subjects who discontinue for other reasons and have no available measurements will be categorized according to the data from multiple imputations.

An As Observed (AO) analysis will also be performed. This analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. AO will include all values collected in the study.

Multiple Imputation (MI) for NRI-C and HMI: PROC MI will be used to generate 30 datasets using the regression method. The variables to be included in the imputation model are: treatment group,

stratification factors, Baseline measurement, and if applicable, post-baseline measurements at each visit up to the end of the analysis period. The imputed post-baseline measurements will be rounded to the same precision as the observed data before the determination of responder status. Subjects will be characterized as responders or non-responders based on MI imputed datasets. Note that measurements will be set to missing at or after the occurrence of the UC-related corticosteroids intercurrent event before applying MI.

For continuous endpoints, missing data will be handled using Mixed-Effect Model Repeat Measurement (MMRM). The MMRM will be conducted using mixed model including observed measurements at all visits, except that measurements at or after the occurrence of UC-related corticosteroids intercurrent event will be excluded.

Efficacy Analyses

Categorical variables will be analyzed using Cochran-Mantel-Haenszel (CMH) test, stratified by bio-IR status (bio-IR vs. non-bio-IR), Baseline corticosteroid use (yes vs. no) and Baseline Adapted Mayo score (≤ 7 vs. > 7). Any subject who was randomized under the wrong stratum will be analyzed according to the actual stratum the subject belongs to. Continuous variables collected longitudinally will be analyzed using Mixed-Effect Model Repeat Measurement (MMRM) method. Continuous variables collected at only one post-baseline visit (such as Mayo score) will be analyzed using an Analysis of Covariance (ANCOVA) model.

The primary analysis will compare the proportion of subjects achieving clinical remission in upadacitinib treatment group and placebo group in the ITT1 population. The difference between the treatment groups in the primary efficacy endpoint will be assessed using the CMH test as specified above and a CMH based two-sided 95% confidence interval for the difference between treatment groups will be calculated. For the primary efficacy endpoint, the same CMH analysis will be performed using As Observed (AO) data handling without any imputation as an additional analysis. The analysis will be conducted on the ITT1 population who have the efficacy measurement at Week 8 visit. Furthermore, a supplementary analysis will be conducted to evaluate the potential impact of deviations. In this analysis, subjects with deviations that could potentially impact the analysis of primary endpoint will be excluded. Treatment difference between upadacitinib 45 mg QD and placebo with point estimate and 95% CI will be presented using NRI-C approach with the CMH method.

Secondary efficacy endpoints in Part 1 will be analyzed by comparing upadacitinib treatment group and placebo group. The binary secondary endpoints will be analyzed by CMH. The NRI-C will be the primary approach for missing data handling in the analyses of binary secondary efficacy endpoints. The NRI-NC approach will be used as sensitivity analyses. Furthermore, an analysis using As Observed (AO) data handling without any imputation will also be performed.

The continuous secondary endpoints will be analyzed by MMRM with an AO analysis as sensitivity analysis.

Overall Type-I Error Control

The overall type I error rate of the primary and the ranked secondary endpoints will be strongly controlled using the fixed-sequence multiple testing procedure. Specifically, the testing will utilize the endpoint sequence of the primary and ranked secondary endpoints in the order specified. The analysis for additional efficacy endpoints will be performed at the nominal α level of 0.05 (two-sided).

Maintenance study M14-234 substudy 3

Analysis populations

Significant non-compliance was identified at an investigational site (original Investigator ID 527969). There were 6 subjects enrolled at this site in the Induction Studies who continued into the Maintenance Study. As a result of this finding, efficacy data for these subjects will be excluded from the statistical analyses for the Maintenance Study.

The following ITT populations were analyzed in Substudy 3:

ITT population: All subjects who received at least 1 dose of study drug in the Maintenance Study.

ITT_A population: The subset of ITT population who were the first randomized 451 (actual) upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1. The ITT_A population is the primary analysis population in Cohort 1 for efficacy endpoints. The planned number of subjects in the ITT_A population was 450; however, the actual number of subjects is 451 due to the tie in enrollment date of subjects #450 and #451.

ITT_B population: The subset of ITT population in Cohort 3 who were upadacitinib 45 mg QD 16-week induction responders.

ITT_C population: The subset of ITT population who were enrolled under the original protocol, Amendment 1 or 2 for 44-week maintenance treatment period.

ITT_D population: The subset of ITT population who were upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1.

ITT_E population: The subset of ITT who were placebo, upadacitinib 7.5 mg QD, 15 mg QD, or 30 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period.

The above populations were annotated as ITT3, ITT3_A, ITT3_B, ITT3_C, ITT3_D and ITT3_E in the protocol.

For ITT populations, subjects were included in the analysis according to the treatment groups that they were randomized to, as applicable.

Estimands

The estimand corresponding to the primary efficacy objective is defined as follows:

- Difference in the percentage of subjects achieving clinical remission per Adapted Mayo score at Week 52 regardless of premature discontinuation of study drug and without use of UC-related rescue medications in the upadacitinib 15 mg QD, upadacitinib 30 mg QD and placebo groups in the ITT_A population.

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

Regardless of premature discontinuation of study drug and without use of UC-related rescue medications in the upadacitinib 15 mg QD, upadacitinib 30 mg QD and placebo groups in the ITT_A population:

- Difference in the percentage of subjects achieving endoscopic improvement at Week 52;
- Difference in the percentage of subjects achieving clinical remission per Adapted Mayo score at Week 52 among subjects who achieved clinical remission at the end of the induction treatment in the Induction Study;

- Difference in the percentage of subjects achieving clinical remission per Adapted Mayo score at Week 52 and corticosteroid free for ≥ 90 days immediately preceding Week 52 among subjects who achieved clinical remission at the end of the induction treatment in the Induction Study;
- Difference in the percentage of subjects achieving endoscopic improvement at Week 52 among subjects who achieved endoscopic improvement at the end of the induction treatment in the Induction Study;
- Difference in the percentage of subjects achieving endoscopic remission at Week 52;
- Difference in the percentage of subjects achieving clinical response per Adapted Mayo score at Week 52 among subjects who achieved clinical response at the end of the induction treatment in the Induction Study;
- Difference in the percentage of subjects achieving histologic-endoscopic mucosal improvement at Week 52;
- Difference in the mean change from Baseline in IBDQ total score at Week 52;
- Difference in the percentage of subjects achieving mucosal healing at Week 52;
- Difference in the percentage of subjects achieving no bowel urgency at Week 52;
- Difference in the percentage of subjects achieving no abdominal pain at Week 52;
- Difference in the mean change from Baseline in FACIT-F score at Week 52

Intercurrent events

Intercurrent events will be handled using the following methods for the efficacy analysis:

Premature Discontinuation of Study Drug: If the subjects prematurely discontinued study drug but stayed in the study, data collected after premature discontinuation of study drug will be used.

Use of UC-related rescue medications (UC-Related corticosteroids or UC-related non-corticosteroid rescue medications): For categorical endpoints, subjects will be considered as "non-responder" at or after the occurrence of the UC-related rescue medication intercurrent event through the end of the Maintenance Study except for the As Observed (AO) analysis. For continuous endpoints, all measurements from the date of UC-related rescue medications intercurrent event through the end of the Maintenance Study will not be used in the analysis except for the As Observed (AO) analysis.

Missing data

For binary efficacy endpoints, missing data will be handled using the following approaches:

- The primary approach for handling missing data will be Non-Responder Imputation while incorporating Multiple Imputation (MI) to handle missing data due to COVID-19 (NRI-C). This includes non-responder imputation at and after the UC-related rescue medications intercurrent event.
- A sensitivity analysis will use NRI with No special data handling for missing due to COVID-19 (NRI-NC). Subjects at or after the occurrence of the UC-related rescue medications intercurrent event will still be counted as non-responders.
- A Sensitivity analysis will be performed using Hybrid Multiple Imputation Method (HMI) for the primary endpoint. Subjects who discontinue study drug prior to Week 52 due to lack of efficacy or AEs and have no available measurements will be considered as "non-responder" for clinical remission. Subjects who discontinue for other reasons and have no available measurements, or subjects who has missing Week 52 evaluations will be categorized according to the data from

multiple imputations. In addition, at and after the UC-related rescue medications intercurrent event subjects will be counted as non-responders.

- An As Observed (AO) analysis will also be performed. This analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. AO will include all values collected in the study regardless the occurrence of UC-related rescue medication intercurrent event.

Multiple Imputation (MI) for NRI-C and HMI: PROC MI will be used to generate 30 datasets using the regression method. The variables to be included in the imputation model are: treatment group, stratification factors, Baseline measurement, and if applicable, post-baseline measurements at each visit up to the end of the analysis period. The imputed post-baseline measurements will be rounded to the same precision as the observed data before the determination of responder status. Subjects will be characterized as responders or non-responders based on MI imputed datasets. Note that measurements will be set to missing at or after the occurrence of the UC-related rescue medications intercurrent event before applying MI.

For continuous endpoints, missing data will be handled using the following approaches:

- The primary approach is Multiple Imputation Incorporating Return-to-Baseline to Handle Visits After UC-related Rescue Medication Use (RTB-MI). To assess the potential departures from the missing-at-random (MAR) assumptionfor visits after the intercurrent event of UC-related rescue medication use, the Return-to-Baseline (RTB) approach which assumes subjects received UC-related rescue medication will have a washout "return to baseline" of any potential treatment effect, will be performed as following:
    - Step 1: after setting data after the intercurrent event of UC-related rescue medication use as missing, missing values due to all causes will first be imputed via MI under the MAR assumption.
    - Step 2: subject's efficacy assessments after the intercurrent event of UC-related rescue medication will be assumed to have returned to baseline. For each imputed dataset, missing change from baseline data due to the intercurrent event of UC-related rescue medication will be replaced by a value from a normal distribution (0, V), where V is the variance of change from baseline estimated from all observed values regardless of treatment groups, excluding those after UC-related rescue medication use.
    - Step 3: For each imputed dataset, the MMRM/ANCOVA model will be applied to each completed set and the inference will be drawn using Rubin's combination rules (SAS proc MIANALYZE).
- MMRM/ANCOVA: Assuming any unobserved data (including the missing due to the intercurrent event of UC-related rescue medication use) can be considered as MAR, an MMRM/ANCOVA model excluding data after the intercurrent event of UC-related rescue medication use will be performed as a sensitivity analysis.
- Delta-Based Multiple Imputation (DBMI). A missing-not-at-random (MNAR) model that varies assumptions for data after the intercurrent event of UC-related rescue medication use will be implemented through Delta-Based Multiple Imputation (DBMI). The DBMI is two-dimensional, i.e., assumptions about the missing outcomes on the upadacitinib treatment groups and the placebo group are allowed to vary independently. After setting data after the intercurrent event of UC-related rescue medication use as missing, missing values due to all causes will first be imputed via MI under the MAR assumption, and then a shift parameter (i.e., delta) will be

applied to the imputed values for the missing data due to UC-related rescue medication use. For each pair of deltas, the MMRM/ANCOVA model will be applied to each completed set and the inference will be drawn using Rubin's combination rules (SAS proc MIANALYZE). For each endpoint to be analyzed, the analysis will be repeated for a range of delta values corresponding to 0 to ±100% of the unadjusted mean observed for all subjects.

- As Observed (AO): The AO analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. AO will include all values collected in the study regardless the occurrence of UC-related rescue medication intercurrent event.

Efficacy analysis

Categorical variables will be analyzed using Cochran-Mantel-Haenszel (CMH) test, stratified by Bio-IR status (Bio-IR or Non-Bio-IR) at the Baseline of Induction Study, clinical remission status at Week 0 (yes or no), and corticosteroid use at Week 0 (yes or no). Any subject who was randomized under the wrong stratum will be analyzed according to the actual stratum the subject belongs to. Continuous variables collected longitudinally will be analyzed using Mixed-Effect Model Repeat Measurement (MMRM) model. Continuous variables collected at only one post-baseline visit will be analyzed using an Analysis of Covariance (ANCOVA) model. MMRM model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, randomization stratification factors (Bio-IR status (Bio-IR or Non-Bio-IR) at the Baseline of the Induction Study, clinical remission status a Week 0 (yes or no), and corticosteroid use at Week 0 (yes or no)), and the continuous fixed covariates of Baseline measurements. An unstructured variance covariance matrix (UN) will be used. If the model cannot converge, autoregressive (1) covariance structure matrix will be used. The parameter estimations are based on the method of restrictive maximum likelihood (REML). The fixed effects will be used to report model-based means at corresponding visits. ANCOVA model includes the categorical fixed effects of treatment, randomization stratification factors (Bio-IR status: Bio-IR or Non-Bio-IR) at the Baseline of the Induction Study, clinical remission status at Week 0 (yes or no), and corticosteroid use at Week 0 (yes or no)), and the continuous fixed covariates of Baseline measurements.

Type I error control

The overall type I error rate of the primary and ranked secondary endpoints for the two upadacitinib doses will be strongly controlled using iterative graphical testing procedure described in the figure. Specifically, the testing will utilize the sequence of hypothesis testing for the primary endpoint followed by the ranked key secondary endpoints in the order as specified, and will begin with testing the primary endpoint using α of 0.025 for each upadacitinib dose compared to placebo. Continued testing will follow a pre-specified weight of α allocation between the single hypothesis within the family, as well as between the families of hypotheses across the doses (denoted as node). In the graph, the arrows specify the weight of α allocation between nodes. Once a hypothesis is rejected (i.e., deemed the endpoint is significant) at its assigned significance level, its significance level will be allocated to the subsequent node. If more than one arrow originates from a node, the significance level will be split between multiple subsequent nodes following the pre-specified weight.

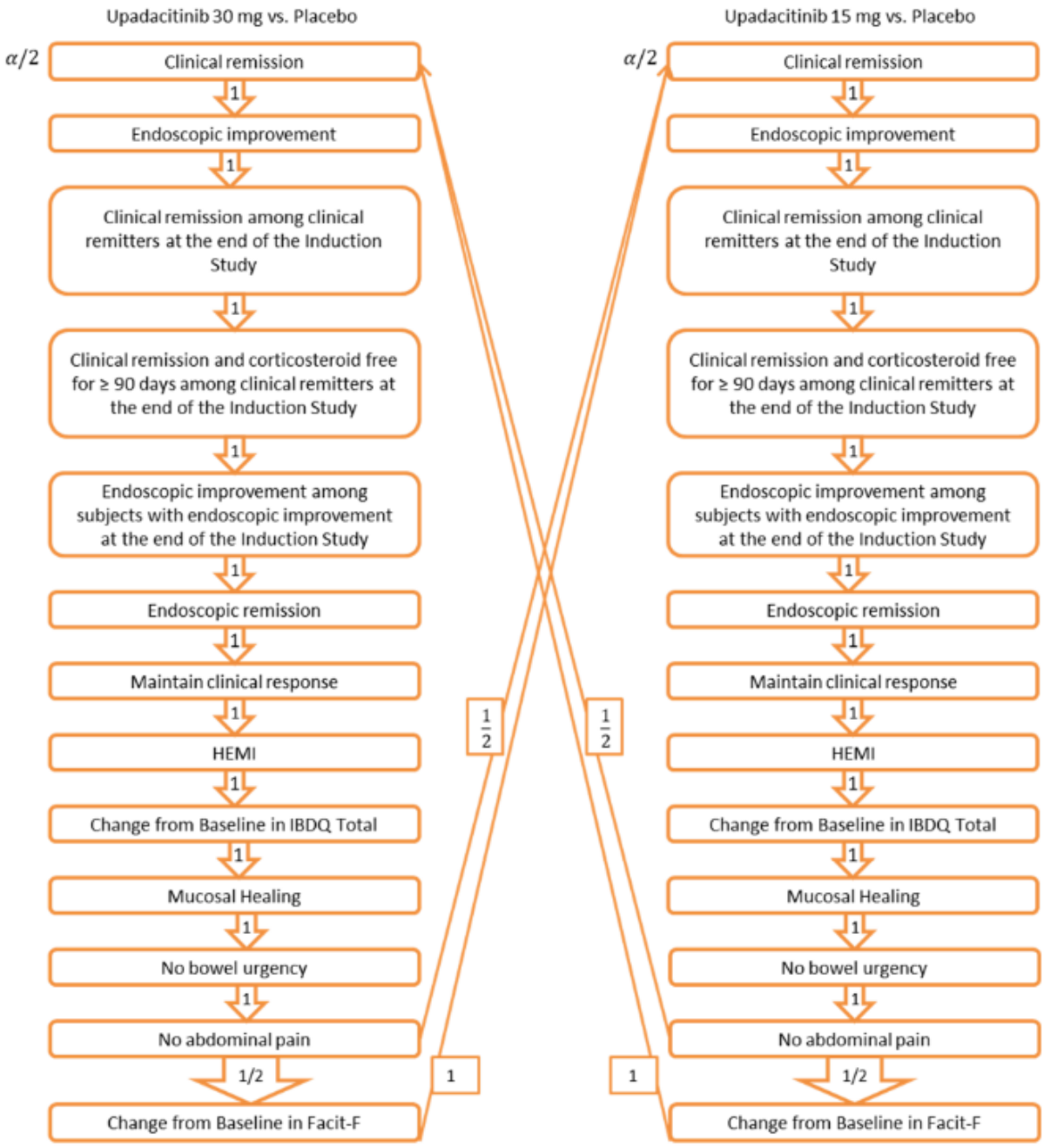


Figure 8 Graphical multiple testing procedure for primary and ranked secondary efficacy endpoints (ITT_A population)

Results

Participant flow

Induction studies

M14-234 Substudy 2 Induction study

A total of 474 subjects were randomized at 199 sites in the following countries:

Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Canada, China, Croatia, Czech

Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Korea (Republic of), Latvia, Lithuania, Malaysia, Mexico, Netherlands, Norway, Poland, Portugal, Russian Federation, Serbia, Slovakia, South Africa, Spain, Switzerland, Taiwan, Turkey, United Kingdom, and United States, including Puerto Rico.

Table 12 M14-234 Substudy 2 – Subject Accountability (All Randomized Subjects)

Sites Treatment	Randomized n	Treated n	Study Drug Completed n	Study Drug Discontinued n	Study Discontinued n
All sites					
Placebo	155	155	136	19	20
UPA 45 mg	319	319	307	12	13
Placebo/UPA 45 mg		85	75	10	11
UPA 45 mg/UPA 45 mg		59	48	11	12
Part 1 total	474	474	443	31	33
Part 2 total		144	123	21	23

UPA = upadacitinib

Table 13 M14-234 substudy 2 – Subject Disposition (ITT1 and ITT2 Populations)

	Part 1		Part 2	
	Placebo (N = 154) n (%)	UPA 45 mg (N = 319) n (%)	Placebo/ UPA 45 mg (N = 84) n (%)	UPA 45 mg / UPA 45 mg (N = 59) n (%)
Discontinuation of study drug due to				
Primary Reason[a]	19 (12.3)	12 (3.8)	9 (10.7)	11 (18.6)
Adverse event	7 (4.5)	7 (2.2)	2 (2.4)	0
Withdrew consent	2 (1.3)	1 (0.3)	3 (3.6)	1 (1.7)
Lack of efficacy	9 (5.8)	2 (0.6)	3 (3.6)	7 (11.9)
Lost to follow-up	0	1 (0.3)	0	1 (1.7)
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	0	0	0
Other	1 (0.6)	1 (0.3)	1 (1.2)	2 (3.4)
Discontinuation of study due to				
Primary Reason[b]	20 (13.0)	13 (4.1)	10 (11.9)	12 (20.3)
Adverse event	9 (5.8)	6 (1.9)	3 (3.6)	0
Withdrew consent	3 (1.9)	2 (0.6)	3 (3.6)	1 (1.7)
Lost to follow-up	1 (0.6)	1 (0.3)	0	1 (1.7)
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	1 (0.3)	0	2 (3.4)
Other	7 (4.5)	3 (0.9)	4 (4.8)	8 (13.6)

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

Note: In Part 1, all randomized subjects were treated.

Induction study M14-675

A total of 522 subjects were randomized at 204 sites in the following countries: Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Canada, Chile, China, Colombia, Croatia, Czech Republic, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Japan, Korea (Republic of), Latvia, Lithuania, Malaysia, Mexico, Norway, Poland, Portugal, Russian Federation, Serbia, Singapore, Slovakia, South Africa, Spain, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, and United States, including Puerto Rico.

A total of 333 subjects in the upadacitinib 45 mg group completed 8 weeks of study drug treatment in Part 1; 11 subjects discontinued active treatment compared with 13 subjects in the placebo group.

Table 14 Induction study M14-675 Subject Accountability (All Randomized Subjects)

Sites Treatment	Randomized n	Treated n	Study Drug Completed n	Study Drug Discontinued n	Study Discontinued n
All sites					
Placebo	177	177	164	13	13
UPA 45 mg	345	344	333	11	12
Placebo/UPA 45 mg		116	111	5	5
UPA 45 mg/UPA 45 mg		68	64	4	3
Part 1 total	522	521	497	24	25
Part 2 total		184	175	9	8

UPA = upadacitinib

Table 15 Induction study M14-675 Subject Disposition (ITT1 and ITT2 Populations)

	Part 1		Part 2	
	Placebo (N = 174) n (%)	UPA 45 mg (N = 341) n (%)	Placebo/ UPA 45 mg (N = 113) n (%)	UPA 45 mg/ UPA 45 mg (N = 66) n (%)
Discontinuation of study drug due to				
Primary Reason[a]	13 (7.5)	11 (3.2)	5 (4.4)	4 (6.1)
Adverse event	5 (2.9)	5 (1.5)	2 (1.8)	2 (3.0)
Withdrew consent	4 (2.3)	6 (1.8)	2 (1.8)	1 (1.5)
Lack of efficacy	4 (2.3)	0	0	0
Lost to follow-up	0	0	0	0
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	0	0	0
Other	0	0	1 (0.9)	1 (1.5)
Discontinuation of study due to				
Primary Reason[b]	13 (7.5)	11 (3.2)	5 (4.4)	3 (4.5)
Adverse event	6 (3.4)	5 (1.5)	1 (0.9)	1 (1.5)
Withdrew consent	4 (2.3)	6 (1.8)	2 (1.8)	1 (1.5)
Lost to follow-up	0	0	0	0
COVID-19 infection	0	0	0	0
COVID-19 logistical restrictions	0	0	0	0
Other	3 (1.7)	0	2 (1.8)	1 (1.5)

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

Maintenance study

A total of 1046 subjects entered Substudy 3 at 302 sites in the following countries: Argentina, Australia, Austria, Belgium, Bosnia and Herzegovina, Brazil, Canada, Chile, China, Colombia,

Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Japan, Korea (Republic of), Latvia, Lithuania, Malaysia, Mexico, Netherlands, Norway, Poland, Portugal, Russian Federation, Serbia, Singapore, Slovakia, South Africa, Spain, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, United States, including Puerto Rico.

Among all enrolled subjects, 445 subjects had completed the study, 413 subjects had prematurely discontinued from the study at the time of the data cutoff date, and 188 subjects were ongoing. Among the 1044 subjects who received at least 1 dose of study drug, 6 were excluded from the ITT population and efficacy analysis due to site non-compliance.

Table 16 M14-234 substudy 3 Subject Accountability (All Enrolled Subjects)

			Study Drug			Study		
Cohort Treatment	Enrolled n	Treated n	Completed n	DC n	Ongoing n	Completed n	DC n	Ongoing n
All								
Placebo	386	385	106	238	41	106	239	41
UPA 7.5 mg	20	20	11	9	0	11	9	0
UPA 15 mg	324	323	157	103	63	157	104	63
UPA 30 mg	316	316	171	62	83	171	61	84
Total	1046	1044	445	412	187	445	413	188
Cohort 1								
Placebo	282	281	71	180	30	71	181	30
UPA 15 mg	289	288	144	88	56	144	89	56
UPA 30 mg	276	276	155	53	68	155	52	69
Total	847	845	370	321	154	370	322	155
Cohort 2								
Placebo	104	104	35	58	11	35	58	11
Cohort 3								
UPA 15 mg	35	35	13	15	7	13	15	7
UPA 30 mg	40	40	16	9	15	16	9	15
Total	75	75	29	24	22	29	24	22
Cohort 4								
UPA 7.5 mg	20	20	11	9	0	11	9	0

DC = discontinued; UPA = upadacitinib

Table 17 M14-234 Substudy 3 Subject Disposition (ITT_A Population)

		Study Drug		Study	
Treatment	Treated n	Completed n	Discontinued n	Completed n	Discontinued n
Placebo	149	51	98	51	98
UPA 15 mg	148	99	49	99	49
UPA 30 mg	154	121	33	121	33

ITT_A = primary analysis population in Cohort 1; UPA = upadacitinib

Table 18 M14-234 Substudy 3 Summary of Study Drug Discontinuation Due to Primary Reason for Discontinuation (ITT_A Population)

Discontinuation due to	Placebo (N = 149) n (%)	UPA 15 mg (N = 148) n (%)	UPA 30 mg (N = 154) n (%)	Total (N = 451) n (%)
All Reasons[a]	98 (65.8)	49 (33.1)	33 (21.4)	180 (39.9)
Adverse event	17 (11.4)	6 (4.1)	11 (7.1)	34 (7.5)
Withdrew consent	2 (1.3)	1 (0.7)	6 (3.9)	9 (2.0)
Lost to follow-up	0	0	1 (0.6)	1 (0.2)
Lack of efficacy	75 (50.3)	35 (23.6)	12 (7.8)	122 (27.1)
COVID-19 infection	0	0	1 (0.6)	1 (0.2)
COVID-19 logistical restrictions	0	0	1 (0.6)	1 (0.2)
Other	10 (6.7)	10 (6.8)	6 (3.9)	26 (5.8)
Primary Reason	98 (65.8)	49 (33.1)	33 (21.4)	180 (39.9)
Adverse event	14 (9.4)	4 (2.7)	8 (5.2)	26 (5.8)
Withdrew consent	1 (0.7)	1 (0.7)	4 (2.6)	6 (1.3)
Lack of efficacy	74 (49.7)	35 (23.6)	12 (7.8)	121 (26.8)
Lost to follow-up	0	0	1 (0.6)	1 (0.2)
COVID-19 infection	0	0	1 (0.6)	1 (0.2)
COVID-19 logistical restrictions	0	0	1 (0.6)	1 (0.2)
Other	9 (6.0)	9 (6.1)	6 (3.9)	24 (5.3)

COVID-19 = coronavirus disease 2019; ITT_A = primary analysis population in Cohort 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.

Recruitment

M14-234 Substudy 2

First Subject First Visit: 03 October 2018

Last Subject Last Visit: 07 September 2020

M14-675

First Subject First Visit: 06 December 2018

Last Subject Last Visit: 14 January 2021

M14-234 Substudy 3

First Subject First Visit: 14 December 2016
Data Cut off Date: 30 April 2021

Conduct of the study

Protocol amendments in study M14-234 (substudy 1, substudy 2, substudy 3

The original protocol (03 June 2016, 0 subjects) had 7 global amendments, 7 country- or region-specific amendments, and 5 global or country-specific administrative changes.

Global amendment 1 (29 September 2016, 184 subjects). Corrected the definition of clinical response per Adapted Mayo score, removed proportion of subjects with stool frequency subscore ≤ 1 and proportion of subjects with rectal bleeding subscore of 0 as ranked secondary endpoints and included them as non-ranked secondary endpoints.

Global amendment 2 (10 October 2017, 190 subjects) updated the percentage of subjects with a history of inadequate response or intolerance to biologic therapies expected to enroll in Substudy 1 from 50% to 75% and made several administrative changes

Global amendment 3 (03 July 2018, 164 subjects) updated the protocol to reflect the selected Phase 3 Substudy 2 induction dose of upadacitinib 45 mg and updated the study design for both induction and maintenance studies. Added the Extended Treatment Period in Substudy 2. Increased the duration of the maintenance period to 52 weeks

Global amendment 4 (24 April 2019, 244 subjects) aligned Study M14-234 and Study M14-675 protocols.

Global amendment 5 (29 April 2020, 0 subjects) revised wording to improve consistency and readability, provide clarity, and ensure that team information was current

Global amendment 6 (31 July 2020, 0 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 the COVID-19 pandemic and associated changes in global/local regulations, updated the wording on enrollment to note that enrollment is closed for Substudy 2.

Global amendment 7 (10 May 2021, 0 subjects) Clarified the primary ITT and Substudy 3 ITT populations, Added non-responder imputation (NRI) while incorporating multiple imputation (MI) to handle missing data due to COVID-19 (NRI-C) and mixed-effect model repeated measurement (MMRM) methods to ensure clarity of statistical analysis; clarified rescue handling approaches used.

Protocol amendment in study M14-675

The original protocol (29 June 2018, 96 subjects) had 4 global amendments, 5 country- or region-specific amendments, and 2 global or country-specific administrative changes.

Global Amendment 1 (12 September 2018, 45 subjects):
Clarified the study objective to outline both the primary and secondary endpoints.

Global amendment 2 (24 April 2019, 295 subjects) aligned Study M14-234 and Study M14-675 protocols.

Global amendment 3 (29 April 2020, 48 subjects) revised wording to improve consistency and readability, provide clarity, and ensure that team information was current

Global amendment 4 (31 July 2020, 22 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 the COVID-19 pandemic and associated changes in global/local regulations.

Baseline data

Table 19 M14-234 Substudy 2 Key demographic characteristics (ITT1 Population)

Variable	Placebo (N = 154)	UPA 45 mg (N = 319)	Total (N = 473)
Sex - n (%)			
Female	57 (37.0)	121 (37.9)	178 (37.6)
Male	97 (63.0)	198 (62.1)	295 (62.4)
Age (years)			
n	154	319	473
Mean (SD)	44.4 (14.63)	43.6 (14.04)	43.8 (14.22)
Median	44.5	43.0	43.0
Min, Max	18, 76	19, 76	18, 76
Age Group 1 - n (%)			
< 18 years	0	0	0
≥ 18 years - < 40 years	64 (41.6)	133 (41.7)	197 (41.6)
≥ 40 years - < 65 years	73 (47.4)	161 (50.5)	234 (49.5)
≥ 65 years	17 (11.0)	25 (7.8)	42 (8.9)
Ethnicity - n (%)			
Hispanic or Latino	12 (7.8)	28 (8.8)	40 (8.5)
not Hispanic or Latino	142 (92.2)	291 (91.2)	433 (91.5)
Race - n (%)			
White	100 (64.9)	206 (64.6)	306 (64.7)
Black or African American	4 (2.6)	12 (3.8)	16 (3.4)
Asian	46 (29.9)	95 (29.8)	141 (29.8)
American Indian or Alaska Native	2 (1.3)	0	2 (0.4)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	1 (0.2)
Multiple	2 (1.3)	5 (1.6)	7 (1.5)
Body Mass Index (kg/m^2)			
n	153	318	471
Mean (SD)	25.7 (6.68)	24.7 (5.10)	25.0 (5.67)
Median	24.0	23.8	23.9
Min, Max	16.1, 56.4	15.8, 47.4	15.8, 56.4

Variable	Placebo (N = 154)	UPA 45 mg (N = 319)	Total (N = 473)
Body Mass Index Group - n (%)			
< 25 kg/m^2	84 (54.9)	194 (61.0)	278 (59.0)
≥ 25 - 30 kg/m^2	38 (24.8)	77 (24.2)	115 (24.4)
≥ 30 kg/m^2	31 (20.3)	47 (14.8)	78 (16.6)
Missing	1	1	2

ITT1 = intent-to-treat population for Part 1; SD = standard deviation; UPA = upadacitinib

Note: Percentages calculated on non-missing values.

Table 20 Study M14-675 Key Demographic Characteristics (ITT1 Population)

Variable	Placebo (N = 174)	UPA 45 mg (N = 341)	Total (N = 515)
Sex - n (%)			
Female	67 (38.5)	127 (37.2)	194 (37.7)
Male	107 (61.5)	214 (62.8)	321 (62.3)
Age (years)			
n	174	341	515
Mean (SD)	42.2 (14.35)	42.1 (14.74)	42.2 (14.59)
Median	42.0	40.0	40.0
Min, Max	17, 75	17, 74	17, 75
Age Group 1 - n (%)			
< 18 years	3 (1.7)	6 (1.8)	9 (1.7)
≥ 18 years - < 40 years	79 (45.4)	158 (46.3)	237 (46.0)
≥ 40 years - < 65 years	79 (45.4)	144 (42.2)	223 (43.3)
≥ 65 years	13 (7.5)	33 (9.7)	46 (8.9)
Ethnicity - n (%)			
Hispanic or Latino	16 (9.2)	26 (7.6)	42 (8.2)
not Hispanic or Latino	158 (90.8)	315 (92.4)	473 (91.8)
Race - n (%)			
White	124 (71.3)	234 (68.6)	358 (69.5)
Black or African American	6 (3.4)	11 (3.2)	17 (3.3)
Asian	41 (23.6)	94 (27.6)	135 (26.2)
American Indian or Alaska Native	1 (0.6)	0	1 (0.2)
Native Hawaiian or other Pacific Islander	1 (0.6)	0	1 (0.2)
Multiple	1 (0.6)	2 (0.6)	3 (0.6)
Body Mass Index (kg/m^2)			
n	174	341	515
Mean (SD)	25.4 (5.94)	25.1 (5.33)	25.2 (5.54)
Median	24.2	24.2	24.2
Min, Max	15.6, 49.2	14.9, 51.1	14.9, 51.1
Body Mass Index Group - n (%)			
< 25 kg/m^2	96 (55.2)	195 (57.2)	291 (56.5)
≥ 25 - 30 kg/m^2	45 (25.9)	100 (29.3)	145 (28.2)
≥ 30 kg/m^2	33 (19.0)	46 (13.5)	79 (15.3)

ITT1 = intent-to-treat population for Part 1; SD = standard deviation; UPA = upadacitinib

Note: Percentages calculated on non-missing values.

Table 21 M14-234 Substudy 2 baseline Key disease characteristics (ITT1 Population)

Variable	Placebo (N = 154)	UPA 45 mg (N = 319)	Total (N = 473)
Disease Duration (years)			
n	154	319	473
Mean (SD)	9.116 (8.7610)	8.621 (7.1719)	8.782 (7.7194)
Median	5.980	6.580	6.410
Min, Max	0.04, 47.96	0.09, 33.97	0.04, 47.96
Disease Duration Group 1 - n (%)			
≤ 3 years	43 (27.9)	88 (27.6)	131 (27.7)
> 3 years	111 (72.1)	231 (72.4)	342 (72.3)
Bio-IR Status - n (%)			
Bio-IR	78 (50.6)	168 (52.7)	246 (52.0)
Non-Bio-IR	76 (49.4)	151 (47.3)	227 (48.0)
Baseline Corticosteroid Use - n (%)			
Yes	61 (39.6)	124 (38.9)	185 (39.1)
No	93 (60.4)	195 (61.1)	288 (60.9)
Baseline Immunosuppressant Use - n (%)			
Yes	3 (1.9)	2 (0.6)	5 (1.1)
No	151 (98.1)	317 (99.4)	468 (98.9)
Baseline Aminosalicylates Use - n (%)			
Yes	103 (66.9)	220 (69.0)	323 (68.3)
No	51 (33.1)	99 (31.0)	150 (31.7)
Baseline Adapted Mayo score - n (%)			
≤ 7	94 (61.0)	195 (61.3)	289 (61.2)
> 7	60 (39.0)	123 (38.7)	183 (38.8)
Missing	0	1	1
Baseline Full Mayo score - n (%)			
≤ 9	79 (51.3)	162 (50.9)	241 (51.1)
> 9	75 (48.7)	156 (49.1)	231 (48.9)
Missing	0	1	1

Variable	Placebo (N = 154)	UPA 45 mg (N = 319)	Total (N = 473)
hsCRP (mg/L)			
n	154	319	473
Mean (SD)	12.223 (21.2272)	9.412 (15.2639)	10.327 (17.4577)
Median	4.675	4.100	4.400
Min, Max	0.20, 179.00	0.20, 105.00	0.20, 179.00
Baseline hsCRP - n (%)			
≤ 5 mg/L	80 (51.9)	178 (55.8)	258 (54.5)
> 5 mg/L	74 (48.1)	141 (44.2)	215 (45.5)
Fecal Calprotectin (mg/kg)			
n	137	277	414
Mean (SD)	3135.5 (3986.79)	3910.1 (5698.72)	3653.8 (5202.88)
Median	1902.0	1780.0	1804.0
Min, Max	30, 28800	30, 28800	30, 28800
IBDQ score - Total			
n	150	315	465
Mean (SD)	121.5 (30.96)	122.2 (36.50)	122.0 (34.78)
Median	119.0	119.0	119.0
Min, Max	57, 202	40, 218	40, 218
FACIT-F			
n	150	315	465
Mean (SD)	31.6 (10.88)	30.5 (11.73)	30.8 (11.46)
Median	32.5	31.0	32.0
Min, Max	4, 50	1, 52	1, 52

BIO-IR = biologic therapy-intolerant or inadequate responder; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; hsCRP = high sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT1 = intent-to-treat population for Part 1; SD = standard deviation; UPA = upadacitinib

Note: Percentages calculated on non-missing values.

Table 22 Study M14-675 Baseline Disease Characteristics (ITT1 Population)

Variable	Placebo (N = 174)	UPA 45 mg (N = 341)	Total (N = 515)
Disease Duration (years)			
n	174	341	515
Mean (SD)	7.387 (7.2040)	7.278 (6.4482)	7.315 (6.7063)
Median	4.890	5.550	5.330
Min, Max	0.32, 49.67	0.05, 42.46	0.05, 49.67

Variable	Placebo (N = 174)	UPA 45 mg (N = 341)	Total (N = 515)
Disease Duration Group 1 - n (%)			
≤ 3 years	51 (29.3)	105 (30.8)	156 (30.3)
> 3 years	123 (70.7)	236 (69.2)	359 (69.7)
Bio-IR Status - n (%)			
Bio-IR	89 (51.1)	172 (50.4)	261 (50.7)
Non-Bio-IR	85 (48.9)	169 (49.6)	254 (49.3)
Baseline Corticosteroid Use - n (%)			
Yes	72 (41.4)	120 (35.2)	192 (37.3)
No	102 (58.6)	221 (64.8)	323 (62.7)
Baseline Immunosuppressant Use - n (%)			
Yes	3 (1.7)	1 (0.3)	4 (0.8)
No	171 (98.3)	340 (99.7)	511 (99.2)
Baseline Aminosalicylates Use - n (%)			
Yes	120 (69.0)	233 (68.3)	353 (68.5)
No	54 (31.0)	108 (31.7)	162 (31.5)
Baseline Adapted Mayo score - n (%)			
≤ 7	103 (59.2)	205 (60.3)	308 (59.9)
> 7	71 (40.8)	135 (39.7)	206 (40.1)
Missing	0	1	1
Baseline Full Mayo score – n (%)			
≤ 9	86 (49.4)	160 (47.1)	246 (47.9)
> 9	88 (50.6)	180 (52.9)	268 (52.1)
Missing	0	1	1
hs-CRP (mg/L)			
n	174	341	515
Mean (SD)	10.782 (19.9449)	9.283 (15.3126)	9.789 (17.0145)
Median	4.730	3.820	4.200
Min, Max	0.20, 166.00	0.20, 107.00	0.20, 166.00

Variable	Placebo (N = 174)	UPA 45 mg (N = 341)	Total (N = 515)
Baseline hs-CRP - n (%)			
≤ 5 mg/L	89 (51.1)	193 (56.6)	282 (54.8)
> 5 mg/L	85 (48.9)	148 (43.4)	233 (45.2)
Fecal Calprotectin (mg/kg)			
n	152	296	448
Mean (SD)	3126.7 (4742.09)	3130.5 (4719.82)	3129.2 (4722.08)
Median	1552.5	1654.5	1609.0
Min, Max	84, 28800	46, 28800	46, 28800
IBDQ score - Total			
n	172	334	506
Mean (SD)	122.7 (37.66)	122.8 (34.52)	122.8 (35.58)
Median	122.0	123.5	123.0
Min, Max	46, 200	41, 214	41, 214
FACIT-F			
n	171	331	502
Mean (SD)	31.4 (12.64)	29.8 (11.76)	30.4 (12.08)
Median	33.0	31.0	31.0
Min, Max	2, 52	1, 51	1, 52

Bio-IR = biologic therapy-intolerant or inadequate responder; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; hs-CRP = high sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT1 = intent-to-treat population for Part 1; SD = standard deviation; UPA = upadacitinib

Note: Percentages calculated on non-missing values.

Table 23 M14-234 Substudy 2 – Summary of Key Prior UC-Related Medications Taken by ≥ 10% of Subjects in Either Group by Medication Category and Generic Name (ITT1 Population)

Medication Category Generic Name (WHO 2020Q1)	Placebo (N = 154) n (%)	UPA 45 mg (N = 319) n (%)	Total (N = 473) n (%)
Any previous UC-related medications	154 (100)	317 (99.4)	471 (99.6)
Aminosalicylates	125 (81.2)	259 (81.2)	384 (81.2)
Mesalazine	123 (79.9)	250 (78.4)	373 (78.9)
Sulfasalazine	15 (9.7)	37 (11.6)	52 (11.0)
Biologics (Including Anti-TNF)	82 (53.2)	174 (54.5)	256 (54.1)
Adalimumab	42 (27.3)	76 (23.8)	118 (24.9)
Golimumab	13 (8.4)	32 (10.0)	45 (9.5)
Infliximab	51 (33.1)	124 (38.9)	175 (37.0)
Vedolizumab	47 (30.5)	91 (28.5)	138 (29.2)
Corticosteroids	131 (85.1)	278 (87.1)	409 (86.5)
Budesonide	45 (29.2)	90 (28.2)	135 (28.5)
Methylprednisolone	26 (16.9)	38 (11.9)	64 (13.5)
Prednisolone	42 (27.3)	96 (30.1)	138 (29.2)
Prednisone	55 (35.7)	129 (40.4)	184 (38.9)
Immunosuppressants	87 (56.5)	185 (58.0)	272 (57.5)
Azathioprine	73 (47.4)	163 (51.1)	236 (49.9)
Other IBD medications	38 (24.7)	40 (12.5)	78 (16.5)

IBD = inflammatory bowel disease; ITT1 = intent-to-treat population for Part 1; TNF = tumor necrosis factor; UC = ulcerative colitis; UPA = upadacitinib; WHO = World Health Organization

Note: Subjects are counted once in each row, regardless of the number of medications they may have taken.

Table 24 M14-234 Substudy 2 – Number of Previous UC-Related Medications Per Subject (ITT1 Population)

Categories	Placebo (N = 154) n (%)	UPA 45 mg (N = 319) n (%)	Total (N = 473) n (%)
Aminosalicylates			
1	108 (70.1)	217 (68.0)	325 (68.7)
2	17 (11.0)	41 (12.9)	58 (12.3)
3	0	1 (0.3)	1 (0.2)
≥ 4	0	0	0
At Least One Medication	125 (81.2)	259 (81.2)	384 (81.2)
Antibiotics			
1	15 (9.7)	21 (6.6)	36 (7.6)
2	8 (5.2)	14 (4.4)	22 (4.7)
3	0	1 (0.3)	1 (0.2)
≥ 4	1 (0.6)	0	1 (0.2)
At Least One Medication	24 (15.6)	36 (11.3)	60 (12.7)
Biologics (Including Anti-TNF)			
1	29 (18.8)	64 (20.1)	93 (19.7)
2	31 (20.1)	64 (20.1)	95 (20.1)
3	18 (11.7)	35 (11.0)	53 (11.2)
≥ 4	4 (2.6)	11 (3.4)	15 (3.2)
At Least One Medication	82 (53.2)	174 (54.5)	256 (54.1)
Corticosteroids			
1	62 (40.3)	165 (51.7)	227 (48.0)
2	55 (35.7)	83 (26.0)	138 (29.2)
3	12 (7.8)	27 (8.5)	39 (8.2)
≥ 4	2 (1.3)	3 (0.9)	5 (1.1)
At Least One Medication	131 (85.1)	278 (87.1)	409 (86.5)
Immunosuppressants			
1	72 (46.8)	149 (46.7)	221 (46.7)
2	13 (8.4)	35 (11.0)	48 (10.1)
3	2 (1.3)	1 (0.3)	3 (0.6)
≥ 4	0	0	0
At Least One Medication	87 (56.5)	185 (58.0)	272 (57.5)

ITT1 = intent-to-treat population for Part 1; TNF = tumor necrosis factor; UC = ulcerative colitis; UPA = upadacitinib

Note: N is the ITT1 population in each treatment group and total.

Subjects are counted once in each row, regardless of the number of medications they may have taken..

Table 25 M14-675 Summary of Key Prior UC-Related Medications Taken by ≥ 10% of Subjects in Either Group by Medication Category and Generic Name (ITT1 Population)

Medication Category Generic Name (WHO 2020Q1)	Placebo (N = 174) n (%)	UPA 45 mg (N = 341) n (%)	Total (N = 515) n (%)
Any previous UC-related medications	170 (97.7)	336 (98.5)	506 (98.3)
Aminosalicylates	120 (69.0)	267 (78.3)	387 (75.1)
Mesalazine	116 (66.7)	257 (75.4)	373 (72.4)
Sulfasalazine	20 (11.5)	29 (8.5)	49 (9.5)
Antibiotics	27 (15.5)	44 (12.9)	71 (13.8)
Metronidazole	19 (10.9)	35 (10.3)	54 (10.5)
Biologics (Including Anti-TNF)	93 (53.4)	173 (50.7)	266 (51.7)
Adalimumab	48 (27.6)	81 (23.8)	129 (25.0)
Infliximab	47 (27.0)	114 (33.4)	161 (31.3)
Vedolizumab	44 (25.3)	91 (26.7)	135 (26.2)
Corticosteroids	147 (84.5)	286 (83.9)	433 (84.1)
Budesonide	59 (33.9)	102 (29.9)	161 (31.3)
Methylprednisolone	19 (10.9)	43 (12.6)	62 (12.0)
Prednisolone	46 (26.4)	100 (29.3)	146 (28.3)
Prednisone	74 (42.5)	135 (39.6)	209 (40.6)
Immunosuppressants	95 (54.6)	170 (49.9)	265 (51.5)
Azathioprine	89 (51.1)	149 (43.7)	238 (46.2)

ITT1 = intent-to-treat population for Part 1; TNF = tumor necrosis factor; UC = ulcerative colitis; UPA = upadacitinib; WHO = World Health Organization

Note: Subjects are counted once in each row, regardless of the number of medications they may have taken.

Table 26 M14-675 Number of Previous UC-Related Medications Per Subject (ITT1 Population)

Categories	Placebo (N = 174) n (%)	UPA 45 mg (N = 341) n (%)	Total (N = 515) n (%)
Aminosalicylates			
1	101 (58.0)	234 (68.6)	335 (65.0)
2	16 (9.2)	31 (9.1)	47 (9.1)
3	3 (1.7)	2 (0.6)	5 (1.0)
≥ 4	0	0	0
At Least One Medication	120 (69.0)	267 (78.3)	387 (75.1)
Antibiotics			
1	17 (9.8)	25 (7.3)	42 (8.2)
2	9 (5.2)	15 (4.4)	24 (4.7)
3	1 (0.6)	1 (0.3)	2 (0.4)
≥ 4	0	3 (0.9)	3 (0.6)
At Least One Medication	27 (15.5)	44 (12.9)	71 (13.8)
Biologics (Including Anti-TNF)			
1	39 (22.4)	64 (18.8)	103 (20.0)
2	36 (20.7)	67 (19.6)	103 (20.0)
3	15 (8.6)	34 (10.0)	49 (9.5)
≥ 4	3 (1.7)	8 (2.3)	11 (2.1)
At Least One Medication	93 (53.4)	173 (50.7)	266 (51.7)
Corticosteroids			
1	83 (47.7)	162 (47.5)	245 (47.6)
2	48 (27.6)	87 (25.5)	135 (26.2)
3	16 (9.2)	33 (9.7)	49 (9.5)
≥ 4	0	4 (1.2)	4 (0.8)
At Least One Medication	147 (84.5)	286 (83.9)	433 (84.1)
Immunosuppressants			
1	77 (44.3)	139 (40.8)	216 (41.9)
2	17 (9.8)	27 (7.9)	44 (8.5)
3	1 (0.6)	3 (0.9)	4 (0.8)
≥ 4	0	1 (0.3)	1 (0.2)
At Least One Medication	95 (54.6)	170 (49.9)	265 (51.5)

ITT1 = intent-to-treat population for Part 1; TNF = tumor necrosis factor; UC = ulcerative colitis; UPA = upadacitinib

Note: N is the ITT1 population in each treatment group and total.
Subjects are counted once in each row, regardless of the number of medications they may have taken.

Table 27 M14-234 substudy 2 UC-Related Medications Taken at Baseline by Generic Name (ITT1 Population)

Medication Category Generic Name (WHO 2020Q1)	Placebo (N=154) n (%)	UPA 45 mg QD (N=319) n (%)	Total (N=473) n (%)
Any UC-related medications	133 (86.4)	268 (84.0)	401 (84.8)
Aminosalicylates	103 (66.9)	220 (69.0)	323 (68.3)
BALSALAZIDE	2 (1.3)	2 (0.6)	4 (0.8)
MESALAZINE	92 (59.7)	204 (63.9)	296 (62.6)
SULFASALAZINE	10 (6.5)	16 (5.0)	26 (5.5)
Antibiotics	1 (0.6)	3 (0.9)	4 (0.8)
PIPERACILLIN;TAZOBACTAM	1 (0.6)	0	1 (0.2)
VANCOMYCIN	1 (0.6)	3 (0.9)	4 (0.8)
Corticosteroids	60 (39.0)	121 (37.9)	181 (38.3)
BECLOMETASONE	3 (1.9)	1 (0.3)	4 (0.8)
BUDESONIDE	2 (1.3)	12 (3.8)	14 (3.0)
MEPREDNISONE	0	1 (0.3)	1 (0.2)
METHYLPREDNISOLONE	10 (6.5)	14 (4.4)	24 (5.1)
PREDNISOLONE	19 (12.3)	39 (12.2)	58 (12.3)
PREDNISONE	27 (17.5)	54 (16.9)	81 (17.1)
Immunosuppressants	2 (1.3)	2 (0.6)	4 (0.8)
METHOTREXATE	2 (1.3)	2 (0.6)	4 (0.8)
Other IBD medications	33 (21.4)	58 (18.2)	91 (19.2)
ALVERINE;DL-METHIONINE	0	1 (0.3)	1 (0.2)
ANTIBIOTICS-RESISTANT LACTIC ACID BACTERIAE	1 (0.6)	0	1 (0.2)
ASCORBIC ACID;BIOTIN;CYANOCOBALAMIN;FOLIC ACID;FURSULTIAMINE;IRON;NICOTINAMIDE;PYRIDOXINE;RIBOFLAVIN;SELENIUM;TOCOPHEROL;ZINC	1 (0.6)	0	1 (0.2)
ASCORBIC ACID;DL-ALPHA TOCOPHEROL;FURSULTIAMINE;HYDROXOCOBALAMIN;PYRIDOXAL;RIBOFLAVIN	0	1 (0.3)	1 (0.2)

Note: Subjects are counted once in each row, regardless of the number of medications they may have taken.

Table 28 M14-675 UC-Related Medications Taken at Baseline by Generic Name (ITT1 Population)

Medication Category Generic Name (WHO 2020Q1)	Placebo (N=174) n (%)	UPA 45 mg QD (N=341) n (%)	Total (N=515) n (%)
Any UC-related medications	147 (84.5)	287 (84.2)	434 (84.3)
Aminosalicylates	120 (69.0)	231 (67.7)	351 (68.2)
BALSALAZIDE	6 (3.4)	2 (0.6)	8 (1.6)
MESALAZINE	109 (62.6)	220 (64.5)	329 (63.9)
SULFASALAZINE	6 (3.4)	11 (3.2)	17 (3.3)
Corticosteroids	69 (39.7)	119 (34.9)	188 (36.5)
BECLOMETASONE	0	4 (1.2)	4 (0.8)
BUDESONIDE	11 (6.3)	16 (4.7)	27 (5.2)
MEPREDNISONE	1 (0.6)	1 (0.3)	2 (0.4)
METHYLPREDNISOLONE	8 (4.6)	5 (1.5)	13 (2.5)
PREDNISOLONE	17 (9.8)	28 (8.2)	45 (8.7)
PREDNISONE	32 (18.4)	65 (19.1)	97 (18.8)
Immunosuppressants	1 (0.6)	0	1 (0.2)
METHOTREXATE	1 (0.6)	0	1 (0.2)
Other IBD medications	34 (19.5)	57 (16.7)	91 (17.7)
ALBUMIN TANNATE	0	1 (0.3)	1 (0.2)
ASCORBIC ACID;MACROGOL 3350;POTASSIUM;SODIUM CHLORIDE;SODIUM SULFATE	0	2 (0.6)	2 (0.4)
ATROPINE;DIPHENOXYLATE	1 (0.6)	0	1 (0.2)
BACILLUS MESENTERICUS;CLOSTRIDIUM BUTYRICUM;ENTEROCOCCUS FAECALIS	3 (1.7)	7 (2.1)	10 (1.9)
BACILLUS SUBTILIS;ENTEROCOCCUS FAECIUM	0	1 (0.3)	1 (0.2)
BERBERINE	0	1 (0.3)	1 (0.2)
BERBERINE;GERANIUM THUNBERGII	1 (0.6)	2 (0.6)	3 (0.6)
BIFIDOBACTERIUM ANIMALIS;LACTOBACILLUS ACIDOPHILUS;LACTOBACILLUS PLANTARUM;LACTOBACILLUS SALIVARIUS	1 (0.6)	0	1 (0.2)
BIFIDOBACTERIUM BIFIDUM;BIFIDOBACTERIUM INFANTIS	0	1 (0.3)	1 (0.2)

Note: Subjects are counted once in each row, regardless of the number of medications they may have taken.

Maintenance study (M14-234 substudy 3)

Table 29 M14-234 Substudy 3 Demographic Characteristics (ITT_A Population)

Variable	Placebo (N = 149)	UPA 15 mg (N = 148)	UPA 30 mg (N = 154)	Total (N = 451)
Sex - n (%)				
Female	64 (43.0)	53 (35.8)	68 (44.2)	185 (41.0)
Male	85 (57.0)	95 (64.2)	86 (55.8)	266 (59.0)
Age (years)				
n	149	148	154	451
Mean (SD)	43.3 (14.37)	42.6 (14.10)	42.6 (14.75)	42.8 (14.38)
Median	40.0	40.0	41.0	41.0
Min, Max	17, 75	21, 75	17, 76	17, 76
Age Group 1 - n (%)				
< 18 years	1 (0.7)	0	1 (0.6)	2 (0.4)
≥ 18 years - < 40 years	68 (45.6)	67 (45.3)	69 (44.8)	204 (45.2)
≥ 40 years - < 65 years	68 (45.6)	68 (45.9)	69 (44.8)	205 (45.5)
≥ 65 years	12 (8.1)	13 (8.8)	15 (9.7)	40 (8.9)
Age Group 2 - n (%)				
≤ Median (42.0 years)	79 (53.0)	84 (56.8)	82 (53.2)	245 (54.3)
> Median (42.0 years)	70 (47.0)	64 (43.2)	72 (46.8)	206 (45.7)
Body Mass Index (kg/m^2)				
n	149	148	153	450
Mean (SD)	25.0 (5.35)	25.5 (5.93)	25.3 (6.52)	25.2 (5.95)
Median	23.8	24.2	23.9	24.0
Min, Max	15.9, 49.2	16.2, 48.5	15.8, 56.4	15.8, 56.4
Body Mass Index Group - n (%)				
Normal: < 25 kg/m^2	89 (59.7)	88 (59.5)	83 (54.2)	260 (57.8)
Overweight: ≥ 25 - 30 kg/m^2	36 (24.2)	30 (20.3)	43 (28.1)	109 (24.2)
Obese: ≥ 30 kg/m^2	24 (16.1)	30 (20.3)	27 (17.6)	81 (18.0)
Missing	0	0	1	1
Ethnicity - n (%)				
Hispanic or Latino	7 (4.7)	13 (8.8)	9 (5.8)	29 (6.4)
Not Hispanic or Latino	142 (95.3)	135 (91.2)	145 (94.2)	422 (93.6)

Variable	Placebo (N = 149)	UPA 15 mg (N = 148)	UPA 30 mg (N = 154)	Total (N = 451)
Race - n (%)				
White	93 (62.4)	97 (65.5)	101 (65.6)	291 (64.5)
Black or African American	6 (4.0)	7 (4.7)	3 (1.9)	16 (3.5)
Asian	42 (28.2)	44 (29.7)	48 (31.2)	134 (29.7)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or other Pacific Islander	1 (0.7)	0	1 (0.6)	2 (0.4)
Multiple	7 (4.7)	0	1 (0.6)	8 (1.8)

ITT_A = primary analysis population in Cohort 1; SD = standard deviation; UPA = upadacitinib

Note: Percentages calculated on non-missing values.

Table 30 M14-234 Substudy 3 Disease-Related Baseline Characteristics (ITT_A Population)

Variable	Placebo (N = 149)	UPA 15 mg (N = 148)	UPA 30 mg (N = 154)	Total (N = 451)
Disease Duration (years)				
n	149	148	154	451
Mean (SD)	8.748 (7.9964)	8.915 (8.0973)	8.214 (7.6173)	8.620 (7.8909)
Median	6.170	6.435	6.035	6.170
Min, Max	0.17, 47.96	0.09, 44.33	0.05, 35.26	0.05, 47.96
Disease Duration Group 1 - n (%)				
≤ 3 years	41 (27.5)	42 (28.4)	53 (34.4)	136 (30.2)
> 3 years	108 (72.5)	106 (71.6)	101 (65.6)	315 (69.8)
Disease Duration Group 2 - n (%)				
≤ Median (6.1 years)	74 (49.7)	73 (49.3)	78 (50.6)	225 (49.9)
> Median (6.1 years)	75 (50.3)	75 (50.7)	76 (49.4)	226 (50.1)
Disease Extent - n (%)				
Rectosigmoid	0	0	0	0
Left-sided	79 (53.0)	66 (44.6)	68 (44.2)	213 (47.2)
Extensive/Pancolitis	70 (47.0)	82 (55.4)	86 (55.8)	238 (52.8)
Bio-IR Status - n (%)				
Bio-IR	81 (54.4)	71 (48.0)	73 (47.4)	225 (49.9)
Non-Bio-IR	68 (45.6)	77 (52.0)	81 (52.6)	226 (50.1)
Baseline Corticosteroid Use - n (%)				
Yes	60 (40.3)	55 (37.2)	57 (37.0)	172 (38.1)
No	89 (59.7)	93 (62.8)	97 (63.0)	279 (61.9)
Baseline Immunosuppressant Use - n (%)				
Yes	0	1 (0.7)	1 (0.6)	2 (0.4)
No	149 (100)	147 (99.3)	153 (99.4)	449 (99.6)
Baseline Aminosalicylates Use - n (%)				
Yes	99 (66.4)	99 (66.9)	106 (68.8)	304 (67.4)
No	50 (33.6)	49 (33.1)	48 (31.2)	147 (32.6)
Baseline Adapted Mayo Score				
n	149	148	152	449
Mean (SD)	7.00 (1.231)	6.98 (1.201)	7.08 (1.301)	7.02 (1.243)
Median	7.00	7.00	7.00	7.00
Min, Max	4.0, 9.0	5.0, 9.0	3.3, 9.0	3.3, 9.0

Variable	Placebo (N = 149)	UPA 15 mg (N = 148)	UPA 30 mg (N = 154)	Total (N = 451)
Baseline Adapted Mayo Score - n (%)				
≤ 7	87 (58.4)	89 (60.1)	88 (57.9)	264 (58.8)
> 7	62 (41.6)	59 (39.9)	64 (42.1)	185 (41.2)
Missing	0	0	2	2
Full Mayo Score				
n	149	148	152	449
Mean (SD)	9.33 (1.404)	9.25 (1.391)	9.42 (1.498)	9.33 (1.431)
Median	9.30	9.00	9.30	9.30
Min, Max	6.3, 12.0	6.0, 12.0	6.0, 12.0	6.0, 12.0
Baseline Full Mayo Score - n (%)				
≤ 9	74 (49.7)	75 (50.7)	73 (48.0)	222 (49.4)
> 9	75 (50.3)	73 (49.3)	79 (52.0)	227 (50.6)
Missing	0	0	2	2
hsCRP (mg/L)				
n	149	148	154	451
Mean (SD)	9.827 (15.8896)	8.362 (12.4433)	8.626 (14.7480)	8.936 (14.4213)
Median	4.250	3.810	4.080	4.100
Min, Max	0.20, 105.00	0.20, 83.30	0.20, 107.00	0.20, 107.00
Baseline hsCRP - n (%)				
≤ 5 mg/L	81 (54.4)	84 (56.8)	88 (57.1)	253 (56.1)
> 5 mg/L	68 (45.6)	64 (43.2)	66 (42.9)	198 (43.9)
Fecal Calprotectin (mg/kg)				
n	127	130	129	386
Mean (SD)	3620.3 (5222.27)	3141.7 (4694.00)	2737.3 (4326.71)	3164.0 (4760.45)
Median	1991.0	1718.0	1465.0	1658.5
Min, Max	30, 28800	30, 28800	30, 28800	30, 28800
IBDQ Score - Total				
n	148	148	152	448
Mean (SD)	122.6 (33.44)	125.8 (35.93)	121.3 (34.95)	123.2 (34.76)
Median	121.0	127.0	119.5	123.0
Min, Max	57, 202	52, 218	43, 206	43, 218

Table 31 M14-234 Substudy 3 Previous UC-Related Medications Taken by ≥ 10% of Subjects in Any Group (ITT_A Population

Medication Category Generic Name (WHO 2020Q1)	Placebo (N = 149) n (%)	UPA 15 mg (N = 148) n (%)	UPA 30 mg (N = 154) n (%)	Total (N = 451) n (%)
Any previous UC-related medications	149 (100)	148 (100)	154 (100)	451 (100)
Aminosalicylates	140 (94.0)	141 (95.3)	148 (96.1)	429 (95.1)
Mesalazine	134 (89.9)	136 (91.9)	144 (93.5)	414 (91.8)
Sulfasalazine	20 (13.4)	25 (16.9)	20 (13.0)	65 (14.4)
Antibiotics	21 (14.1)	20 (13.5)	25 (16.2)	66 (14.6)
Metronidazole	11 (7.4)	18 (12.2)	18 (11.7)	47 (10.4)
Biologics	84 (56.4)	73 (49.3)	77 (50.0)	234 (51.9)
Adalimumab	41 (27.5)	31 (20.9)	30 (19.5)	102 (22.6)
Golimumab	16 (10.7)	16 (10.8)	12 (7.8)	44 (9.8)
Infliximab	51 (34.2)	44 (29.7)	53 (34.4)	148 (32.8)
Vedolizumab	42 (28.2)	33 (22.3)	37 (24.0)	112 (24.8)
Corticosteroids	137 (91.9)	139 (93.9)	140 (90.9)	416 (92.2)
Budesonide	49 (32.9)	53 (35.8)	46 (29.9)	148 (32.8)
Methylprednisolone	20 (13.4)	20 (13.5)	29 (18.8)	69 (15.3)
Prednisolone	43 (28.9)	49 (33.1)	51 (33.1)	143 (31.7)
Prednisone	77 (51.7)	64 (43.2)	64 (41.6)	205 (45.5)
Immunosuppressants	82 (55.0)	75 (50.7)	86 (55.8)	243 (53.9)
Azathioprine	67 (45.0)	62 (41.9)	78 (50.6)	207 (45.9)
Mercaptopurine	12 (8.1)	15 (10.1)	6 (3.9)	33 (7.3)
Other IBD medications	46 (30.9)	34 (23.0)	40 (26.0)	120 (26.6)

IBD = inflammatory bowel disease; ITT_A = primary analysis population in Cohort 1; UPA = upadacitinib; WHO = World Health Organization

Numbers analysed

See participant flow.

Outcomes and estimation

Primary endpoint

Table 32 Study M14-234 Substudy 2 and Study M14-675 – Primary Endpoint: Clinical Remission per Adapted Mayo Score at Induction Week 8 (NRI-C) (ITT1 Population)

Strata Treatment	N	Within Group Point Estimate (%)	 [95% CI]	Between Group Difference (UPA 45 mg - Placebo) Point Estimate (%)	 [95% CI]	 *P*-value
Study M14-234 Substudy 2						
Placebo	154	4.8	[1.3, 8.2]			
UPA 45 mg	319	26.1	[21.3, 31.0]	21.6	[15.8, 27.4]	< 0.001[S]
Study M14-675						
Placebo	174	4.1	[1.1, 7.1]			
UPA 45 mg	341	33.5	[28.5, 38.5]	29.0	[23.2, 34.7]	< 0.001[S]

CI = confidence interval; NRI-C = Non-responder imputation incorporating multiple imputation to handle missing data due to COVID 19; UPA = upadacitinib

S The endpoint achieved statistical significance based on pre-specified multiple testing procedure controlling the overall type 1 error rate at the 0.05 level.

Notes: Adjusted treatment difference, 95% CI and *P*-value were calculated according to the Cochran-Mantel-Haenszel (CMH) test adjusted for baseline stratification factors. 95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure.

In Study M14-234 Substudy 2, 1 subject in the Placebo group and 6 subjects in the UPA 45 mg group had missing values due to COVID-19.

In Study M14-675, 3 subjects in the Placebo group and 1 subject in the UPA 45 mg group had missing values due to COVID-19.

Results from all sensitivity analyses including NRI-NC (NRI with no special data handling for missing due to COVID-19), As observed (AO), and HMI (hybrid multiple imputation) demonstrated consistent results with p < 0.001.

Table 33 Study M14-234 Substudy 2 and Study M14-675 (NRI-C/MMRM) (ITT1 Population): Ranked Secondary Endpoints

M14-234 Substudy 2

Strata Treatment	N	Within Group Point Estimate	 [95% CI][a]	Between Group Difference (UPA 45 mg – Placebo) Point Estimate	 [95% CI][b]	 *P*-value
Endoscopic Improvement at Week 8[c] (%)						
Placebo	154	7.4	[3.2, 11.5]			
UPA 45 mg	319	36.3	[31.0, 41.7]	29.3	[22.6, 35.9]	< 0.001***
Endoscopic Remission at Week 8[c] (%)						
Placebo	154	1.3	[0.0, 3.1]			
UPA 45 mg	319	13.7	[9.9, 17.6]	12.7	[8.4, 17.0]	< 0.001***

Strata Treatment	N	Within Group Point Estimate	[95% CI][a]	Between Group Difference (UPA 45 mg – Placebo) Point Estimate	[95% CI][b]	*P*-value
Clinical Response per Adapted Mayo score at Week 8[c] (%)						
Placebo	154	27.3	[20.2, 34.3]			
UPA 45 mg	319	72.6	[67.7, 77.5]	46.3	[38.4, 54.2]	< 0.001***S
Clinical Response per Partial Adapted Mayo score at Week 2[c] (%)						
Placebo	154	27.3	[20.2, 34.3]			
UPA 45 mg	319	60.1	[54.7, 65.5]	33.3	[24.8, 41.8]	< 0.001***S
Histologic-Endoscopic Mucosal Improvement at Week 8[c] (%)						
Placebo	154	6.6	[2.6, 10.5]			
UPA 45 mg	319	30.1	[25.0, 35.1]	23.7	[17.5, 30.0]	< 0.001***S
No Reported Bowel Urgency at Week 8[c] (%)						
Placebo	154	21.4	[14.9, 27.9]			
UPA 45 mg	319	48.4	[42.9, 53.9]	27.4	[19.2, 35.6]	< 0.001***S
No Reported Abdominal Pain at Week 8[c] (%)						
Placebo	154	23.4	[16.7, 30.1]			
UPA 45 mg	319	46.6	[41.1, 52.1]	23.6	[15.1, 32.1]	< 0.001***S
Histologic Improvement at Week 8[c] (%)						
Placebo	154	22.5	[15.9, 29.1]			
UPA 45 mg	319	55.0	[49.5, 60.5]	32.2	[23.8, 40.7]	< 0.001***S
Change from Baseline in IBDQ Total score at Week 8[d] (LS mean)						
Placebo	125	21.7	[16.03, 27.28]			
UPA 45 mg	292	55.3	[51.54, 59.15]	33.7	[27.02, 40.36]	< 0.001***S
Mucosal Healing at Week 8[c] (%)						
Placebo	154	1.3	[0.0, 3.1]			
UPA 45 mg QD	319	10.7	[7.3, 14.1]	9.7	[5.7, 13.7]	< 0.001***S

Strata Treatment	N	Within Group Point Estimate	[95% CI][a]	Between Group Difference (UPA 45 mg – Placebo) Point Estimate	[95% CI][b]	*P*-value
Change from Baseline in FACIT-F score at Week 8[d] (LS mean)						
Placebo	125	2.8	[1.23, 4.44]			
UPA 45 mg	291	9.5	[8.44, 10.61]	6.7	[4.79, 8.59]	<0.001***[S]

CI = confidence interval; COVID-19 = coronavirus disease 2019; Diff = difference; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT1A = intent-to treat population for Part 1; LS = least square; UPA = upadacitinib

*** *P*-value < 0.001.

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. Based on the Cochran-Mantel-Haenszel (CMH) test adjusted for baseline stratification factors.

c. NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.

d. MMRM: Mixed-Effect Model Repeat Measurement.

S. Achieved statistical significance based on the pre-specified multiple testing procedure controlling the overall type I error rate at the 0.05 level.

Note: The number of subjects missing due to COVID-19 varied from 0 to 9 per treatment group.
Baseline is defined as the last non-missing value prior to the first dose of study drug. Subjects with only non-missing change from Baseline values are included in analysis.

M14-675

Strata Treatment	N	Within Group Point Estimate	[95% CI][a]	Between Group Difference (UPA 45 mg – Placebo) Point Estimate	[95% CI][b]	Multiplicity-Adjusted *P*-value[c]
Endoscopic Improvement at Week 8[c] (%)						
Placebo	174	8.3	[4.1, 12.5]			
UPA 45 mg	341	44.0	[38.8, 49.3]	35.1	[28.6, 41.6]	<0.001***
Endoscopic Remission at Week 8[c] (%)						
Placebo	174	1.7	[0.0, 3.7]			
UPA 45 mg	341	18.2	[14.1, 22.3]	15.9	[11.4, 20.3]	<0.001***
Clinical Response per Adapted Mayo score at Week 8[c] (%)						
Placebo	174	25.4	[18.9, 31.8]			
UPA 45 mg	341	74.5	[69.9, 79.1]	49.4	[41.7, 57.1]	<0.001***
Clinical Response per Partial Adapted Mayo score at Week 2[c] (%)						
Placebo	174	25.9	[19.4, 32.4]			
UPA 45 mg	341	63.3	[58.2, 68.5]	37.0	[28.8, 45.1]	<0.001***
Histologic-Endoscopic Mucosal Improvement at Week 8[c] (%)						
Placebo	174	5.9	[2.3, 9.4]			
UPA 45 mg	341	36.7	[31.6, 41.8]	30.1	[24.1, 36.2]	<0.001***
No Reported Bowel Urgency at Week 8[c] (%)						
Placebo	174	25.9	[19.4, 32.4]			
UPA 45 mg	341	53.7	[48.4, 59.0]	27.1	[19.0, 35.3]	<0.001***
No Reported Abdominal Pain at Week 8[c] (%)						
Placebo	174	24.1	[17.8, 30.5]			
UPA 45 mg	341	53.7	[48.4, 59.0]	29.1	[20.9, 37.4]	<0.001***

Strata Treatment	N	Within Group Point Estimate	 [95% CI][a]	Between Group Difference (UPA 45 mg – Placebo) Point Estimate	 [95% CI][b]	 Multiplicity-Adjusted *P*-value[c]
Histologic Improvement at Week 8[c] (%)						
Placebo	174	24.5	[18.0, 30.9]			
UPA 45 mg	341	62.2	[57.0, 67.3]	37.9	[29.8, 46.1]	<0.001***
Change from Baseline in IBDQ Total score at Week 8[d] (LS Mean)						
Placebo	156	21.1	[15.98, 26.17]			
UPA 45 mg	315	52.2	[48.57, 55.92]	31.2	[24.98, 37.36]	<0.001***
Mucosal Healing at Week 8[c] (%)						
Placebo	174	1.7	[0.0, 3.7]			
UPA 45 mg	341	13.5	[9.9, 17.1]	11.3	[7.2, 15.3]	<0.001***
Change from Baseline in FACIT-F score at Week 8[d] (LS Mean)						
Placebo	155	3.5	[2.02, 4.92]			
UPA 45 mg	312	9.4	[8.38, 10.48]	6.0	[4.19, 7.73]	<0.001***

CI = confidence interval; COVID-19 = coronavirus disease 2019; Diff = difference;
FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue;
IBDQ = Inflammatory Bowel Disease Questionnaire; ITT1 = intent-to treat population for Part 1; LS = least square;
MMRM = mixed-effect model repeat measurement; NRI = non-responder imputation; SE = standard error;
UC = ulcerative colitis; UPA = upadacitinib

*** *P*-value < 0.001.

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. Across the strata, 95% CI for adjusted difference and p-value are calculated according to the Cochran-Mantel-Haenszel (CMH) test adjusted for strata (Baseline corticosteroid use [yes or no], Baseline Adapted Mayo score [≤ 7 or > 7], bio-IR status [bio-IR or non-bio-IR]) for the comparison of two treatment groups. If zero frequency occurred, the zero count will be replaced by 0.1 to prevent dividing by zero.

c. For binary endpoints, NRI-C is non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19. Subjects will be considered as "non-responder" for binary endpoints at and after the UC-related corticosteroids censoring time point through the end of the Induction Study.

d. MMRM is the Mixed-Effect Model Repeat Measurement with Baseline, treatment, visit, treatment by visit interaction, and strata (Baseline corticosteroid use (yes or no), Baseline Adapted Mayo score (≤ 7 or > 7), bio-IR status (bio-IR or non-bio-IR)) in the model. An unstructured covariance matrix is used. If the model cannot converge, AR(1) or CS covariance matrix will be used.

Additional analysis:

Table 34 M14-675 Proportion of subjects with Rectal Bleeding Score (RBS)=0 over time (ITT1 population)

Visit Treatment	N	Responder n (%)	 [95% CI]&	Missing Due to COVID-19 n	Rate Diff Compared to Placebo Diff(%)	 Adjusted Diff(%)	 [95% CI]#	Response P-value@
Week 2								
Placebo	174	34 (19.5)	[13.6, 25.4]	0				
UPA 45 mg QD	341	162 (47.5)	[42.2, 52.8]	0	28.0	27.6	[20.0, 35.2]	<0.001***
Week 4								
Placebo	174	44 (25.3)	[18.8, 31.7]	0				
UPA 45 mg QD	341	211 (61.9)	[56.7, 67.0]	0	36.6	36.3	[28.4, 44.3]	<0.001***
Week 6								
Placebo	174	47 (27.0)	[20.4, 33.6]	0				
UPA 45 mg QD	341	232 (68.0)	[63.1, 73.0]	0	41.0	40.6	[32.6, 48.6]	<0.001***
Week 8								
Placebo	174	57 (32.8)	[25.8, 39.7]	0				
UPA 45 mg QD	341	235 (68.9)	[64.0, 73.8]	0	36.2	36.1	[27.7, 44.4]	<0.001***

Table 35 M14-675 Proportion of subjects with Stool Frequency Score (SFS) ≤1 over time (ITT1 population)

Visit / Treatment	N	Responder n (%)	Responder [95% CI]&	Response Rate Diff Compared to Placebo Diff(%)	Response Rate Diff Compared to Placebo Adjusted Diff(%)	Response Rate Diff Compared to Placebo Adjusted [95% CI]#	Response Rate Diff Compared to Placebo Adjusted P-value@
Week 2							
Placebo	174	16 (9.2)	[4.9, 13.5]				
UPA 45 mg QD	341	149 (43.7)	[38.4, 49.0]	34.5	33.9	[27.1, 40.6]	<0.001***
Week 4							
Placebo	174	29 (16.7)	[11.1, 22.2]				
UPA 45 mg QD	341	179 (52.5)	[47.2, 57.8]	35.8	34.9	[27.5, 42.3]	<0.001***
Week 6							
Placebo	174	28 (16.1)	[10.6, 21.6]				
UPA 45 mg QD	341	197 (57.8)	[52.5, 63.0]	41.7	41.5	[34.0, 48.9]	<0.001***
Week 8							
Placebo	174	34 (19.5)	[13.6, 25.4]				
UPA 45 mg QD	341	211 (61.9)	[56.7, 67.0]	42.3	41.9	[34.2, 49.5]	<0.001***

Results maintenance study (M14-234 substudy 3):

Table 36 M14-234 substudy 3 Clinical remission per adapted mayo score at week 52

	Within Group			Between Group Difference (Upadacitinib - Placebo)		
Treatment	**N**	**Point Estimate (%)**	**[95% CI]**	**Point Estimate (%)**	**[95% CI]**	**P-value**
Placebo	149	12.1	[6.9, 17.4]			
UPA 15 mg	148	42.3	[34.3, 50.3]	30.7	[21.7, 39.8]	< 0.001***S
UPA 30 mg	154	51.7	[43.6, 59.8]	39.0	[29.7, 48.2]	< 0.001***S

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ITT = intent-to-treat population; ITT_A = primary analysis population in Cohort 1 for efficacy endpoints; UPA = upadacitinib

*** *P*-value < 0.001.

S. Achieved statistical significance based on the pre-specified multiple testing procedure controlling the overall type I error rate at the 0.05 level.

Notes: NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.

Analysis was based on CMH test. Point estimate and 95% CI are the synthetic results based on Student's t-distribution from PROC MIANALYZE procedure.

Sensivity analysis: Seven subjects (4.7%) in the placebo group, 4 subjects (2.7%) in the upadacitinib 15 mg group, and 11 subjects (7.1%) in the upadacitinib 30 mg group had missing values due to COVID-19. Results of the sensitivity analyses supported the primary analysis result.

Table 37 Study M14-234 Substudy 3: Multiplicity-Controlled Secondary Endpoints (NRI-C/RTB-MI) (ITT_A Population)

Endpoint / Treatment	Within Group N	Point Estimate	[95% CI]	Between Group Difference (Upadacitinib - Placebo) Point Estimate	[95% CI]	P-value
Endoscopic Improvement at Week 52 (NRI-C) (%)						
Placebo	149	14.5	[8.7, 20.3]			
UPA 15 mg	148	48.7	[40.5, 56.8]	34.4	[25.1, 43.7]	< 0.001[$]
UPA 30 mg	154	61.6	[53.6, 69.6]	46.3	[36.7, 55.8]	< 0.001[$]
Clinical Remission per Adapted Mayo Score at Week 52 among Subjects Who Achieved Clinical Remission at the End of the Induction Treatment in the Induction Study (NRI-C) (%)						
Placebo	54	22.2	[11.1, 33.3]			
UPA 15 mg	47	59.2	[45.1, 73.4]	37.4	[20.3, 54.6]	< 0.001[$]
UPA 30 mg	58	69.7	[57.7, 81.8]	47.0	[30.7, 63.3]	< 0.001[$]
Clinical Remission per Adapted Mayo Score at Week 52 and Corticosteroid Free for ≥ 90 Days Immediately Preceding Week 52 among Subjects Who Achieved Clinical Remission at the End of the Induction Treatment in the Induction Study (NRI-C) (%)						
Placebo	54	22.2	[11.1, 33.3]			
UPA 15 mg	47	57.1	[42.9, 71.3]	35.4	[18.2, 52.7]	< 0.001[$]
UPA 30 mg	58	68.0	[55.8, 80.2]	45.1	[28.7, 61.6]	< 0.001[$]
Endoscopic Improvement at Week 52 among Subjects Who Achieved Endoscopic Improvement at the End of the Induction Treatment in the Induction Study (NRI-C) (%)						
Placebo	73	19.2	[9.9, 28.4]			
UPA 15 mg	63	61.6	[49.6, 73.7]	42.0	[27.8, 56.2]	< 0.001[$]
UPA 30 mg	79	69.5	[59.1, 80.0]	48.6	[35.5, 61.7]	< 0.001[$]
Endoscopic Remission at Week 52 (NRI-C) (%)						
Placebo	149	5.6	[1.8, 9.3]			
UPA 15 mg	148	24.2	[17.3, 31.2]	18.7	[11.0, 26.4]	< 0.001[$]
UPA 30 mg	154	25.9	[18.8, 33.0]	19.4	[11.7, 27.2]	< 0.001[$]
Clinical Response per Adapted Mayo Score at Week 52 among Subjects Who Achieved Clinical Response at the End of the Induction Treatment in the Induction Study (NRI-C) (%)						
Placebo	134	18.8	[12.1, 25.5]			
UPA 15 mg	135	63.0	[54.8, 71.1]	44.6	[34.5, 54.7]	< 0.001[$]
UPA 30 mg	144	76.6	[69.6, 83.6]	56.6	[47.2, 66.0]	< 0.001[$]
Histologic-Endoscopic Mucosal Improvement at Week 52 (NRI-C) (%)						
Placebo	149	11.9	[6.7, 17.2]			
UPA 15 mg	148	35.0	[27.1, 42.8]	23.8	[14.8, 32.8]	< 0.001[$]
UPA 30 mg	154	49.8	[41.5, 58.0]	37.3	[27.8, 46.8]	< 0.001[$]

Endpoint Treatment	Within Group N	Within Group Point Estimate	Within Group [95% CI]	Between Group Difference (Upadacitinib - Placebo) Point Estimate	Between Group Difference (Upadacitinib - Placebo) [95% CI]	Between Group Difference (Upadacitinib - Placebo) P-value
Change from Baseline in IBDQ Total Score at Week 52 (RTB-MI) (LS Mean)						
Placebo	149	17.9	[10.79, 25.00]			
UPA 15 mg	148	49.2	[42.59, 55.89]	31.3	[21.98, 40.70]	< 0.001***S
UPA 30 mg	154	58.9	[52.14, 65.59]	41.0	[31.39, 50.55]	< 0.001***S
Mucosal Healing at Week 52 (NRI-C) (%)						
Placebo	149	4.7	[1.3, 8.2]			
UPA 15 mg	148	17.6	[11.4, 23.8]	13.0	[6.0, 20.0]	< 0.001***S
UPA 30 mg	154	19.0	[12.6, 25.4]	13.6	[6.6, 20.6]	< 0.001***S
No Bowel Urgency at Week 52 (NRI-C) (%)						
Placebo	149	17.4	[11.4, 23.5]			
UPA 15 mg	148	56.1	[48.1, 64.1]	38.7	[28.9, 48.5]	< 0.001***S
UPA 30 mg	154	63.6	[56.0, 71.2]	45.1	[35.5, 54.8]	< 0.001***S
No Abdominal Pain at Week 52 (NRI-C) (%)						
Placebo	149	20.8	[14.2, 27.3]			
UPA 15 mg	148	45.9	[37.9, 54.0]	24.3	[14.2, 34.5]	< 0.001***S
UPA 30 mg	154	55.3	[47.4, 63.2]	33.7	[23.6, 43.9]	< 0.001***S
Change from Baseline in FACIT-F Score at Week 52 (RTB-MI) (LS Mean)						
Placebo	149	3.7	[1.88, 5.43]			
UPA 15 mg	148	8.7	[7.01, 10.49]	5.1	[2.67, 7.52]	< 0.001***S
UPA 30 mg	154	9.5	[7.80, 11.22]	5.9	[3.44, 8.27]	< 0.001***S

ANCOVA = analysis of covariance; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; COVID-19 = coronavirus disease 2019; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT = intent-to-treat population; ITT_A = primary analysis population in Cohort 1 for efficacy endpoints; UPA = upadacitinib

*** *P*-value < 0.001

S. Achieved statistical significance based on the pre-specified multiple testing procedure controlling the overall type I error rate at the 0.05 level.

NRI-C: non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.

RTB-MI: Multiple Imputation Incorporating Return-to-Baseline.

Additional endpoints

Table 38 Study M14-234 Substudy 3: Selected Additional Efficacy Endpoints (NRI-C/RTB-MI/AO) (ITT_A Population)

		Within Group		Between Group Difference (UPA – Placebo)		
Strata Treatment	**N**	**Point Estimate**	**[95% CI]**	**Point Estimate**	**[95% CI]**	***P*-value**
SFS = 0, RBS = 0, and Endoscopic Subscore = 0 at Week 52 (NRI-C)[b] (%)						
Placebo	149	4.0	[0.9, 7.2]			
UPA 15 mg	148	10.9	[5.8, 15.9]	7.0	[1.0, 12.9]	< 0.022**
UPA 30 mg	154	12.3	[7.0, 17.5]	7.8	[1.7, 13.9]	0.013*
SFS = 0, RBS = 0, and Endoscopic Subscore ≤ 1 at Week 52 (NRI-C)[b] (%)						
Placebo	149	6.7	[2.7, 10.7]			
UPA 15 mg	148	20.5	[13.9, 27.0]	13.7	[6.1, 21.3]	< 0.001***
UPA 30 mg	154	21.2	[14.7, 27.7]	13.8	[6.4, 21.2]	< 0.001***
Histologic Remission at Week 52 (NRI-C)[b] (%)						
Placebo	149	14.5	[8.7, 20.3]			
UPA 15 mg	148	40.0	[31.9, 48.1]	25.4	[16.1, 34.7]	< 0.001***
UPA 30 mg	154	51.8	[43.4, 60.1]	36.5	[26.6, 46.4]	< 0.001***
Change from Baseline in Histologic Score at Week 52 (RTB-MI)[d] (LS mean)						
Placebo	149	–1.6	[-1.98, -1.24]			
UPA 15 mg	148	–2.6	[-2.97, -2.31]	–1.0	[-1.49, -0.57]	< 0.001***
UPA 30 mg	154	–3.1	[-3.45, -2.80]	–1.5	[-2.01, -1.03]	< 0.001***
Clinical Remission per Partial Mayo Score and Corticosteroid Free Over Time among Subjects Taking Corticosteroids at Baseline in the Induction Study (NRI-C)[b] (%)						
Week 4						
Placebo	60	21.7	[11.2, 32.1]			
UPA 15 mg	55	38.2	[25.3, 51.0]	16.1	[1.9, 30.3]	< 0.026*
UPA 30 mg	57	31.6	[19.5, 43.6]	8.5	[-5.5, 22.4]	0.233
Week 8						
Placebo	60	25.0	[14.0, 36.0]			
UPA 15 mg	55	54.5	[41.4, 67.7]	29.9	[14.9, 44.8]	< 0.001***
UPA 30 mg	57	42.1	[29.3, 54.9]	16.1	[0.8, 31.5]	0.039*

Strata Treatment	N	Within Group Point Estimate	 [95% CI]	Between Group Difference (UPA – Placebo) Point Estimate	 [95% CI]	 *P*-value
Week 12						
Placebo	60	31.7	[19.9, 43.4]			
UPA 15 mg	55	54.5	[41.4, 67.7]	22.5	[6.9, 38.2]	0.005**
UPA 30 mg	57	45.6	[32.7, 58.5]	13.1	[-2.9, 29.0]	0.108
Week 20						
Placebo	60	30.0	[18.4, 41.6]			
UPA 15 mg	55	49.1	[35.9, 62.3]	19.2	[3.8, 34.7]	0.014*
UPA 30 mg	57	49.1	[36.1, 62.1]	19.2	[3.6, 34.8]	0.016*
Week 28						
Placebo	60	23.3	[12.6, 34.0]			
UPA 15 mg	55	52.7	[39.5, 65.9]	31.5	[16.4, 46.6]	< 0.001***
UPA 30 mg	57	52.6	[39.7, 65.6]	28.5	[13.3, 43.8]	< 0.001***
Week 36						
Placebo	60	18.3	[8.5, 28.1]			
UPA 15 mg	55	49.1	[35.9, 62.3]	30.4	[15.8, 45.0]	< 0.001***
UPA 30 mg	57	50.9	[37.9, 63.9]	31.8	[17.0, 46.5]	< 0.001***
Week 44						
Placebo	60	13.3	[4.7, 21.9]			
UPA 15 mg	55	43.6	[30.5, 56.7]	29.3	[15.4, 43.2]	< 0.001***
UPA 30 mg	57	52.6	[39.7, 65.6]	37.9	[23.6, 52.2]	< 0.001***
Week 52						
Placebo	60	10.3	[2.5, 18.2]			
UPA 15 mg	55	52.7	[39.5, 65.9]	41.8	[27.5, 56.1]	< 0.001***
UPA 30 mg	57	61.2	[48.5, 73.9]	49.4	[35.8, 63.0]	< 0.001***
Corticosteroid Free Over Time among Subjects Taking Corticosteroids at Baseline in the Induction Study (As Observed)[a] (%)						
Week 4						
Placebo	60	38.3	[26.0, 50.6]			

Strata Treatment	N	Within Group Point Estimate	 [95% CI]	Between Group Difference (UPA – Placebo) Point Estimate	 [95% CI]	 *P*-value
UPA 15 mg	55	52.7	[39.5, 65.9]	13.0	[-3.8, 29.7]	0.128
UPA 30 mg	56	46.4	[33.4, 59.5]	7.3	[-9.4, 23.9]	0.391
Week 8						
Placebo	57	45.6	[32.7, 58.5]			
UPA 15 mg	50	78.0	[66.5, 89.5]	31.3	[15.4, 47.3]	< 0.001***
UPA 30 mg	55	67.3	[54.9, 79.7]	20.6	[3.9, 37.4]	0.016*
Week 12						
Placebo	51	60.8	[47.4, 74.2]			
UPA 15 mg	47	83.0	[72.2, 93.7]	21.3	[4.8, 37.8]	0.011*
UPA 30 mg	52	75.0	[63.2, 86.8]	13.9	[-3.1, 31.0]	0.109
Week 20						
Placebo	42	59.5	[44.7, 74.4]			
UPA 15 mg	45	84.4	[73.9, 95.0]	24.7	[7.4, 42.0]	0.005*
UPA 30 mg	51	74.5	[62.5, 86.5]	15.3	[-2.4, 32.9]	0.089
Week 28						
Placebo	38	60.5	[45.0, 76.1]			
UPA 15 mg	40	90.0	[80.7, 99.3]	28.7	[11.7, 45.7]	< 0.001***
UPA 30 mg	50	76.0	[64.2, 87.8]	16.0	[-1.7, 33.8]	< 0.076
Week 36						
Placebo	35	48.6	[32.0, 65.1]			
UPA 15 mg	39	84.6	[73.3, 95.9]	34.2	[15.7, 52.7]	< 0.001***
UPA 30 mg	50	74.0	[61.8, 86.2]	26.3	[7.4, 45.3]	< 0.007**
Week 44						
Placebo	29	51.7	[33.5, 69.9]			
UPA 15 mg	38	81.6	[69.3, 93.9]	26.8	[6.6, 47.1]	< 0.009**
UPA 30 mg	49	73.5	[61.1, 85.8]	20.5	[0.1, 40.9]	< 0.048*
Week 52						

Strata Treatment	N	Within Group Point Estimate	Within Group [95% CI]	Between Group Difference (UPA – Placebo) Point Estimate	Between Group Difference (UPA – Placebo) [95% CI]	Between Group Difference (UPA – Placebo) *P*-value
Placebo	27	59.3	[40.7, 77.8]			
UPA 15 mg	35	94.3	[86.6, 100.0]	32.6	[13.7, 51.5]	< 0.001***
UPA 30 mg	49	81.6	[70.8, 92.5]	22.1	[1.6, 42.7]	< 0.035*
Change from Baseline in Partial Adapted Mayo Score Over Time (RTB-MI)[c] (LS Mean)						
Week 4						
Placebo	149	–2.87	[-3.055, -2.680]			
UPA 15 mg	148	–3.12	[-3.312, -2.937]	–0.26	[-0.515, 0.001]	< 0.050*
UPA 30 mg	154	–3.27	[-3.452, -3.085]	–0.40	[-0.656, -0.147]	0.002**
Week 8						
Placebo	149	–2.34	[-2.574, -2.103]			
UPA 15 mg	148	–3.01	[-3.248, -2.773]	–0.67	[-0.997, -0.348]	< 0.001***
UPA 30 mg	154	–3.31	[-3.535, -3.076]	–0.97	[-1.291, -0.644]	< 0.001***
Week 12						
Placebo	149	–2.10	[-2.358, -1.839]			
UPA 15 mg	148	–3.00	[-3.248, -2.755]	–0.90	[-1.259, -0.548]	< 0.001***
UPA 30 mg	154	–3.24	[-3.483, -3.007]	–1.15	[-1.494, -0.798]	< 0.001***
Week 20						
Placebo	149	–1.88	[-2.172, -1.598]			
UPA 15 mg	148	–2.89	[-3.151, -2.634]	–1.01	[-1.383, -0.632]	< 0.001***
UPA 30 mg	154	–3.30	[-3.550, -3.054]	–1.42	[-1.781, -1.052]	< 0.001***
Week 28						
Placebo	149	–1.91	[-2.243, -1.581]			
UPA 15 mg	148	–3.01	[-3.268, -2.745]	–1.09	[-1.476, -0.713]	< 0.001***
UPA 30 mg	154	–3.39	[-3.637, -3.152]	–1.48	[-1.868, -1.097]	< 0.001***
Week 36						
Placebo	149	–1.40	[-1.813, -0.982]			
UPA 15 mg	148	–2.87	[-3.159, -2.577]	–1.47	[-1.943, -0.998]	< 0.001***
UPA 30 mg	154	–3.32	[-3.586, -3.045]	–1.92	[-2.403, -1.433]	< 0.001***

Strata Treatment	N	Within Group Point Estimate	Within Group [95% CI]	Between Group Difference (UPA – Placebo) Point Estimate	Between Group Difference (UPA – Placebo) [95% CI]	Between Group Difference (UPA – Placebo) *P*-value
Week 44						
Placebo	149	–1.39	[-1.785, -1.003]			
UPA 15 mg	148	–2.87	[-3.131, -2.601]	–1.47	[-1.907, -1.037]	< 0.001***
UPA 30 mg	154	–3.34	[-3.593, -3.084]	–1.94	[-2.379, -1.509]	< 0.001***
Week 52						
Placebo	149	–1.39	[-1.780, -1.008]			
UPA 15 mg	148	–3.02	[-3.304, -2.744]	–1.63	[-2.067, -1.193]	< 0.001***
UPA 30 mg	154	–3.39	[-3.629, -3.145]	–1.99	[-2.432, -1.553]	< 0.001***

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; COVID-19 = coronavirus disease 2019; ITT = intent-to-treat population; ITT_A = primary analysis population in Cohort 1 for efficacy endpoints; LS = least square; RBS = rectal bleeding subscore; SFS = stool frequency subscore; UPA = upadacitinib

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

a. Analysis was based on CMH test. 95% CI is calculated based on normal approximation to the binomial distribution.

b. Analysis was based on CMH test. Point estimate and 95% CI are the synthetic results based on Student's t-distribution from PROC MIANALYZE procedure.

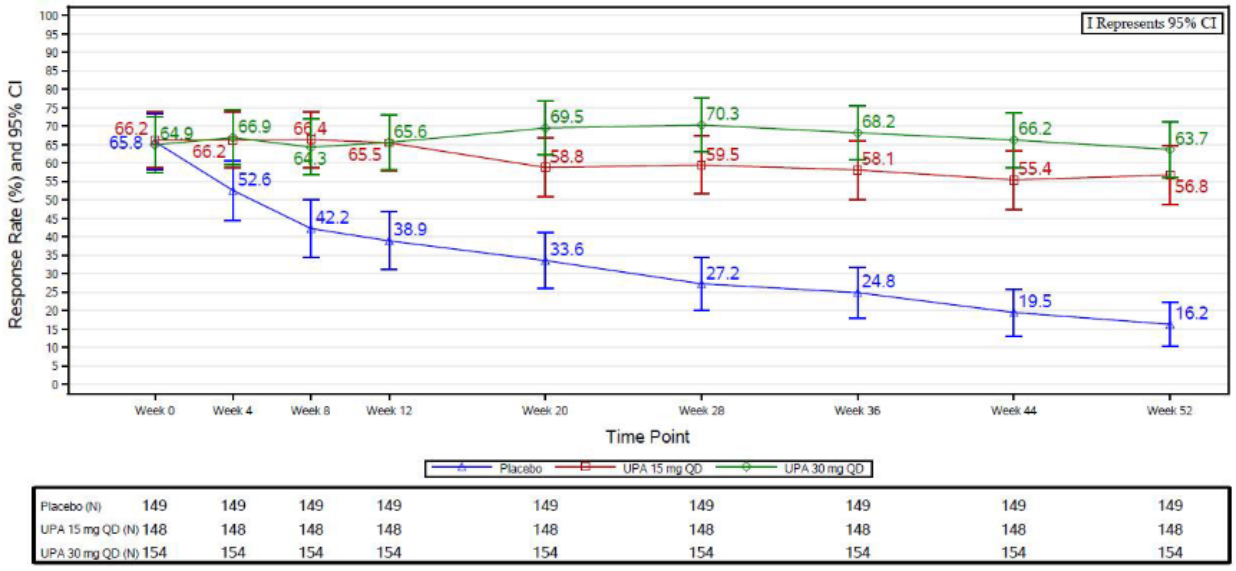
c. The LS mean and 95% CI are the synthetic results based on MMRM from PROC MIANALYZE procedure.

d. The LS mean and 95% CI are the synthetic results based on ANCOVA from PROC MIANALYZE procedure.

Notes: NRI-C: Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.

AO: As observed analysis.

RTB-MI: Multiple Imputation incorporating Return-to-Baseline.



CI = confidence interval; CMH = Cochran-Mantel-Haenszel; COVID-19 = coronavirus disease 2019; ITT = intent-to-treat population; ITT_A = primary analysis population in Cohort 1 for efficacy endpoints; QD = once daily; UPA = upadacitinib

Figure 9 Clinical Remission per Partial Mayo Score Over Time Until Week 52 (NRI-C) (ITT_A Population)

Ancillary analyses

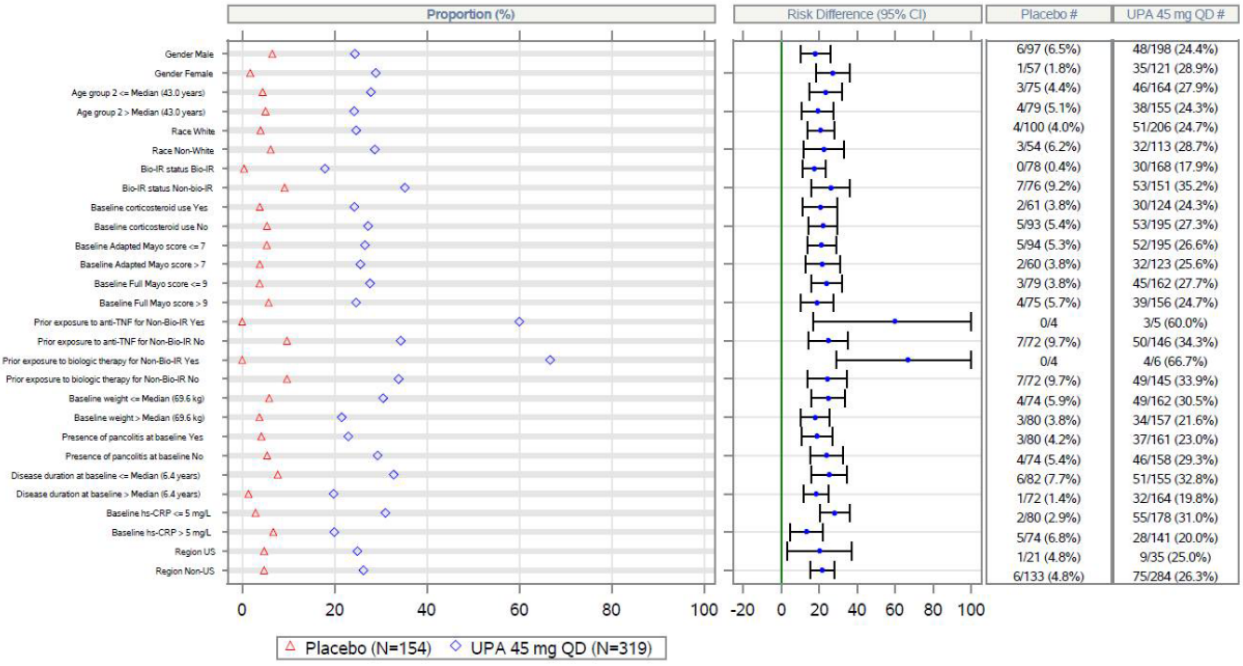


Figure 10 Substudy 2 – Subgroup Analyses of the Primary Endpoint: Clinical Remission per Adapted Mayo Score at Week 8 (NRI-C) (ITT1 Population)

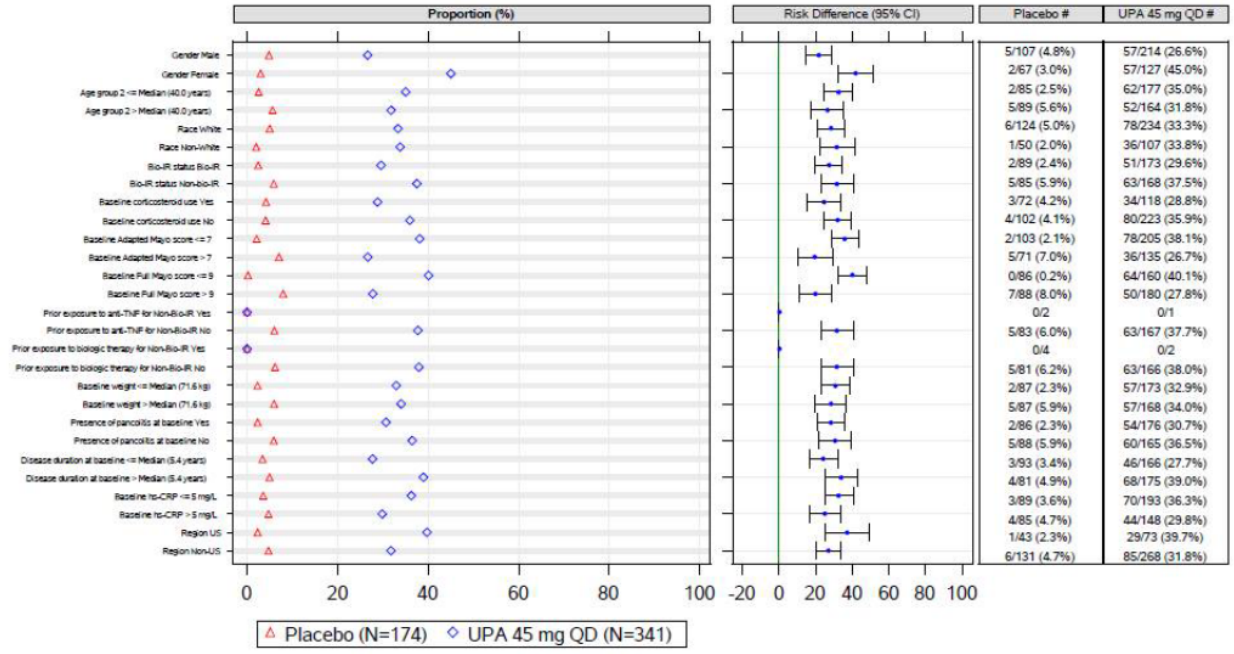


Figure 11 M14-675 Subgroup Analyses of the Primary Endpoint: Clinical Remission per Adapted Mayo Score at Week 8 (NRI-C) (ITT1 Population

Table 39 Study M14-234 Substudy 2 and Study M14-675: Bio-IR Status (NRI-C) (ITT1 Population)

Strata Treatment	N	Within Group (%)	 [95% CI]	Response Rate Difference (UPA 45 mg - Placebo) Difference (%)	 [95% CI]
Clinical Remission per Adapted Mayo Score Week 8					
Study M14-234 Substudy 2					
Bio-IR					
Placebo	78	0.4	[0.0, 2.3]		
UPA 45 mg	168	17.9	[12.1, 23.8]	17.5	[11.4, 23.6]
Non-Bio-IR					
Placebo	76	9.2	[2.7, 15.7]		
UPA 45 mg	151	35.2	[27.6, 42.9]	26.0	[16.0, 36.1]
Study M14-675					
Bio-IR					
Placebo	89	2.4	[0.0, 5.7]		
UPA 45 mg	173	29.6	[22.8, 36.4]	27.1	[19.6, 34.7]
Non-Bio-IR					
Placebo	85	5.9	[0.9, 10.9]		
UPA 45 mg	168	37.5	[30.2, 44.8]	31.6	[22.8, 40.5]
Clinical Response per Partial Adapted Mayo score at Week 8					
Study M14-234 Substudy 2					
Bio-IR					
Placebo	78	12.8	[5.4, 20.2]		
UPA 45 mg	168	64.4	[57.1, 71.6]	51.6	[41.2, 61.9]
Non-Bio-IR					
Placebo	76	42.1	[31.0, 53.2]		
UPA 45 mg	151	81.8	[75.6, 88.0]	39.7	[27.0, 52.4]
Study M14-675					
Bio-IR					
Placebo	89	19.3	[11.0, 27.5]		
UPA 45 mg	173	69.4	[62.5, 76.2]	50.1	[39.4, 60.8]

Strata Treatment	N	Within Group (%)	 [95% CI]	Response Rate Difference (UPA 45 mg - Placebo) Difference (%)	 [95% CI]
Non-Bio-IR					
Placebo	85	31.8	[21.9, 41.7]		
UPA 45 mg	168	79.8	[73.7, 85.8]	48.0	[36.4, 59.6]
Endoscopic Remission at Week 8					
Study M14-234 Substudy 2					
Bio-IR					
Placebo	78	0	[0.0, 0.0]		
UPA 45 mg	168	8.9	[4.6, 13.3]	8.9	[4.6, 13.3]
Non-Bio-IR					
Placebo	76	2.6	[0.0, 6.2]		
UPA 45 mg	151	19.1	[12.7, 25.4]	16.4	[9.1, 23.8]
Study M14-675					
Bio-IR					
Placebo	89	1.2	[0.0, 3.4]		
UPA 45 mg	173	12.7	[7.8, 17.7]	11.6	[6.1, 17.0]
Non-Bio-IR					
Placebo	85	2.4	[0.0, 5.6]		
UPA 45 mg	168	23.8	[17.4, 30.3]	21.5	[14.3, 28.7]
Endoscopic Improvement at Week 8					
Study M14-234 Substudy 2					
Bio-IR					
Placebo	78	1.7	[0.0, 4.8]		
UPA 45 mg	168	27.0	[20.2, 33.7]	25.3	[17.8, 32.7]
Non-Bio-IR					
Placebo	76	13.2	[5.6, 20.8]		
UPA 45 mg	151	46.8	[38.7, 54.8]	33.6	[22.5, 44.7]

Strata Treatment	N	Within Group (%)	 [95% CI][a]	Response Rate Difference (UPA 45 mg - Placebo) Difference (%)	 [95% CI][b]
Study M14-675					
Bio-IR					
Placebo	89	4.8	[0.2, 9.4]		
UPA 45 mg	173	37.1	[29.9, 44.3]	32.3	[23.7, 40.8]
Non-Bio-IR					
Placebo	85	12.0	[5.0, 18.9]		
UPA 45 mg	168	51.2	[43.6, 58.7]	39.2	[29.0, 49.5]

Bio-IR = subject who had demonstrated inadequate response to, loss of response to, or intolerance to biologic therapy (biologic inadequate responders); CI = confidence interval; COVID-19 = coronavirus disease 2019; ITT = intent-to-treat population; ITT_A = primary analysis population in Cohort 1 for efficacy endpoints; Non-bio-IR = subject who had received a prior biologic for up to 1 year but discontinued the biologic for reasons other than inadequate response or intolerance (e.g., change of insurance, well controlled disease) or met the criteria for inadequate response, loss of response or intolerance to aminosalicylates, corticosteroids and/or immunosuppressants as defined in the protocol.; NRI-C = Non-responder imputation incorporating multiple imputation to handle missing data due to COVID 19; UPA = upadacitinib

Note: 95% CI is calculated based on normal approximation to the binomial distribution. Point estimate and 95% CI are the synthetic results based on Student's t-distribution from PROC MIANALYZE procedure.

Extended Induction Treatment Analysis Set

A total of 125 subjects who did not respond to the double blind (DB) 8-week induction treatment with upadacitinib 45 mg entered the extended induction period and received another 8 weeks of OL treatment with upadacitinib 45 mg for a total of up to 16 weeks of treatment. Integrated data from the two induction studies are displayed below:

Table 40 Disease Activity and Symptoms, and Endoscopic and Histologic Assessment: Upadacitinib 45 mg (Extended Induction Treatment Analysis Set) (NRI-C)

Endpoint	Upadacitinib 45 mg QD N = 125
Subjects (%) with:	
Clinical Remission per Adapted Mayo score at Week 16	5.6%
Clinical Response per Adapted Mayo score at Week 16	48.3%
No reported abdominal pain at Week 16	40.0%
No reported bowel urgency at Week 16	30.4%
Endoscopic Improvement Week 16	14.3%
Endoscopic Remission Week 16	4.9%
Histologic-Endoscopic Mucosal Improvement at Week 16	11.0%
Histologic Improvement at Week 16	39.6%
Mucosal Healing at Week 16	3.4%

NRI-C = Non-responder imputation incorporating multiple imputation to handle missing data due to COVID 19; QD = once daily

Note: Extended Induction Treatment Analysis set consists of Part 2 of the Phase 3 Induction Studies (Study M14-234 Substudy 2 and Study M14-675).

Table 41 Efficacy of Maintenance Treatment in Subjects Who Received Induction Treatment of 16-Week Upadacitinib 45 mg QD (ITT_B Population) (NRI-C/RTB-MI)

Endpoint Treatment	N	Point Estimate	[95% CI]
Clinical remission per Adapted Mayo score at Week 52 (NRI-C) (%)			
UPA 15 mg	21	19.0	[2.3, 35.8]
UPA 30 mg	24	33.3	[14.5, 52.2]
Endoscopic Improvement at Week 52 (NRI-C) (%)			
UPA 15 mg	21	23.8	[5.6, 42.0]
UPA 30 mg	24	37.5	[18.1, 56.9]
Clinical Remission per Adapted Mayo Score at Week 52 among Subjects Who Achieved Clinical Remission at the End of the Induction Treatment in the Induction Study (NRI-C) (%)			
UPA 15 mg	1	0	[0.0, 0.0]
UPA 30 mg	2	100.0	[100.0, 100.0]
Proportion of Subjects Achieving Clinical Remission per Adapted Mayo Score at Week 52 and Corticosteroid Free for ≥ 90 Days Immediately Preceding Week 52 among Subjects Who Achieved Clinical Remission at the End of the Induction Treatment in the Induction Study (NRI-C) (%)			
UPA 15 mg	1	0	[0.0, 0.0]
UPA 30 mg	2	100.0	[100.0, 100.0]
Endoscopic Improvement at Week 52 among Subjects Who Achieved Endoscopic Improvement at the End of the Induction Treatment in the Induction Study (NRI-C) (%)			
UPA 15 mg	4	25.0	[0.0, 67.4]
UPA 30 mg	6	50.0	[10.0, 90.0]

Endpoint Treatment	N	Point Estimate	[95% CI]
Endoscopic Remission at Week 52 (NRI-C) (%)			
UPA 15 mg	21	4.8	[0.0, 13.9]
UPA 30 mg	24	12.5	[0.0, 25.7]
Clinical Response per Adapted Mayo Score at Week 52 among Subjects Who Achieved Clinical Response at the End of the Induction Treatment in the Induction Study (NRI-C) (%)			
UPA 15 mg	14	35.7	[10.6, 60.8]
UPA 30 mg	21	66.7	[46.5, 86.8]
Histologic-Endoscopic Mucosal Improvement at Week 52 (NRI-C) (%)			
UPA 15 mg	21	9.5	[0.0, 22.1]
UPA 30 mg	24	25.0	[7.7, 42.3]
Change from Baseline in IBDQ Total Score at Week 52 (RTB-MI) (LS Mean)			
UPA 15 mg	21	42.6	[14.59, 70.63]
UPA 30 mg	24	43.5	[18.33, 68.69]
Mucosal Healing at Week 52 (NRI-C) (%)			
UPA 15 mg	21	4.8	[0.0, 13.9]
UPA 30 mg	24	8.3	[0.0, 19.4]
No Bowel Urgency at Week 52 (NRI-C) (%)			
UPA 15 mg	21	28.6	[9.2, 47.9]
UPA 30 mg	24	41.7	[21.9, 61.4]
No Abdominal Pain at Week 52 (NRI-C) (%)			
UPA 15 mg	21	38.1	[17.3, 58.9]
UPA 30 mg	24	41.7	[21.9, 61.4]
Change from Baseline in FACIT-F Score at Week 52 (RTB-MI) (LS Mean)			
UPA 15 mg	21	9.0	[1.90, 16.13]
UPA 30 mg	24	10.6	[3.93, 17.18]

ANCOVA = analysis of covariance; CI = confidence interval; COVID-19 = coronavirus disease 2019; Diff = difference; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT = intent-to treat; ITT_B = Cohort 3: Subjects who completed 16-weeks of UPA 45 mg/UPA 45 mg in Study M14-234 Substudy 2 or Study M14-675 and achieved response per Adapted Mayo score; LS = least square; UPA = upadacitinib

Maintenance study M14-234 substudy 3

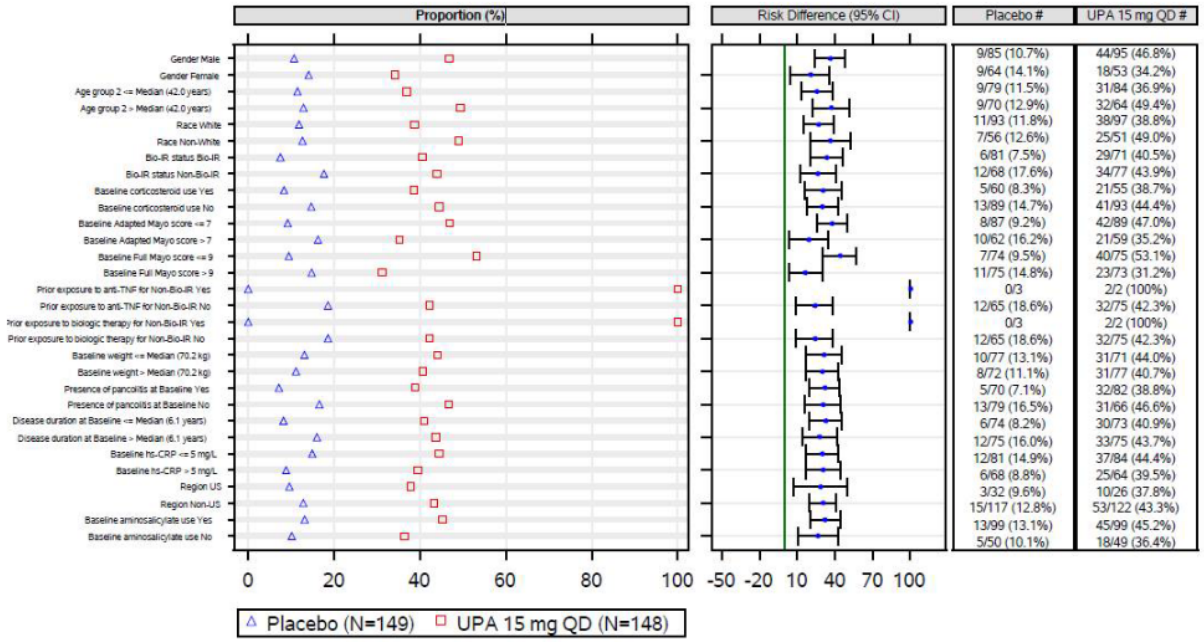


Figure 12 Clinical Remission per Adapted Mayo Score at Week 52 by Subgroup, Upadacitinib 15 mg vs Placebo (NRI-C) (ITT_A Population)

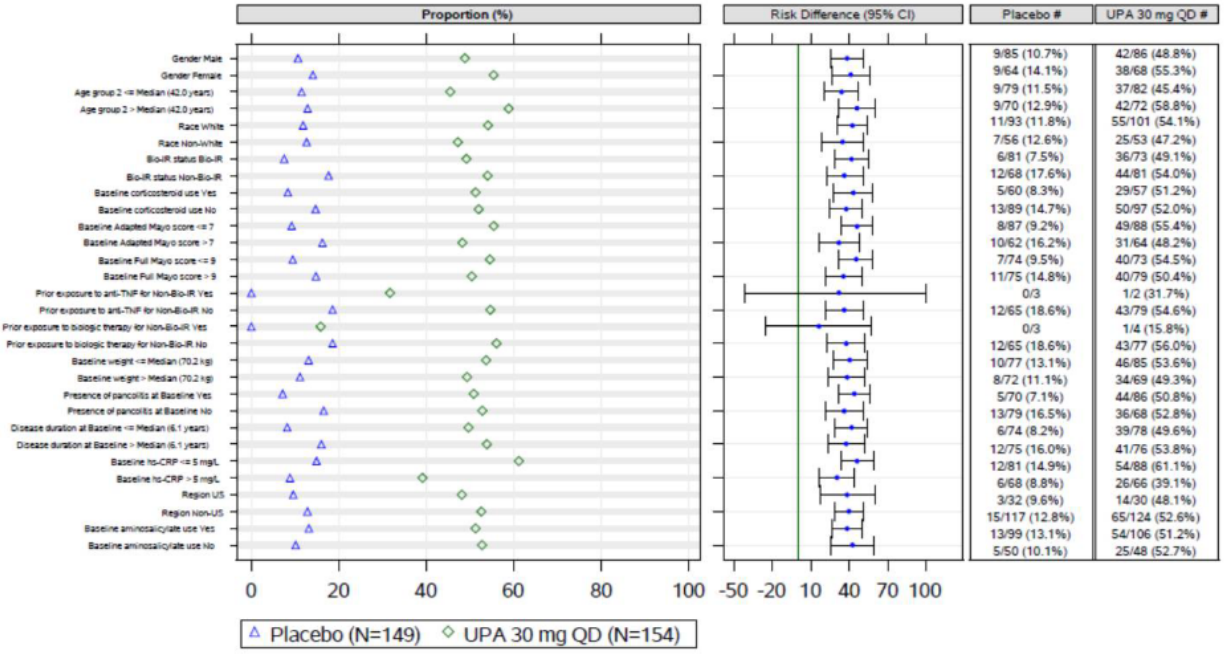


Figure 13 Clinical Remission per Adapted Mayo Score at Week 52 by Subgroup, Upadacitinib 30 mg vs Placebo (NRI-C) (ITT_A Population)

Table 42 M14-234 substudy 3: Analysis by Subgroups of Bio-IR and Non-Bio-IR (NRI-C) (ITT_A Population

Endpoint Subgroup Treatment	N	Within Group Point Estimate	Within Group [95% CI]	Between Group Difference (Upadacitinib - Placebo) Point Estimate	Between Group Difference (Upadacitinib - Placebo) [95% CI]
Endoscopic Improvement at Week 52 (NRI-C) (%)					
Bio-IR					
Placebo	81	7.8	[1.8, 13.8]		
UPA 15 mg	71	48.3	[31.7, 55.0]	35.5	[22.4, 48.6]
UPA 30 mg	73	56.1	[44.3, 67.9]	48.3	[35.0, 61.5]
Non-Bio-IR					
Placebo	68	22.5	[12.2, 32.7]		
UPA 15 mg	77	53.6	[42.3, 64.9]	31.1	[15.9, 46.4]
UPA 30 mg	81	66.6	[56.1, 77.1]	44.1	[29.4, 58.8]
Endoscopic Remission at Week 52 (NRI-C) (%)					
Bio-IR					
Placebo	81	2.5	[0.0, 5.8]		
UPA 15 mg	71	21.5	[11.8, 31.2]	19.0	[8.8, 29.3]
UPA 30 mg	73	20.0	[10.5, 29.5]	17.5	[7.4, 27.7]
Non-Bio-IR					
Placebo	68	9.3	[2.2, 16.4]		
UPA 15 mg	77	26.8	[16.7, 36.8]	17.5	[5.2, 29.8]
UPA 30 mg	81	31.2	[20.8, 41.5]	21.9	[9.3, 34.6]
Clinical Remission per Adapted Mayo Score at Week 52 among Subjects Who Achieved Clinical Remission at the End of the Induction Treatment in the Induction Study (NRI-C) (%)					
Bio-IR					
Placebo	22	13.6	[0.0, 28.0]		
UPA 15 mg	17	76.5	[56.3, 96.6]	62.8	[38.1, 87.6]
UPA 30 mg	20	73.0	[52.8, 93.2]	59.4	[34.6, 84.1]
Non-Bio-IR					
Placebo	32	28.1	[12.5, 43.7]		
UPA 15 mg	30	49.4	[31.4, 67.5]	21.3	[-2.5, 45.2]
UPA 30 mg	38	68.0	[53.0, 82.9]	39.9	[18.3, 61.5]

Endpoint Subgroup Treatment	N	Within Group		Between Group Difference (Upadacitinib - Placebo)	
		Point Estimate	[95% CI]	Point Estimate	[95% CI]
Clinical Remission per Adapted Mayo Score at Week 52 and Corticosteroid Free for ≥ 90 Days Immediately Preceding Week 52 among Subjects Who Achieved Clinical Remission at the End of the Induction Treatment in the Induction Study (NRI-C) (%)					
Bio-IR					
Placebo	22	13.6	[0.0, 28.0]		
UPA 15 mg	17	70.6	[48.9, 92.2]	57.0	[31.0, 82.9]
UPA 30 mg	20	73.0	[52.8, 93.2]	59.4	[34.6, 84.1]
Non-Bio-IR					
Placebo	32	28.1	[12.5, 43.7]		
UPA 15 mg	30	49.4	[31.4, 67.5]	21.3	[-2.5, 45.2]
UPA 30 mg	38	65.4	[50.1, 80.6]	37.2	[15.4, 59.0]
Clinical Response per Adapted Mayo Score at Week 52 (NRI-C) (%)					
Bio-IR					
Placebo	81	15.1	[7.1, 23.1]		
UPA 15 mg	71	56.3	[44.8, 67.9]	41.2	[27.2, 55.3]
UPA 30 mg	73	67.6	[56.8, 78.5]	52.5	[39.0, 66.0]
Non-Bio-IR					
Placebo	68	25.2	[14.8, 35.6]		
UPA 15 mg	77	66.2	[55.7, 76.8]	41.0	[26.2, 55.9]
UPA 30 mg	81	80.1	[71.2, 89.0]	54.9	[41.3, 68.6]
Endoscopic Improvement at Week 52 among Subjects Who Achieved Endoscopic Improvement at the End of the Induction Treatment in the Induction Study (NRI-C) (%)					
Bio-IR					
Placebo	33	9.1	[0.0, 18.9]		
UPA 15 mg	24	70.8	[52.6, 89.0]	61.7	[41.1, 82.4]
UPA 30 mg	29	60.7	[42.5, 78.9]	51.6	[30.9, 72.3]
Non-Bio-IR					
Placebo	41	26.8	[12.8, 40.9]		
UPA 15 mg	39	56.0	[40.3, 71.7]	29.2	[8.1, 50.2]
UPA 30 mg	50	74.7	[62.3, 87.0]	47.8	[29.1, 66.5]

Endpoint Subgroup Treatment	N	Within Group		Between Group Difference (Upadacitinib - Placebo)	
		Point Estimate	[95% CI]	Point Estimate	[95% CI]
Mucosal Healing at Week 52 (NRI-C) (%)					
Bio-IR					
Placebo	81	2.5	[0.0, 5.8]		
UPA 15 mg	71	17.2	[8.3, 26.1]	14.7	[5.2, 24.2]
UPA 30 mg	73	16.1	[7.4, 24.8]	13.6	[4.3, 23.0]
Non-Bio-IR					
Placebo	68	7.5	[1.2, 13.7]		
UPA 15 mg	77	18.0	[9.2, 26.8]	10.6	[-0.2, 21.4]
UPA 30 mg	81	21.6	[12.3, 31.0]	14.2	[2.9, 25.5]
Histologic-Endoscopic Mucosal Improvement at Week 52 (NRI-C) (%)					
Bio-IR					
Placebo	81	5.1	[0.2, 10.0]		
UPA 15 mg	71	32.7	[21.5, 43.9]	27.6	[15.5, 39.7]
UPA 30 mg	73	47.1	[35.3, 58.8]	42.0	[29.2, 54.7]
Non-Bio-IR					
Placebo	68	19.9	[10.2, 29.5]		
UPA 15 mg	77	36.6	[25.6, 47.6]	16.8	[2.1, 31.5]
UPA 30 mg	81	51.4	[39.9, 62.8]	31.5	[16.5, 46.5]

bio-IR = subjects with inadequate response; loss of response; or intolerance to biologic therapy; CI = confidence interval; COVID-19 = coronavirus disease 2019; ITT = intent-to-treat population; ITT_A = primary analysis population in Cohort 1 for efficacy endpoints; non-bio-IR = subjects with inadequate response, loss of response, or intolerance to conventional therapy but subjects had not failed biologic therapy; UPA = upadacitinib

Notes: NRI-C: non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.

95% CI is calculated based on normal approximation to the binomial distribution. Point estimate and 95% CI are the synthetic results based on Student's t-distribution from PROC MIANALYZE procedure.

2.6.5.3. Summary of main efficacy results

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 43 Summary of efficacy for Study M14-675

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Evaluate the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Ulcerative Colitis	
Study identifier	M14-675 (EudraCT Number: 2016-000642-62)
Design	This is a Phase 3 multicenter, randomized, double blind, placebo-controlled induction study to evaluate the efficacy and safety of upadacitinib in subjects with moderately to severely active ulcerative colitis.

	Duration of main phase: Duration of extension phase:		8 weeks (part 1 – double blind placebo controlled) 8 weeks (part 2 – open label)
Hypothesis	upadacitinib 45 mg once daily (QD) as an induction treatment is superior to placebo in inducing clinical remission at Week 8		
Treatments groups	Upadacitinib group		Upadacitinib 45 mg QD (N=345) for 8 weeks
	Placebo group		Placebo QD (N=177) for 8 weeks
Endpoints and definitions	Primary endpoint	Clinical remission per adapted Mayo score at Week 8	Stool frequency subscore (SFS)≤1 and not greater than baseline, rectal bleeding score (RBS)=0, and endoscopic score (ES)≤ 1 without friability
	Ranked secondary endpoint	Endoscopic improvement at Week 8	ES≤1 without friability
	Ranked secondary endpoint	Endoscopic remission at Week 8	ES=0
	Ranked secondary endpoint	Clinical response per Adapted Mayo Score at Week 8	A decrease in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, and a decrease in RBS ≥ 1 from baseline or an absolute RBS ≤ 1
	Ranked secondary endpoint	Clinical response per Partial Adapted Mayo Score at Week 2	A decrease in partial adapted Mayo score ≥ 1 points and ≥ 30% from baseline, and a decrease in RBS≥ 1 from baseline or an absolute RBS ≤ 1
	Ranked secondary endpoint	Histologic-Endoscopic Mucosal Improvement at Week 8	ES≤1 without friability and Geboes score ≤ 3.1
	Ranked secondary endpoint	No Bowel Urgency at Week 8	Subjects reported no bowel urgency
	Ranked secondary endpoint	No Abdominal Pain at Week 8	Subjects reported no abdominal pain
	Ranked secondary endpoint	Histologic Improvement at Week 8	A decrease from Baseline in Geboes score

	Ranked secondary endpoint	Change from Baseline in IBDQ Total at Week 8	Change from Baseline in IBDQ total
	Ranked secondary endpoint	Mucosal Healing at Week 8	ES=0 and Geboes score <2
	Ranked secondary endpoint	Change from Baseline in FACIT-F at Week 8	Change from baseline in FACIT-F score
Database lock	09 February 2021		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat 1 (ITT1) is the primary analysis population which includes subjects who were randomized and received at least one dose of double-blinded study drug in Part 1. Primary and secondary endpoints were evaluated at Week 8 unless otherwise specified.		

Effect estimate per comparison	Treatment group	Placebo	UPA 45 mg QD
	Number of Randomized subjects	177	345
	Number of subjects in ITT1	174	341
	Primary endpoint		
	Clinical Remission per Adapted Mayo Score % responders vs placebo Diff. (95% CI) *p*-value	4.1	33.5 29.0 [23.2, 34.7] < 0.001 ***
	Ranked Secondary Endpoints		
	Endoscopic improvement % responders vs placebo Diff. (95% CI) *p*-value	8.3	44.0 35.1 [28.6, 41.6] < 0.001 ***

	Endoscopic remission % responders vs placebo Diff. (95% CI) *p*-value	1.7	18.2 15.9 [11.4, 20.3] < 0.001 ***
	Clinical response per Adapted Mayo Score % responders vs placebo Diff. (95% CI) *p*-value	25.4	74.5 49.4 [41.7, 57.1] < 0.001 ***
	Clinical response per Partial Adapted Mayo Score at Week 2 % responders vs placebo Diff. (95% CI) *p*-value	25.9	63.3 37.0 [28.8, 45.1] < 0.001 ***
	Histologic-Endoscopic Mucosal Improvement % responders vs placebo Diff. (95% CI) *p*-value	5.9	36.7 30.1 [24.1, 36.2] < 0.001 ***
	No Bowel Urgency % responders vs placebo Diff. (95% CI) *p*-value	25.9	53.7 27.1 [19.0, 35.3] < 0.001 ***
	No Abdominal Pain % responders vs placebo Diff. (95% CI) *p*-value	24.1	53.7 29.1 [20.9, 37.4] < 0.001 ***
	Histologic Improvement % responders vs placebo	24.5	62.2 37.9

	Diff. (95% CI) *p*-value		[29.8, 46.1] < 0.001 ***
	Change from Baseline in IBDQ Total [a] LS Mean vs placebo: Diff. (95% CI) p-value	21.1	 52.2 31.2 [24.98, 37.36] < 0.001 ***
	Mucosal Healing % responders vs placebo Diff. (95% CI) *p*-value	1.7	 13.5 11.3 [7.2, 15.3] < 0.001 ***
	Change from Baseline in FACIT-F [b] LS Mean vs placebo: Diff. (95% CI) p-value	3.5	 9.4 6.0 [4.19, 7.73] < 0.001 ***
Notes	*** Statistically significant at 0.001. The overall type I error rate of the primary and secondary endpoints for upadacitinib 45 mg was strongly controlled at the 2-sided significance level of 0.05 using a fixed sequential testing procedure a. The numbers of subjects for this analysis are 156 and 315 in the Placebo and UPA 45 mg QD arms, respectively. b. The numbers of subjects for this analysis are 155 and 312 in the Placebo and UPA 45 mg QD arms, respectively.		

Table 44 Summary of efficacy for Study M14-234 Substudy 2 and Substudy 3

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis Separate efficacy and safety evaluation for the Induction and Maintenance Phases. Separate randomization after the Induction Phase.	
Study identifier	M14-234 Substudy 2 Induction (EudraCT Number: 2016-000641-31)
Design	A Phase 3 multicenter, randomized, double blind, placebo-controlled induction study to evaluate the efficacy and safety of upadacitinib in subjects with moderately to severely active ulcerative colitis.

	Duration of main phase: Duration of extension phase:		8 weeks (part 1 – double blind placebo controlled) 8 weeks (part 2 – open label)
Hypothesis	Upadacitinib 45 mg once daily (QD) as an induction treatment is superior to placebo in inducing clinical remission at Week 8		
Treatments groups	Upadacitinib group		45 mg QD for 8 weeks (N=319)
	Placebo group		Placebo QD for 8 weeks (N=155)
Endpoints and definitions	Primary endpoint	Clinical remission per adapted Mayo score at Week 8	Stool frequency subscore (SFS)≤1 and not greater than baseline, rectal bleeding score (RBS)=0, and endoscopic score (ES)≤ 1 without friability
	Ranked secondary endpoint	Endoscopic improvement at Week 8	ES≤1 without friability
	Ranked secondary endpoint	Endoscopic remission at Week 8	ES=0
	Ranked secondary endpoint	Clinical response per Adapted Mayo Score at Week 8	A decrease in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, and a decrease in RBS ≥ 1 from baseline or an absolute RBS ≤ 1
	Ranked secondary endpoint	Clinical response per Partial Adapted Mayo Score at Week 2	A decrease in partial adapted Mayo score ≥ 1 points and ≥ 30% from baseline, and a decrease in RBS≥ 1 from baseline or an absolute RBS ≤ 1
	Ranked secondary endpoint	Histologic-Endoscopic Mucosal Improvement at Week 8	ES≤1 without friability and Geboes score ≤ 3.1
	Ranked secondary endpoint	No Bowel Urgency at Week 8	Subjects reported no bowel urgency
	Ranked secondary endpoint	No Abdominal Pain at Week 8	Subjects reported no abdominal pain
	Ranked secondary endpoint	Histologic Improvement at Week 8	A decrease from Baseline in Geboes score
	Ranked secondary endpoint	Change from Baseline in IBDQ Total at Week 8	Change from Baseline in IBDQ total

	Ranked secondary endpoint	Mucosal Healing at Week 8	ES=0 and Geboes score <2
	Ranked secondary endpoint	Change from Baseline in FACIT-F at Week 8	Change from baseline in FACIT-F score
Database lock	November 25, 2020		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat 1 (ITT1) is the primary analysis population which includes subjects who were randomized and received at least one dose of double-blinded study drug in Part 1. Primary and secondary endpoints were evaluated at Week 8 unless otherwise specified.		
Effect estimate per comparison	Treatment group	Placebo	UPA 45 mg QD
	Number of Randomized Subjects	155	319
	Number of subjects in ITT1	154	319
	Primary endpoint		
	Clinical remission per Adapted Mayo Score % responders vs placebo Diff. (95% CI) *p*-value	4.8	 26.1 21.6 [15.8, 27.4] < 0.001 ***
	Ranked Secondary Endpoints		
	Endoscopic improvement % responders vs placebo Diff. (95% CI) *p*-value	7.4	 36.3 29.3 [22.6, 35.9] < 0.001 ***
	Endoscopic remission % responders vs placebo Diff. (95% CI) *p*-value	1.3	 13.7 12.7 [8.4, 17.0] < 0.001 ***
	Clinical response per Adapted Mayo Score % responders vs placebo Diff. (95% CI) *p*-value	27.3	 72.6 46.3 [38.4, 54.2] < 0.001 ***

	Clinical response per Partial Adapted Mayo Score at Week 2 % responders vs placebo Diff. (95% CI) *p*-value	27.3	60.1 33.3 [24.8, 41.8] < 0.001 ***
	Histologic-Endoscopic Mucosal Improvement % responders vs placebo Diff. (95% CI) *p*-value	6.6	30.1 23.7 [17.5, 30.0] < 0.001 ***
	No Bowel Urgency % responders vs placebo Diff. (95% CI) *p*-value	21.4	48.4 27.4 [19.2, 35.6] < 0.001 ***
	No Abdominal Pain % responders vs placebo Diff. (95% CI) *p*-value	23.4	46.6 23.6 [15.1, 32.1] < 0.001 ***
	Histologic Improvement % responders vs placebo Diff. (95% CI) *p*-value	22.5	55.0 32.2 [23.8, 40.7] < 0.001 ***
	Change from Baseline in IBDQ Total [a] LS Mean vs placebo: Diff. (95% CI) *p*-value	21.7	55.3 33.7 [27.02, 40.36] < 0.001 ***
	Mucosal Healing % responders vs placebo Diff. (95% CI) *p*-value	1.3	10.7 9.7 [5.7, 13.7] < 0.001 ***
	Change from Baseline in FACIT-F [b] LS Mean vs placebo:	2.8	9.5

	Diff. (95% CI) *p*-value		6.7 [4.79, 8.59] < 0.001 ***
Notes	*** Statistically significant at 0.001. The overall type I error rate of the primary and secondary endpoints for upadacitinib 45 mg was strongly controlled at the 2-sided significance level of 0.05 using a fixed sequential testing procedure c. The numbers of subjects for this analysis are 125 and 292 in the Placebo and UPA 45 mg QD arms, respectively. d. The numbers of subjects for this analysis are 125 and 291 in the Placebo and UPA 45 mg QD arms, respectively.		

Title: A Multicenter, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis			
Study identifier	M14-234 Substudy 3 Maintenance (EudraCT Number: 2016-000641-31)		
Design	A Phase 3 multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of upadacitinib for maintenance therapy in subjects with moderately to severely active UC who have responded to the induction treatment.		
	Duration of main phase:		52 weeks
Hypothesis	Upadacitinib 15 mg, 30 mg once daily is superior to placebo in achieving clinical remission per adapted Mayo score at Week 52		
Treatments groups	Upadacitinib 15 mg group		Upadacitinib 15 mg QD (n=148) for 52 weeks
	Upadacitinib 30 mg group		Upadacitinib 30 mg QD (n=154) for 52 weeks
	Placebo group		Placebo QD (n=149) for 52 weeks
Endpoints and definitions	Primary endpoint	Clinical remission per Adapted mayo score at Week 52	Stool frequency subscore (SFS)≤1 and not greater than baseline, rectal bleeding score (RBS)=0, and endoscopic score (ES)≤ 1 without friability
	Secondary endpoint	Endoscopic improvement At week 52	ES≤1 without friability
	Secondary endpoint	Maintenance of clinical remission at Week 52	Clinical remission at Week 52 among subjects who have achieved clinical remission in the end of the induction treatment
	Secondary endpoint	Maintenance of corticosteroid-free clinical remission at Week 52	Clinical remission per adapted Mayo score at Week 52 with corticosteroid free at least 90 days prior to the Week 52 visit among subjects who have achieved clinical remission in the end of the induction treatment

	Secondary endpoint	Maintenance of endoscopic improvement at Week 52	ES≤1 without friability at Week 52 among subjects who have achieved endoscopic improvement in the end of the induction treatment
	Secondary endpoint	Endoscopic remission at Week 52	ES=0
	Secondary endpoint	Maintenance of clinical response per adapted Mayo score at Week 52	Clinical response at Week 52 per adapted Mayo score among subjects who have achieved clinical response in the end of the induction treatment
	Secondary endpoint	Histologic-endoscopic mucosal improvement (HEMI) at Week 52	ES≤1 without friability and Geboes score ≤ 3.1
	Secondary endpoint	Change from Baseline in IBDQ Total Score at Week 52	Change from Baseline in IBDQ total
	Secondary endpoint	Mucosal healing at Week 52	ES=0 and Geboes score <2
	Secondary endpoint	No bowel urgency at Week 52	Subjects reported no bowel urgency
	Secondary endpoint	No abdominal pain at Week 52	Subjects reported no abdominal pain
	Secondary endpoint	Change from Baseline in FACIT-F Score at Week 52	Change from baseline in FACIT-F score
Database lock	June 8, 2021		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat 1 (ITTA) is the primary analysis population which includes the first 451 subjects who were upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period and received at least one dose of Maintenance study drug in Cohort 1. Primary and secondary endpoints were evaluated at Week 52		

Effect estimate per comparison	Treatment group	Placebo	UPA 15 mg QD	UPA 30 mg QD
	Number of subjects in ITTA	149	148	154
	Primary endpoint			
	Clinical remission per Adapted Mayo Score			
	% responders	12.1	42.3	51.7
	vs placebo		30.7	39.0
	Diff. (95% CI)		[21.7, 39.8]	[29.7, 48.2]
	p-value		< 0.001 ***	< 0.001 ***

	Multiplicity-Controlled Secondary Endpoints			
	Endoscopic improvement			
	% responders	14.5	48.7	61.6
	vs placebo		34.4	46.3
	Diff. (95% CI)		[25.1, 43.7]	[36.7, 55.8]
	p-value		< 0.001 ***	< 0.001 ***
	Maintenance of clinical remission [a]			
	% responders	22.2	59.2	69.7
	vs placebo		37.4	47.0
	Diff. (95% CI)		[20.3, 54.6]	[30.7, 63.3]
	p-value		< 0.001 ***	< 0.001 ***
	Maintenance of corticosteroid-free clinical remission [b]			
	% responders	22.2	57.1	68.0
	vs placebo		35.4	45.1
	Diff. (95% CI)		[18.2, 52.7]	[28.7, 61.6]
	p-value		< 0.001 ***	< 0.001 ***
	Maintenance of endoscopic improvement [c]			
	% responders	19.2	61.6	69.5
	vs placebo		42.0	48.6
	Diff. (95% CI)		[27.8, 56.2]	[35.5, 61.7]
	p-value		< 0.001 ***	< 0.001 ***
	Endoscopic remission			
	% responders	5.6	24.2	25.9
	vs placebo		18.7	19.4
	Diff. (95% CI)		[11.0, 26.4]	[11.7, 27.2]
	p-value		< 0.001 ***	< 0.001 ***
	Maintenance of clinical response [d]			
	% responders	18.8	63.0	76.6
	vs placebo		44.6	56.6
	Diff. (95% CI)		[34.5, 54.7]	[47.2, 66.0]
	p-value		< 0.001 ***	< 0.001 ***
	HEMI			
	% responders	11.9	35.0	49.8
	vs placebo		23.8	37.3
	Diff. (95% CI)		[14.8, 32.8]	[27.8, 46.8]
	p-value		< 0.001 ***	< 0.001 ***

	Change from Baseline in IBDQ Total Score LS Mean vs placebo: Diff. (95% CI) p-value	17.9	49.2 31.3 [21.98, 40.70] < 0.001 ***	58.9 41.0 [31.39, 50.55] < 0.001 ***
	Mucosal healing % responders vs placebo Diff. (95% CI) *p*-value	4.7	17.6 13.0 [6.0, 20.0] < 0.001 ***	19.0 13.6 [6.6, 20.6] < 0.001 ***
	No bowel urgency % responders vs placebo Diff. (95% CI) *p*-value	17.4	56.1 38.7 [28.9, 48.5] < 0.001 ***	63.6 45.1 [35.5, 54.8] < 0.001 ***
	No abdominal pain % responders vs placebo Diff. (95% CI) *p*-value	20.8	45.9 24.3 [14.2, 34.5] < 0.001 ***	55.3 33.7 [23.6, 43.9] < 0.001 ***
	Change from Baseline in FACIT-F Score LS Mean vs placebo: Diff. (95% CI) p-value	3.7	8.7 5.1 [2.67, 7.52]	9.5 5.9 [3.44, 8.27]

Notes	*** Statistically significant at 0.001. The overall type I error rate of the primary and secondary endpoints for upadacitinib 15 mg QD and 30 mg QD were strongly controlled at the 2-sided significance level of 0.05 using a graphical multiple testing procedure a. Defined as clinical remission per Adapted Mayo Score among subjects who achieved clinical remission at the end of the induction treatment in the induction studies. The number of subjects who achieved clinical remission at the end of the induction treatment are 54, 47 and 58 in the Placebo, UPA 15 mg QD and UPA 30 mg QD, respectively. b. Clinical remission per Adapted Mayo Score and corticosteroid free for ≥ 90 Days immediately preceding week 52 among subjects who achieved clinical remission at the end of the induction treatment in the induction study. The number of subjects who achieved clinical remission at the end of the induction treatment are 54, 47 and 58 in the Placebo, UPA 15 mg QD and UPA 30 mg QD, respectively. c. Endoscopic improvement among subjects who achieved endoscopic improvement at the end of the induction treatment in the induction study. The number of subjects who achieved endoscopic improvement at the end of the induction treatment are 74, 63 and 79 in the Placebo, UPA 15 mg QD and UPA 30 mg QD, respectively. d. Clinical response per Adapted Mayo Score among subjects who achieved clinical response at the end of the induction treatment in the induction study. The number of subjects who achieved clinical response at the end of the induction treatment are 134, 135 and 144 in the Placebo, UPA 15 mg QD and UPA 30 mg QD, respectively.

2.6.5.4. Supportive study

Long-Term Extension Study M14-533

The study includes 2 cohorts:

Cohort 1: 562 subjects who had not responded at the end of the induction period in Study M14-234 Substudy 1 or who had loss of response during the maintenance period of Study M14-234 Substudy 3. Subjects received OL upadacitinib 15 mg beginning at Week 0 (last visit in Study M14-234 or up to 14 days later). At or after Week 2, subjects receiving upadacitinib 15 mg who experienced inadequate response and no safety concerns identified by the investigator could have been escalated to upadacitinib 30 mg.

Cohort 1 also included subjects who reached Week 44 of Study M14-234 Substudy 3 prior to protocol amendment 3 (21 August 2018), based on the previous protocol requirements for entry into Study M14-533.

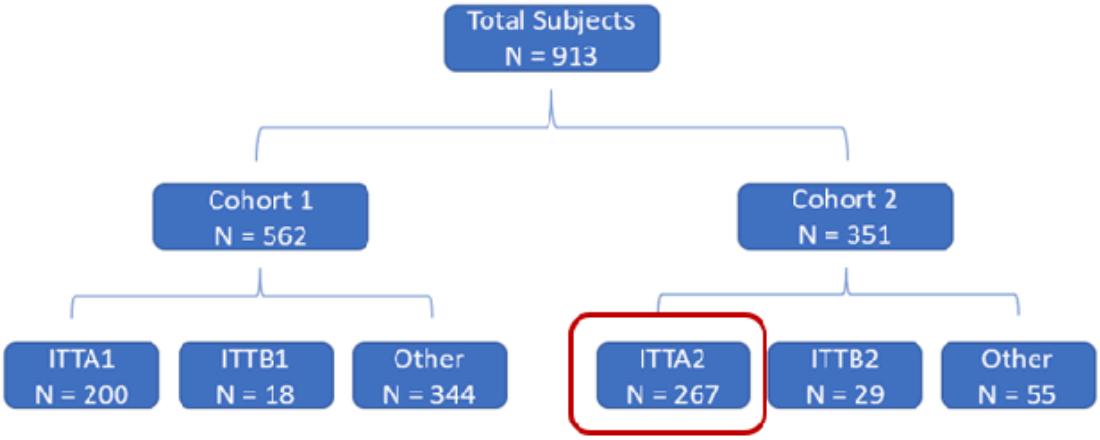
Cohort 2: All subjects who completed M14-234 Substudy 3 through Week 52 (136 subjects [15 mg upadacitinib], 178 subjects [30 mg upadacitinib], 36 [placebo]) were eligible to enroll in Cohort 2 (*Figure 14*).

In Cohort 2, at Week 0, all subjects who achieved clinical remission in Study M14-234 Substudy 3 continued to receive their original assigned double-blind treatment (placebo, upadacitinib 7.5, 15, or 30 mg).

Subjects who were not in clinical remission at Week 0 were eligible to dose escalate in a blinded manner and receive:

- Upadacitinib 15 mg for those originally assigned to placebo or upadacitinib 7.5 mg
- Upadacitinib 30 mg for those originally assigned to upadacitinib 15 mg treatment in Study M14-234 Substudy 3

- Upadacitinib 30 mg treatment if they were already receiving that dose



Note: Subjects included in the "Other" group did not meet the definition of the ITTA or ITTB population as specified in the SAP.

Figure 14 Long-Term Extension Study M14-533 Subject Distribution

The ITT population included subjects who entered Cohort 1 (ITTA1 and ITTB1); and subjects who entered Cohort 2 (ITTA2 and ITTB2) (Figure above). The ITTA population included subjects who were upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1 of the Maintenance Study. ITTA1 and ITTA2 are subsets of ITTA in Cohort 1 and 2 of the LTE Study, respectively. The ITTB population included subjects who were upadacitinib 45 mg QD 16-week induction responders in Cohort 3 of the Maintenance Study. ITTB1 and ITTB2 are subsets of ITTB in Cohort 1 and 2 of the LTE Study, respectively. To support the continued long-term efficacy following the induction and maintenance treatment, this efficacy presentation is focused on ITTA2 (highlighted in the figure above) among subjects who have successfully completed the induction and maintenance treatment. Only Week 48 data from the LTE study are presented as there are too few patients who have reached later time points at the date of the data cut off to be evaluable.

Table 45 Study M14-533: Clinical Remission per Adapted Mayo Score at Week 0 and Week 48 (As Observed) (ITTA2 Population)

Visit		Responder	
Treatment	**N**	**n (%)**	**[95% CI][a]**
Week 0			
Upadacitinib 15 mg	95	59 (62.1)	[52.3, 71.9]
Upadacitinib 30 mg	147	84 (57.1)	[49.1, 65.1]
Week 48			
Upadacitinib 15 mg	14	10 (71.4)	[47.8, 95.1]
Upadacitinib 30 mg	29	21 (72.4)	[56.1, 88.7]

CI = confidence interval

a. 95% CI for response rate is based on the normal approximation to the binomial distribution.

Note: Data included are subject to a cutoff date of 30 April 2021.

2.6.6. Discussion on clinical efficacy

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 ulcerative colitis 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 replicate phase 3 induction studies (M14-234 Substudy 2 and M14-675) and one ongoing phase 3 maintenance study (M14-234 Substudy 3) which were all double-blind, randomised, placebo-controlled multi-centre studies. Additional information is provided from the dose finding study (M14-234 Substudy 1) and the long term extension study (M14-533). As stated in the EMA Guideline (CHMP/EWP/18463/2006 Rev.1 Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis) “to fulfil a claim for the treatment of ulcerative colitis, 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 (EMA/CHMP/SAWP/336739/2016 EMEA/H/SA/3190/2/2016/II), where the rather complex study design of study M14-234 (a three part study with a seamless design including one dose finding part (substudy 1), one induction study (substudy 2) and a maintenance study (substudy 3) was discussed and approved. Most of the CHMP advices were followed with some minor deviations discussed below.

The dose finding study (M14-234 Substudy 1) was a Phase 2b dose-ranging study designed to evaluate the efficacy and safety of 4 oral doses of upadacitinib (7.5 mg, 15 mg, 30 mg and 45 mg) compared to placebo as 8-week induction therapy in subjects with moderately to severely active UC. The study duration included a Screening Period of up to 5 weeks and an 8-week double-blind (DB) Induction Period.

The two replicate induction studies (M14-234 Substudy 2 and M14-675) were two-part Phase 3 dose-confirming studies designed to evaluate the efficacy and safety of oral administration of upadacitinib 45 mg compared to placebo as induction therapy for up to 16 weeks. The studies included a Screening Period of up to 5 weeks followed by a placebo controlled part with a duration of 8 weeks where patients were randomized in a 2:1 ratio to receive Upadacitinib 45 mg once daily or placebo. The studies also included a second part were patients who did not achieve a clinical response at week 8 received Upadacitinib 45 mg open label for additional 8 weeks.

Subjects who completed either one of the three studies (M14-234 substudy 1, M14-234 substudy 2 or study M14-675) and achieved a clinical response per adapted mayo score at week 8 (or week 16) were rerandomized into the Maintenance Study. Clinical response per adopted mayo score was defined as a decrease from baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1. The subjects were randomized into four different cohorts depending on the treatment received in the induction studies. Cohort 1 included subjects who received Upadacitinib 15 mg, 30 mg or 45 mg in the M14-234 Substudy 1, Upadacitinib 45 mg for 8 weeks in the M14-234 substudy 2 or in study M14-675 (either blinded for 8 weeks in part 1 or placebo in part 1 followed by open label 45 mg upadacitinib for 8 weeks). Patients were rerandomized 1:1:1 to receive eighter upadacitinib 15mg, upadacitinib 30 mg or placebo except for the 15 mg group, which only received 15 mg or placebo. Cohort 2 included placebo patients with a clinical response from the three studies. These patients were not rerandomized but continued to receive placebo during the maintenance phase. Cohort 3 included patients who received upadacitinib 45 mg for 16 weeks in study M14-234 substudy 2 or in study M14-675. These patients were rerandomized 1:1 to upadacitinib 15 mg or 30 mg. Cohort 4 included patients who received upadacitinib 7.5 mg during Study M14-234 Substudy 1 and continued to receive blinded treatment of upadacitinib 7.5 mg in the maintenance study.

The primary analysis regarding the maintenance phase is conducted in a subgroup of patients from the Cohort 1 defined as “the subset of ITT population who were the first randomized 451 (actual)

upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1". This is acceptable.

Subjects who had not responded at the end of the induction period in Study M14-234 Substudy 1, had loss of response during the maintenance period of Study M14-234 Substudy 3, or had completed Study M14-234 Substudy 3 could proceed to the long term extension study. Only limited data is provided from this study regarding efficacy.

The inclusion and exclusion criteria were similar in the two induction studies and the dose-finding study and uses Adapted Mayo Score (Adapted Mayo Score of 5 to 9 and endoscopy subscore of 2 to 3) to define patients with moderately to severely active ulcerative colitis. The Adapted Mayo score uses three parts of the 4 part Mayo score, excluding the physician global assessment (PGA). It is acknowledged that several previous studies for approved UC treatments have used a Mayo score 6-12 to define moderate to severe disease (with inclusion of and endoscopy subscore of ≥2 and in later studies also a definition of a minimal level of symptom burden). Although it would have been preferred to have a definition also regarding a minimal level of symptoms (as also stated in the EMA UC GL), it was concluded in the CHMP SA that "using the modified Mayo definition to recruit subjects with moderately or severely active UC into a registration trial can be acceptable but the interchangeability with the full Mayo score should be demonstrated convincingly with a view on common clinical practice and external validity of trial results". Upon request the MAH verified that almost all patients (>99%) also fulfilled the full Mayo score definition of moderate to severe disease. In addition, >75% of the patients had a RBS ≥ 1 and SFS >1 at baseline, indicating a relevant amount of symptom burden at inclusion, and in these patients, the results were in line with the whole population.

Patients should also demonstrate inadequate response, loss of response, or intolerance to at least one of the following treatments including, oral aminosalicylates, corticosteroids, immunosuppressants and/or biologic therapies. It is noted that although the doses and timespan defined for corticosteroid and bio-therapy treatment seems adequate, the doses for 5-ASA and thiopurines seem low, especially in active disease. Concomitant stable medication with aminosalicylates, corticosteroids and Mtx were allowed during the study; however, thiopurines were not allowed during the study. At the CHMP's request, the patient description in section 5.1 of the SmPC has been updated accordingly. Since the concomitant use of thiopurines, including 6-mercaptopurin, has not been evaluated in clinical studies, Section 4.4 of the SmPC has been updated to reflect this information at the CHMP's request.

The suggested indication text "Upadacitinib is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent" adequately reflects the intended population and is in line with other products with the same indication.

The primary endpoint used in the studies "clinical remission per adapted mayo score" is a composite endpoint evaluating symptoms and endoscopic features of UC, using 3 parts of the well-known Mayo Score, however with exclusion of the Physician global scale. To be a responder the patient should have a stool frequency score (SFS) ≤1 and not greater than baseline, a rectal bleeding score (RBS) of 0, and endoscopic subscore ≤ 1 (with no friability). Similar (but not identical) endpoints have been used in other studies of approved treatments for UC, however a composite endpoint such as this is not fully in line with the EMA UC GL (CHMP/EWP/18463/2006 rev 1), which states that clinical (symptoms) and endoscopic remission should be evaluated as co-primary endpoints to ensure a beneficial effect over placebo in both parts. However, the sub-scoring levels chosen are consistent with the guideline, which states that a score of 0 or 1 may be used for defining endoscopic healing and symptomatic remission should include cessation of rectal bleeding. The study also started before the publication of the updated EMA guideline, and the endpoint was accepted during the SA, although with some comments.

Nonetheless, some additional analyses were requested to further evaluate the contributions of the different parts of the composite endpoint to the overall results (see further below).

The studies have several ranked secondary outcomes, evaluating different levels of endoscopic remission/response, histologic remission/response, time to response, partial response and for long term also corticosteroid free remission and maintenance of remission. The CHMP/EWP/18463/2006 guideline requires that for a claim of “maintenance of remission”, it needs to be demonstrated that patients being in complete remission at study entry remain in remission throughout a full 52-week study period. As the maintenance study included both responders and remitters after induction, the most relevant endpoints in the assessment of the maintenance study are therefore the key secondary endpoints maintenance of remission and corticosteroid-free remission. The study also includes IBDQ and FACIT-F (a fatigue score) and two new endpoints regarding abdominal pain and bowel urgency.

In induction study M14-234 Substudy 2, 667 patients were screened, and 474 subjects were randomized (319 patients to 45 mg upadacitinib and 155 patients to placebo).

In induction study M14-675, 769 patients were screened, and 522 subjects were randomized (345 patients to 45 mg upadacitinib and 177 patients to placebo).

The numbers of screening failures were between 29% and 35% in the three induction studies. The predominant reason for screening failure was disease activity that did not meet the criteria for moderately to severely active UC.

The percentage of subjects who discontinued study drug in the induction studies was low (3.8% and 3.2% for Upadacitinib 45 mg and 12.3% and 7.5% for placebo). Study drug discontinuation due to lack of efficacy and due to AEs was more frequent in the placebo group.

A total of 1046 patients continued to the M14-234 substudy 3 maintenance study. Among all enrolled subjects, 445 subjects have completed the study, 413 subjects have prematurely discontinued from the study at the time of the data cut-off date, and 188 subjects were still ongoing. More patients in the placebo group discontinued the study drug (65.8%), than in the Upadacitinib 15 mg group (33.1%) and Upadacitinib 30 mg group (21.4%). The main reason for discontinuation were lack of efficacy (49.7%, 23.6% and 7.8%) and adverse events (9.4%, 2.7% and 5.2%) in placebo, Upadacitinib 15 and Upadacitinib 30 group respectively.

Among the 1044 subjects who received at least 1 dose of study drug, 6 were excluded from the ITT population and efficacy analysis due to site non-compliance, which are not supposed to alter the study conclusion. The prespecified primary analysis cohort ITT-A consisted of a subpopulation of the whole ITT population: the first randomized 451 upadacitinib 45 mg QD 8-week induction responders and who were enrolled under the protocol for 52-week maintenance treatment period in Cohort 1. Upon request the MAH clarified that 21 patients (4.7%) from M14-234 substudy 1, 278 patients (61.6%) from M14-234 Substudy 2 and 152 patients (33.7%) from study M14-675 were included in analyses of the maintenance study.

In the induction studies (M14-234 substudy 2 and M14-675 respectively), demographics was well balanced between the treatment groups and similar in both induction studies. The majority of patients were male (62%) and mean age was 42 and 44 years. In study M14-675, 9 persons (1.7%) were <18 years, however none of the participants were <16 years. The MAH does not make any claims for treating adolescents which is acceptable. The majority of patients were white. Baseline disease characteristics were also well balanced between the treatment groups and similar in both induction studies. In the M14-234 substudy 2 and M14-675 study respectively, the mean disease duration was 8.8 and 7.3 years, 52% and 50.7% were Bio IR (intolerant or inadequate responders). Around 30% in both studies had tried >2 biologics.

Around 49% and 52% had a Mayo score >9 at baseline, indicating severe disease. Thus, the study population comprises of patients with an active moderate to severe disease which are in line with the proposed indication. However, the definition of moderate UC in the SmPC as adapted mayo score < 7 was not correct and upon request, the MAH corrected this to a score ≥5 and ≤7.

With respect to concomitant UC medications use, the proportions of subjects taking immunosuppressive treatment at baseline were few, and it should be noted that thiopurines (eg azathioprine and 6-MP) were not allowed during the studies. Immunosuppressive treatment was received by 5 patients (1.1%) in the M14-234 substudy 2 and 4 patients (0.8%) in study M14-675. From the tables regarding concomitant medication provided by the MAH the immunosuppressive treatment are referring mainly to Methotrexate. Since immunosuppressive/immunomodulator treatment in UC usually refers to thiopurines (methotrexate is not commonly used in UC), using the term immunomodulators when describing concomitant medication in the SmPC could therefore be misleading and, at CHMP request, the MAH corrected the wording in the SmPC. Aminosalicylates were taken by 68% in both studies and corticosteroids were taken by 38% and 36% in study M14-234 substudy 2 and M14-675 respectively. The proportion of subjects with concomitant use of systemic corticosteroids, aminosalicylates or immunosuppressive at baseline was evenly distributed across treatment groups. However, since the patients were not allowed to continue with thiopurines, there were some concerns regarding insufficient treatment in the placebo group and thus, the MAH was asked to report the doses of concomitant medication in respective group including the cumulative use of steroids. The results provided show that, although a baseline standard dose of aminosalicylates could not be provided, only a few patients received aminosalicylates as rescue treatment. Regarding corticosteroid treatment, corticosteroids use were balanced across treatment arms at baseline of the induction studies and also at the beginning of the maintenance study. Corticosteroids was as expected the most commonly used rescue therapy and subjects on placebo were more likely to receive rescue corticosteroids (17.4% of subjects) compared to those on 15 mg (4.7%) and 30 mg (4.5%) upadacitinib treatment. Cumulative steroid dose were lowest in the group receiving Upadacitinib 30 mg.

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

Efficacy data and additional analyses

In the induction studies, clinical remission per adapted Mayo score at week 8 were reached in 83/319 (26.1%) and 114/341 (33.5%) in the Upadacitinib 45 mg group and 7/154 (4.8%) and 7/174 (4.1%) in the placebo group. The between group difference was 21.6 % (95% CI 15.8, 27.4 p<0.001) and 29.0% (95% CI 23.2, 34.7, p<0.001) in the M14-234 substudy 2 and the M14-675 study respectively. The results are considered highly statistically significant and clinically relevant and well in line with other approved products with the same indication. In addition, all ranked secondary endpoints were statistically significant (p<0.001) and supports the results from the primary endpoint. According to the EMA UC guideline, efficacy should be apparent on both symptoms and endoscopic evaluation and the secondary endpoints provides several reassurances that a beneficial efficacy is achieved also regarding improvement/healing of the mucosa. Endoscopic improvement (endoscopic mayo score ≤1) was seen in 116/319 (36.3%) vs 11/154 (7.4%), (difference 29.3%, p<0.001) and 150/341 (44%) vs 14/174 (8.3%) (difference 35.7%, p<0.001) and endoscopic remission (endoscopic mayo score 0) was seen in 44/319 (13.7%) vs 2/154 (1.3%), (difference 12.4%, p>0.001) and 62/341 (18.2%) vs 3/174 (1.7%) (difference 16.4%, p<0.001). Also, the strictest endpoint “Mucosal healing”, which required both endoscopic and histological normalisation of the mucosa (Endoscopic score = 0 and Geboes score < 2) were in favour of Upadacitinib. Regarding symptomatic response, the ranked secondary endpoint

“subjects with clinical response per partial adapted Mayo score at Week 2” revealed that symptom relieve was seen in a higher proportion of Upadacitinib treated patients than placebo already at week 2; however, this endpoint allows the patients to still have some rectal bleeding (RBS score ≤1), which is not in line with the EMA UC GL.

Additional analysis provides information regarding both “subjects with RBS of 0 over time” and “subjects with SFS ≤1 over time”. In these analyses 234/319(73.4%) and 235/341 (68.9%) vs 43/154 (27.9%) and 57/174 (32.8%) had no rectal bleeding at week 8 and 191/319 (59.9%) 211/341 (61.9%) vs 40/154 (26.0%) and 34/174 (19.5%) had a SFS ≤1 at week 8. This is reassuring. However, to substantiate the contributions of the clinical (symptomatic) part to the composite endpoint, the MAH was asked to evaluate the numbers and proportions of patients in clinical symptomatic remission (ie patients with stool frequency score ≤1 (and also with the stricter endpoint SFS=0) and a rectal bleeding score 0). In addition, as suggested in the CHMP SA, since RBS and SFS are calculated from subjects’ diaries’ entries as an average of subscores based on 3 days prior to each study visit, the MAH was asked to use an alternate calculation method using worst score instead of average score and/or an alternate timeframe to ensure that the study results are robust. These additional analyses confirms that improvements were observed compared to placebo also when only symptomatic components (SFS and RBS) were evaluated, and the results were similar when using average or worst report of SFS and RBS of 3 days. The MAH initially included information in the proposed SmPC regarding clinical (symptomatic) remission over time, using a definition which not only includes PGA, but also allows the patient to have some rectal bleeding (i.e an EBS score 0-1). At CHMP’s request, a new figure of symptomatic remission over time using the definitions SFS≤1 and EBS=0 was included instead in the SmPC.

The MAH has also analysed two other symptoms as ranked secondary endpoints: abdominal pain and bowel urgency, and both endpoints were statistically in favour for upadacitinib. Although both endpoints could be of clinical relevance, these are new outcome measures. The validation of these endpoints is not considered sufficiently robust for these endpoints to be included in the SmPC. Two PROs, rectal bleeding and stool frequency, are already included in the composite primary endpoint and will provide some information regarding the patient’s symptoms. In addition, both abdominal pain and bowel urgency are in some aspects covered in the questionaries of IBDQ. Regarding the IBDQ, additional analyses provided by the MAH showed that the results are robust, with a difference between the Upadacitinib treated patients and the placebo group seen in all four domain scores (Bowel Symptoms, Systemic Symptoms, Emotional Functioning, and Social Functioning). The result is clinically relevant with 80%–81% of subjects on treatment compared to 44% placebo achieving a change of ≥ 16 points on the IBDQ total score, and 61%–62% of subjects on treatment vs 23%–28% in the placebo group had a total score associated with remission (≥ 170) at Week 8. Similar results were demonstrated in the Phase 3 maintenance study. Regarding the fatigue score FACIT-F, the results seen with the additional treatment policy analysis are in line with the results from the primary analysis and the results seems to be clinically relevant. However, since the validation regarding FACIT-F for UC patients in a long term perspective is sparce, and some aspects of fatigue are already covered within the IBDQ questionaries, additional information regarding a change in fatigue score does not seems to be crucial for the prescribers. Hence, it is not included in the SmPC.

For both the induction studies the data bases were locked before the respective SAPs were finalised.

In total seven subjects were excluded from efficacy analysis based on significant non-compliance at one site. This is not expected to have altered any conclusions and is hence accepted. Randomised subjects who did not receive any study treatment were to be excluded from ITT population; however, no such cases occurred.

The primary estimand for the primary endpoint handles the intercurrent Event (ICE) treatment discontinuations with a treatment policy approach and initiation or dose escalation of UC-related corticosteroids with a composite approach. This is in accordance with the EMA Guideline (CHMP/EWP/18463/2006 Rev.1 Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis) and hence acceptable as the primary estimand. For secondary endpoints, binary endpoints are handled in the same way as the primary whereas for continuous endpoints a hypothetical approach is used for the ICE initiation or dose escalation of UC-related corticosteroids. This is a somewhat inconsistent approach. No true treatment policy estimand has been defined neither for binary nor for continuous endpoints. However, this issue was not further pursued by 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 with sensitivity analyses with a hybrid approach and an observed cases approach. The MMRM method used for continuous endpoints is dependent on the MAR assumption. No sensitivity analysis challenging this assumption has been presented.

Upon request the MAH was asked to define a supplementary estimand for each of the pivotal induction studies for primary and ranked secondary endpoints (both binary and continuous), that handles intercurrent events with a treatment policy approach. The results are consistent with and support the results of the primary analyses of the primary and ranked secondary endpoints.

The overall type I error rate of the primary and the ranked secondary endpoints are controlled using the fixed-sequence multiple testing procedure. This is acceptable.

A beneficial efficacy in favour for Upadacitinib was seen also in all prespecified subgroups, suggesting a beneficial efficacy in different age groups, disease stages and races. Results of the subgroup analysis by bio-IR status shows a clinically important and robust efficacy in both patients with previous failure/intolerance to biological treatment (bio-IR) and patients with previous failure/intolerance to conventional therapy only (bio-non IR). It should be noted that also the bio non-IR group could have received a biologic treatment before (but should not had failed it but could have discontinued it because of insurance reason or remission). Only a few patients in the bio non-IR group had received previous biologic treatment. In the biologic-IR group clinical remission per adapted Mayo score at week 8 was achieved by 17.9% and 29.6% in the Upadacitinib group, and 0.4% and 2.4% in the placebo group. Also, all the key secondary endpoints were in favour for upadacitinib in both groups.

The findings from the two induction studies support the suggested posology of 45 mg upadacitinib for an 8 week induction treatment. See 2.6.3. However, the MAH also suggests additional 8 weeks of 45 mg induction treatment for patients who did not achieve a clinical response at week 8. This suggestion is based on the results from the second part of the induction studies, where 125 patients who did not achieve a clinical response at week 8 on 45 mg Upadacitinib continued to receive the same dose open label for in total 16 weeks. Integrated data from the two pivotal induction studies showed that 48.3% of these patients achieved a clinical response per Adapted Mayo at Week 16 although only 5.6% achieved clinical remission per adapted Mayo score at week 16. Endoscopic response at week 16 were seen in only 14.3% patients. Of the 45 patients that continued to the maintenance phase, 8/24 (33.3%) of the patients randomised to 30mg Upadacitinib and 4/21 (19%) of the patients randomised to 15 mg were in clinical remission at week 52. At CHMP's request, the MAH was asked to explore whether any clinical features could identify patients who may require the 16 week induction treatment. Most of the patients represented a difficult to treat patient population, with 66.4% of patients previous failed biologics. Since some patients without any evidence of initial response at all could benefit of a prolonged treatment, the MAH's suggestion to provide this for all patients who may require it per the physician's judgment based on the condition of each patient was agreed by the CHMP. At CHMP's

request, a cross-reference to available efficacy and safety data in sections 4.8 and 5.1 has been included in section 4.2. The dosing recommendation in the SmPC reads as follows: “For patients who do not achieve adequate therapeutic benefit by week 8, upadacitinib 45 mg once daily may be continued for an additional 8 weeks (see sections 4.8 and 5.1). Upadacitinib should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.”

In the maintenance study, statistically significant (<0.001) and clinically relevant treatment differences between both Upadacitinib doses (15 mg and 30 mg) and placebo were observed for the primary and all key secondary endpoints. The primary endpoint, clinical remission per adapted Mayo score at week 52, was reached by 42.3% of the upadacitinib 15 mg patients, 51.7% of the upadacitinib 30 mg patients and 12.1% of the placebo patients. Difference in proportion between the 15 mg group and the placebo group was 34.7% (CI: 20.3, 54.6, p<0.001) and between the 30 mg group and placebo group 47% (CI: 30.7,63.3, p<0.001). Maintenance of remission was seen in 59.2% of the 15 mg upadacitinib patients, 69.7% of the 30 mg upadacitinib patients and 22.2% of the placebo patients. Similar numbers were seen when analysing corticosteroid-free sustained remission (corticosteroid free for > 90 days before week 52); however this number is based on the population in clinical remission at the end of the induction studies. Upon request, the MAH provided additional information regarding corticosteroid free symptomatic remission and corticosteroid free endoscopic remission. In the whole population, corticosteroid free (for >90 days preceding week 52) symptomatic remission was seen in 17.4% of the placebo patients, 54.7% of the upa 15mg patients and 61.8% of the upa 30 mg patients. Corticosteroid free endoscopic remission (ES=0) was seen in 7/149 (4.9%) of the placebo patients, 34/148 (22.9%) of the upa 15mg patients and 39/154 (25.1%) of the upa 30 mg patients. In patients with corticosteroids at the beginning of the maintenance study, 6/54 (11.1%) of the placebo patients, 22/49 (44.9%) of the upa 15mg patients and 26/49 (53.1%) of the upa 30 mg patients were in corticosteroid free symptomatic remission, and no patient in the placebo group, 6/49 (12.7%) in the upa 15 mg and 9/49 (19.1%) were in corticosteroid free endoscopic remission. These results confirm a clinically relevant effect both in clinical symptoms and mucosal healing. Section 4.2 of the SmPC was updated to state that, in patients who have responded to treatment with upadacitinib, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

To further explore the benefit of maintenance treatment in responders only, the MAH was asked to provide numbers and proportion of patients with adapted mayo response at week 8 (without being in remission) who achieved adapted mayo remission at week 52. Of the patients who were clinical responders and non-remitters at Week 8 of induction studies, 34.4% and 40.8% of patients randomized to upadacitinib 15 mg and 30 mg achieved clinical remission in the maintenance study at Week 52.

The treatment effects of both the 15 mg and 30 mg doses were superior compared with placebo with a difference in point estimate of >20% in both the primary and several ranked secondary endpoints. This supports the MAH’s conclusion that both doses are effective in treating UC. Also, when analysing the subgroups with regards to the primary endpoint, a beneficial efficacy compared to placebo was seen with both doses. For bio IR patients clinical remission was seen in 40.5% and 49.1%. The 30 mg dose appears to provide a slightly better efficacy in the majority of the subgroups; however, in most of the groups the difference in proportion between the two doses were less than 10%. This indicates that a 15 mg maintenance dose is good enough to provide efficacy in the majority of the population, but a higher dose could be of value in some population (e.g., patients with higher disease activity or disease severity). The MAH clarified that patients with high disease burden (severe disease, pancolitis or extra-intestinal manifestations) as well as patients who needed a prolonged induction might benefit from a higher 30 mg maintenance dose. At CHMP’s request, section 4.2 of the SmPC was updated accordingly:

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

- *A dose of 30 mg once daily may be appropriate for some patients, such as those with high disease burden or requiring 16-week induction treatment.*
- *A dose of 30 mg once daily may be appropriate for patients who do not show adequate therapeutic benefit to 15 mg once daily.*
- *The lowest effective dose for maintenance should be considered."*

The estimands and intercurrent events are defined in similar manner as in the induction studies. No true treatment policy estimand has been defined. For the maintenance study, a supplementary estimand was asked to be defined for primary and ranked secondary endpoints (both binary and continuous), that handles intercurrent events with a treatment policy approach using all available data in the analysis and with missing data imputed using MI with occurrence of corticosteroid related ICEs included in the model. The results are consistent with and support the results of the primary analyses of the primary and ranked secondary endpoints. The only exception being the "No abdominal pain" endpoint for which the placebo responder rate increased from 21 % with NRI to 44 % with MI. Upon request the MAH also confirmed that the database lock of the study was 08 Jun 2021.

2.6.7. 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 remission in patients with moderate to severe ulcerative colitis after 8 weeks of induction treatment. A prolonged induction for additional 8 week (in total 16 week) may be useful for patients without an initial response, but the safety concerns regarding e.g herpes zoster should be taken into consideration and the treatment should be stopped if no response is seen at week 16.

In the maintenance study statistically significant (<0.001) and clinically relevant treatment differences between both Upadacitinib doses (15 mg and 30 mg) and placebo were observed for the primary and all key secondary endpoints at week 52. The additional beneficial effect seen with the higher 30 mg dose could be of clinical importance in some patients, and the SmPC has been updated to include a statement that the lowest effective dose for maintenance should be considered.

The CHMP concluded that the efficacy data was adequate to support the new strength of 45mg and the new indication in *the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent*.

The following dosing recommendations were endorsed by the CHMP:

Induction

The recommended induction dose of upadacitinib is 45 mg once daily for 8 weeks. For patients who do not achieve adequate therapeutic benefit by week 8, upadacitinib 45 mg once daily may be continued for an additional 8 weeks (see sections 4.8 and 5.1). Upadacitinib should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

Maintenance

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

- *A dose of 30 mg once daily may be appropriate for some patients, such as those with high disease burden or requiring 16 week induction treatment.*

- *A dose of 30 mg once daily may be appropriate for patients who do not show adequate therapeutic benefit to 15 mg once daily.*

- *The lowest effective dose for maintenance should be considered.*

2.6.1. Clinical safety

Rinvoq was approved for the treatment of rheumatoid arthritis (RA) in December 2019, and subsequently for treatment of psoriatic arthritis (PsA), ankylosing spondylitis (AS) and atopic dermatitis (AD). The recommended dose in RA, PsA and AS is 15 mg once daily, while in AD the recommended dose is either 15 or 30 mg once daily. In UC, the proposed induction dose is 45 mg for 8 weeks (with the option to prolong induction for additional 8 weeks) followed by 15 or 30 mg as maintenance treatment. Thus, the induction dose proposed for UC is higher than the recently approved dose.

The global clinical development program includes a Phase 2b dose-ranging induction study (Study M14-234 Substudy 1), two Phase 3 induction studies (Study M14-675 and Study M14-234 Substudy 2), a Phase 3 maintenance study (Study M14 234 Substudy 3, currently ongoing), and a Phase 3 long-term extension (LTE) study (Study M14-533). A summary of the overall clinical studies is provided in the efficacy section.

The safety profile of upadacitinib was characterized based on the following datasets:

- Placebo-Controlled Induction (PC_IND) Analysis Set: to evaluate induction dosing in subjects who received up to an 8-week treatment with upadacitinib 45 mg or placebo;

- Extended Induction (EXT_IND) Analysis Set: to evaluate induction dosing in subjects who received up to a 16-week treatment with upadacitinib 45 mg; and

- Responders Maintenance (RESP_MAIN) Analysis Set: to evaluate maintenance dosing in subjects who responded to upadacitinib 45 mg 8-week induction treatment and were re-randomized to upadacitinib 15 mg or 30 mg or placebo during the maintenance period. This set also evaluates long-term data of maintenance dosing with continuous exposure to upadacitinib 15 mg and 30 mg during the maintenance period through the LTE period in subjects who responded to either upadacitinib 45 mg 8-week or 16-week induction treatment for which data were censored at dose switching.

The patients are assigned to the following cohorts based on the treatment they achieved in the induction studies:

- Cohort 1: Responders on 8-week induction with UPA 15 mg, 30 mg, 45 mg, re-randomised to UPA 15 mg, UPA 30 mg or placebo in the maintenance phase
- Cohort 2: Responders on 8-week induction with placebo, continuing placebo in the maintenance phase
- Cohort 3: Responders on 16-week induction with upadactinib 45 mg, re-randomised to UPA 15 mg or UPA 30 mg in the maintenance phase
- Cohort 4: Responders on 8-week induction with UPA 7.5 mg, continuing UPA 7,5 mg in the maintenance phase

2.6.1.1. Patient exposure

A total of 1,304 subjects received at least 1 dose of upadacitinib in the UC global Phase 2b and Phase 3 studies, representing a total of 1,821.1 patient-years (PY) of upadacitinib exposure included in the safety analyses.

For induction treatment, a total of 987 subjects received at least 1 dose of upadacitinib 45 mg, representing a total of 169.2 PY of upadacitinib 45 mg exposure.

Among subjects who responded to upadacitinib 45 mg induction or extended induction treatment, a total of 285 subjects received at least 1 dose of upadacitinib 15 mg as maintenance treatment, representing a total of 316.9 PY of combined upadacitinib exposure during maintenance treatment and any additional exposure during LTE treatment while maintaining the same dose (*Table 46*)

Likewise, among subjects who responded to upadacitinib 45 mg induction or extended induction treatment, a total of 291 subjects received at least 1 dose of upadacitinib 30 mg as maintenance treatment, representing a total of 304.0 PY of combined upadacitinib exposure during maintenance treatment and any additional exposure during LTE treatment while maintaining the same dose. Of the 576 subjects who received either upadacitinib 15 mg or 30 mg maintenance treatment, 242 (84.9%) and 237 (81.4%) had exposure to upadacitinib 15 mg or upadacitinib 30 mg treatment, respectively, for at least 26 weeks, and 131 (46.0%) and 137 (47.1%) had exposure to upadacitinib 15 mg or upadacitinib 30 mg treatment, respectively, for at least 52 weeks.

Table 46. Number and Percentage of Subjects Exposed to Study Drug by Duration Intervals (RESP_MAIN Analysis Set)

Cumulative Duration	M14-234 SS3 (Cohort 1)[a]			M14-234 SS3 (Cohorts 1 and 3)[b]	
	Placebo (N = 245)	Upadacitinib 15 mg QD (N = 250)	Upadacitinib 30 mg QD (N = 251)	Upadacitinib 15 mg QD (N = 285)	Upadacitinib 30 mg QD (N = 291)
	n (%)				
≥ 1 dose	245 (100)	250 (100)	251 (100)	285 (100)	291 (100)
≥ 4 weeks	241 (98.4)	249 (99.6)	250 (99.6)	284 (99.6)	290 (99.7)
≥ 8 weeks	204 (83.3)	232 (92.8)	242 (96.4)	284 (99.6)	278 (95.5)
≥ 12 weeks	175 (71.4)	223 (89.2)	233 (92.8)	281 (98.6)	268 (92.1)
≥ 16 weeks	152 (62.0)	215 (86.0)	226 (90.0)	273 (95.8)	259 (89.0)
≥ 26 weeks (about 6 months)	116 (47.3)	190 (76.0)	208 (82.9)	242 (84.9)	237 (81.4)
≥ 39 weeks (about 9 months)	75 (30.6)	143 (57.2)	167 (66.5)	188 (66.0)	190 (65.3)
≥ 52 weeks (about 1 year)	37 (15.1)	65 (26.0)	86 (34.3)	131 (46.0)	137 (47.1)
≥ 78 weeks (about 18 months)	0	0	0	58 (20.4)	70 (24.1)
≥ 104 weeks (about 2 years)	0	0	0	24 (8.4)	16 (5.5)
≥ 130 weeks (about 2.5 years)	0	0	0	16 (5.6)	5 (1.7)
≥ 156 weeks (about 3 years)	0	0	0	15 (5.3)	1 (0.3)
≥ 208 weeks (about 4 years)	0	0	0	3 (1.1)	0
Mean duration (weeks)	27.3	38.1	41.3	58.0	54.5
Duration in PY	128.1	182.4	198.7	316.9	304.0

a. Only exposure from Study M14-234 Substudy 3 (Cohort 1) are included.

b. All exposure from the 45 mg responders who entered into Study M14-234 Substudy 3 and any additional upadacitinib exposure for these subjects who rolled over to Study M14-533 while maintaining the same DB dose are included.

Notes: The duration (weeks) is defined as (last dose date – first dose date + 1 – excluded time)/7.

The first dose date is first dose of study drug (placebo or upadacitinib) during the maintenance period.

For Cohort 1, the last dose date is last dose of study drug received in Study M14-234 Substudy 3. For Cohorts 1 and 3, for subjects who enter Study M14-533 on the same upadacitinib dose they received during Study M14-234 Substudy 3, the last dose date is the last date of entry dose in Study M14-533 or last dose prior to the subject changing their dose; for all other subjects, the last dose date is last dose of study drug received in Study M14-234 Substudy 3.

2.6.1.2. Adverse events

2.6.1.2.1. Overview of adverse events

Induction phase

In the PC_IND Analysis Set, the percentage of subjects with TEAEs overall was similar in the upadacitinib 45 mg and placebo groups (Table 47).

Table 47. Overview of Subjects with Treatment-Emergent Adverse Events (PC_IND Analysis Set)

Subjects With	Placebo (N = 378) n (%) [SSA %]	Upadacitinib 45 mg QD (N = 719) n (%) [SSA %]	Treatment Comparison (95% CI)[a] Upadacitinib 45 mg QD – Placebo
Any AE	199 (52.6) [52.2]	398 (55.4) [55.5]	
COVID-19 infection-related AE	0	1 (0.1) [0.1]	0.1 (–0.5, 0.8)
Any SAE	22 (5.8) [5.7]	22 (3.1) [3.1]	–2.6 (–5.3, 0.1)
Any AE leading to discontinuation of study drug	27 (7.1) [7.1]	17 (2.4) [2.5]	–4.7 (–7.5, –1.8)
Any severe AE	28 (7.4) [7.2]	22 (3.1) [3.1]	–4.1 (–7.0, –1.2)
Any AE with reasonable possibility of being related to study drug[b]	65 (17.2) [16.7]	189 (26.3) [26.4]	9.7 (4.9, 14.6)
Any AE leading to death	0	0	0.0
Deaths[c]	0	0	0.0

a. SSA risk difference between treatment groups.

b. As assessed by investigator.

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

Adverse events by induction period length

In the EXT_IND Analysis Set, the EAERs of TEAEs overall, SAEs, severe TEAEs, and TEAEs with a reasonable possibility of being related to study drug in the upadacitinib 45 mg group through Week 16 were similar to or lower than rates observed during the initial 8 weeks of treatment (Table 48).

Table 48. Overview of Treatment-Emergent Adverse Events per 100 PY (EXT_IND Analysis Set)

	Upadacitinib 45 mg QD (N = 127)	
	End of DB Induction[a] (Week 0 – Week 8)	**End of OL Extended Induction[b] (Week 0 – Week 16)**
EAER	**(PY = 20.0) E (E/100 PY)**	**(PY = 39.1) E (E/100 PY)**
Any AE	133 (665.0)	259 (662.2)
Any COVID-19 infection-related AE	0	1 (2.6)
Any SAE	4 (20.0)	7 (17.9)
Any AE leading to discontinuation of study drug	0	2 (5.1)
Any severe AE	2 (10.0)	3 (7.7)
Any AE with reasonable possibility of being related to study drug[c]	45 (225.0)	92 (235.2)
Any AE leading to death	0	0
EAIR	**n/PY**	**n/PY**
Deaths[d]	0/20.0	0/39.1

a. All events and exposure time from Part 1 of the induction studies (for the EXT_IND Analysis Set).

b. All events and exposure time from Parts 1 and 2 of the induction studies (for the EXT_IND Analysis Set).

c. As assessed by investigator.

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

Note: PY is defined as the sum of the study drug duration of all subjects in the respective time periods (8-week induction period [for Week 8], and 8-week induction period plus 8-week extended induction period [for Week 16]) normalized by 365.25.

Maintenance phase

Between the RESP_MAIN and ALL_TRT Analysis Sets and across upadacitinib treatment groups, the rates of overall AEs and most AESIs were generally similar or there was no consistent trend based on induction period length, *Table 49* and

Table 50 respectively. The rates of TEAEs of anaemia were higher in subjects who received up to 16 weeks of induction treatment compared to those who received up to 8 weeks.

Table 49. TEAEs by induction period length (responders maintenance analysis set)

MedDRA 23.0 System Organ Class Preferred Term	8 Weeks - M14-234 Substudy 3 (Cohorts 1 and 3) - UPA 15 mg QD (N=250) (PYs=284.0) Events(E/100 PYs) [SSA E/100 PYs]	8 Weeks - M14-234 Substudy 3 (Cohorts 1 and 3) - UPA 30 mg QD (N=251) (PYs=267.3) Events(E/100 PYs) [SSA E/100 PYs]	16 Weeks - M14-234 Substudy 3 (Cohorts 1 and 3) - UPA 15 mg QD (N=35) (PYs=32.9) Events(E/100 PYs) [SSA E/100 PYs]	16 Weeks - M14-234 Substudy 3 (Cohorts 1 and 3) - UPA 30 mg QD (N=40) (PYs=36.7) Events(E/100 PYs) [SSA E/100 PYs]
Any adverse event	836 (294.4) [293.8]	795 (297.5) [306.3]	76 (231.2) [228.7]	124 (337.8) [339.4]

Table 50. AESIs by induction period length (responders maintenance analysis set)

	8 Weeks -M14-234 Substudy 3 (Cohorts 1 and 3) [B]- UPA 15 mg QD (N=250) n/PYs (n/100 PYs) [SSA n/100 PYs]	8 Weeks -M14-234 Substudy 3 (Cohorts 1 and 3) [B]- UPA 30 mg QD (N=251) n/PYs (n/100 PYs) [SSA n/100 PYs]	16 Weeks -M14-234 Substudy 3 (Cohorts 1 and 3) [B]- UPA 15 mg QD (N=35) n/PYs (n/100 PYs) [SSA n/100 PYs]	16 Weeks -M14-234 Substudy 3 (Cohorts 1 and 3) [B]- UPA 30 mg QD (N=40) n/PYs (n/100 PYs) [SSA n/100 PYs]
Any serious infections	10/275.3 (3.6) [3.7]	9/263.7 (3.4) [3.3]	2/32.0 (6.2) [6.3]	3/35.5 (8.4) [8.6]
Any opportunistic infection excluding tuberculosis and herpes zoster	2/283.2 (0.7) [0.7]	1/267.2 (0.4) [0.4]	0/32.9	0/36.7
Any active tuberculosis	0/284.0	0/267.3	0/32.9	0/36.7
Any herpes zoster	17/264.0 (6.4) [6.3]	14/257.5 (5.4) [5.3]	1/32.4 (3.1) [2.9]	2/35.6 (5.6) [5.6]
Any adjudicated gastrointestinal perforations	0/284.0	0/267.3	0/32.9	0/36.7
Any anemia	14/272.4 (5.1) [5.5]	12/258.9 (4.6) [4.7]	2/31.5 (6.3) [6.4]	3/35.0 (8.6) [8.4]
Any neutropenia	10/273.9 (3.7) [3.7]	18/251.4 (7.2) [6.9]	1/32.1 (3.1) [3.0]	2/35.8 (5.6) [5.6]
Any lymphopenia	9/278.0 (3.2) [3.3]	7/263.9 (2.7) [3.0]	0/32.9	0/36.7
Any creatine phosphokinase (CPK) elevation	15/262.5 (5.7) [5.7]	24/249.7 (9.6) [9.2]	3/29.6 (10.1) [10.2]	4/34.8 (11.5) [11.6]
Any hepatic disorder	22/263.1 (8.4) [8.7]	15/258.2 (5.8) [5.8]	0/32.9	3/34.8 (8.6) [8.8]
Any renal dysfunction	1/284.0 (0.4) [0.4]	1/267.3 (0.4) [0.3]	0/32.9	0/36.7
Any malignancy	1/284.0 (0.4) [0.4]	7/265.0 (2.6) [2.6]	0/32.9	1/35.2 (2.8) [3.1]
Any malignancies excluding non-melanoma skin cancer (NMSC)	1/284.0 (0.4) [0.4]	3/267.2 (1.1) [1.2]	0/32.9	0/36.7
Any NMSC	0/284.0	4/265.1 (1.5) [1.4]	0/32.9	1/35.2 (2.8) [3.1]
Any lymphoma	0/284.0	0/267.3	0/32.9	0/36.7
Any adjudicated MACE *	0/284.0	1/266.5 (0.4) [0.4]	0/32.9	1/35.1 (2.9) [3.1]
Any adjudicated VTE **	2/280.4 (0.7) [0.6]	2/267.2 (0.7) [0.7]	1/32.9 (3.0) [2.9]	0/36.7

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 period or until one day prior to the first dose of study drug in the LTE period (for Cohort 1) and up to 30 days after the last dose of study drug in the maintenance or LTE period or until one day prior to the first dose of study drug in which the subject's dose was changed during the LTE period.
n/100PYs = Number of subjects per 100 patient-years.
[B] Includes 15 mg and 30 mg subjects from Cohort 1 plus M14-234 substudy 2 (Part 2) and M14-675 (Part 2) 45/45 mg responders who were re-randomized to 15 mg or 30 mg and entered into M14-234 substudy 3 (Cohort 3) and additional time from M14-533 while subject remained on same double-blind dose.
SSA = Study-size adjusted.
* MACE: Major Adverse Cardiovascular Events, defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.
** VTE: Venous Thromboembolic Events, defined as deep vein thrombosis (DVT) and pulmonary embolism (PE)(fatal and non-fatal).

In Cohort 1 of the RESP_MAIN Analysis Set, the EAERs of TEAE categories, including 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 lower in both upadacitinib treatment groups compared with the placebo group (*Table 51*). There was a higher rate of TEAEs leading to discontinuation of study drug in the upadacitinib 30 mg compared with the upadacitinib 15 mg group.

In Cohorts 1 and 3 of the RESP_MAIN Analysis Set, the EAERs of the TEAE categories were generally comparable between the upadacitinib 15 mg and 30 mg groups (*Table 51*).

There was 1 death that occurred within 30 days after the subject's last dose of study drug (i.e., treatment-emergent). The subject received upadacitinib 15 mg in Study M14-234 Substudy 3 and rolled over to LTE Study M14-533 while maintaining the same dose. The death was due to a brain injury and was considered by the investigator to have no reasonable possibility of being related to study drug.

Table 51. Overview of Treatment-Emergent Adverse Events per 100 PY (RESP_MAIN Analysis Set)

	M14-234 SS3 (Cohort 1)[a]					M14-234 SS3 (Cohorts 1 and 3)[c]	
				Differences[b]			
	Placebo (N = 245) (PY = 128.1)	**Upadacitinib 15 mg QD (N = 250) (PY = 182.4)**	**Upadacitinib 30 mg QD (N = 251) (PY = 198.7)**	**Upadacitinib 15 mg QD – Placebo**	**Upadacitinib 30 mg QD – Placebo**	**Upadacitinib 15 mg QD (N = 285) (PY = 316.9)**	**Upadacitinib 30 mg QD (N = 291) (PY = 304.0)**
EAER	**E (E/100 PY) [SSA E/100 PY]**			**Risk Difference (95% CI)**		**E (E/100 PY) [SSA E/100 PY]**	
Any AE	652 (509.0) [507.1]	599 (328.4) [327.5]	636 (320.0) [318.9]			912 (287.8) [287.2]	919 (302.3) [310.0]
Any COVID-19 infection-related AE	10 (7.8) [8.3]	4 (2.2) [2.2]	10 (5.0) [5.1]	–6.1 (–11.6, –0.5)	–3.2 (–9.2, 2.8)	13 (4.1) [4.2]	22 (7.2) [6.9]
Any SAE	28 (21.9) [22.0]	24 (13.2) [13.2]	21 (10.6) [10.6]	–8.9 (–18.6, 0.9)	–11.4 (–20.8, –2.1)	34 (10.7) [10.6]	34 (11.2) [11.4]
Any AE leading to discontinuation of study drug	26 (20.3) [20.1]	6 (3.3) [3.3]	12 (6.0) [6.1]	–16.8 (–25.0, –8.6)	–14.1 (–22.6, –5.6)	14 (4.4) [4.6]	16 (5.3) [5.3]
Any severe AE	29 (22.6) [22.6]	18 (9.9) [9.7]	22 (11.1) [11.1]	–13.0 (–22.4, –3.6)	–11.5 (–21.0, –2.0)	29 (9.2) [9.0]	32 (10.5) [10.7]
Any AE with reasonable possibility of being related to study drug[d]	190 (148.3) [145.0]	170 (93.2) [94.6]	219 (110.2) [109.5]	–50.4 (–75.6, –25.3)	–35.5 (–60.7, –10.2)	271 (85.5) [85.1]	309 (101.7) [104.8]
Any AE leading to death	0	0	0	0.0	0.0	1 (0.3) [0.2]	0

a. Includes subjects who responded to upadacitinib 45 mg in Studies M14-234 Substudy 1, M14-234 Substudy 2, or M14-675 and were subsequently re-randomized to upadacitinib 15 mg or 30 mg or placebo in Study M14-234 Substudy 3 (Cohort 1) and received at least 1 dose of study drug. Only exposure and events from Study M14-234 Substudy 3 (Cohort 1) are included.

b. SSA risk differences between treatment groups.

c. Includes subjects who responded to upadacitinib 45 mg in Studies M14-234 Substudy 1, M14-234 Substudy 2, or M14-675 and were subsequently re-randomized to upadacitinib 15 mg or 30 mg in Study M14-234 Substudy 3 (Cohorts 1 or 3) and received at least 1 dose of study drug. All exposure and events from the 45 mg responders who entered into Study M14-234 Substudy 3 and any additional upadacitinib exposure and events for these subjects who rolled over to Study M14-533 while maintaining the same DB dose are included.

d. As assessed by investigator.

In the ALL_TRT Analysis Set (ALL_TRT[subj] categorization), overall, the EAERs 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 not notably different between the upadacitinib 45 mg/15 mg and upadacitinib 45 mg/30 mg cohorts (Table 52).

Two deaths, both treatment-emergent, were reported. One death occurred in the upadacitinib 45 mg/15 mg cohort and is described in the RESP_MAIN Analysis Set section above. The other death (due to pancreas adenocarcinoma) occurred in a subject who received upadacitinib 30 mg for induction, upadacitinib 15 mg for maintenance, and upadacitinib 30 mg in the LTE study.

Table 52. Overview of TEAEs per 100 PY (ALL_TRT Analysis Set; ALL_TRT$_{[subj]}$ Categorization)

	Induction Dose UPA 45 mg QD[a]		
	UPA 45 mg/PBO (N = 245) (PY = 358.9)	**UPA 45 mg/15 mg (N = 306) (PY = 466.1)**	**UPA 45 mg/30 mg (N = 307) (PY = 443.4)**
EAER		**E (E/100 PY)**	
Any AE	1530 (426.3)	1507 (323.3)	1614 (364.0)
Any COVID-19 infection-related AE	29 (8.1)	19 (4.1)	31 (7.0)
Any SAE	52 (14.5)	61 (13.1)	49 (11.1)
Any AE leading to discontinuation of study drug	23 (6.4)	24 (5.1)	21 (4.7)
Any severe AE	55 (15.3)	45 (9.7)	50 (11.3)
Any AE with reasonable possibility of being related to study drug[b]	456 (127.1)	507 (108.8)	531 (119.8)
Any AE leading to death	0	1 (0.2)	0
EAIR		**n/PY (n/100 PY)**	
Deaths[c]	0/358.9	1/466.1 (0.2)	0/443.4
Occurring ≤ 30 days after last dose of study drug	0/358.9	1/466.1 (0.2)	0/443.4
Occurring > 30 days after last dose of study drug	0/358.9	0/466.1	0/443.4
COVID-19 infection-related deaths	0/358.9	0/466.1	0/443.4

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. As assessed by investigator.

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

2.6.1.2.2. Common adverse events

Induction phase

In the PC_IND Analysis Set, the most frequent TEAEs by SOC (≥ 10% of subjects) were infections and infestations, GI disorders, skin and subcutaneous tissue disorders, and investigations in the upadacitinib 45 mg group, and GI disorders, infections and infestations, and musculoskeletal and connective tissue disorders in the placebo group.

The most frequently reported TEAEs (≥ 5% of subjects) were acne and blood CPK increased in the upadacitinib 45 mg group and worsening of UC in the placebo group (Table 53).

Table 53. TEAEs Reported in ≥ 2% of Subjects in Any Group by Decreasing Frequency (PC_IND Analysis Set)

MedDRA 23.0 Preferred Term	Placebo (N = 378) n (%) [SSA %]	Upadacitinib 45 mg QD (N = 719) n (%) [SSA %]	Treatment Comparison (95% CI)[a] Upadacitinib 45 mg QD – Placebo
Any AE	199 (52.6) [52.2]	398 (55.4) [55.5]	
Acne	4 (1.1) [1.1]	40 (5.6) [5.5]	4.4 (2.4, 6.5)
Blood creatine phosphokinase increased	5 (1.3) [1.4]	37 (5.1) [5.2]	3.8 (1.7, 5.9)
Nasopharyngitis	13 (3.4) [3.4]	31 (4.3) [4.3]	1.0 (–1.4, 3.4)
Headache	18 (4.8) [4.5]	26 (3.6) [3.7]	–0.8 (–3.4, 1.7)
Anaemia	16 (4.2) [4.2]	22 (3.1) [3.0]	–1.2 (–3.6, 1.3)
Neutrophil count decreased	0	20 (2.8) [2.8]	2.8 (1.4, 4.1)
Pyrexia	6 (1.6) [1.6]	18 (2.5) [2.5]	0.9 (–0.9, 2.7)
Rash	2 (0.5) [0.5]	17 (2.4) [2.4]	1.8 (0.3, 3.3)
Folliculitis	2 (0.5) [0.5]	16 (2.2) [2.2]	1.7 (0.3, 3.1)
Upper respiratory tract infection	7 (1.9) [1.9]	16 (2.2) [2.2]	0.3 (–1.6, 2.1)
Colitis ulcerative	35 (9.3) [9.2]	13 (1.8) [1.9]	–7.3 (–10.4, –4.2)
Arthralgia	11 (2.9) [3.0]	10 (1.4) [1.4]	–1.6 (–3.6, 0.4)
Nausea	9 (2.4) [2.3]	7 (1.0) [1.0]	–1.4 (–3.1, 0.4)

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.

Prolonged induction

In the EXT_IND Analysis Set, the EAERs for the most frequently reported TEAEs (≥ 10 E/100 PY) in the upadacitinib 45 mg group through Week 16 were generally similar to or not higher than rates reported during the initial 8 weeks of treatment (Table 54); exceptions included herpes zoster, worsening of UC, and hepatic enzyme increased, where rates were higher through Week 16 compared with Week 8.

Table 54. TEAEs Reported in ≥ 10 Events per 100 PY at Week 16 with Upadacitinib 45 mg Treatment by Decreasing Frequency (EXT_IND Analysis Set)

	Upadacitinib 45 mg QD (N = 127)	
MedDRA 23.0 Preferred Term	**End of DB Induction[a] (Week 0 – Week 8) (PY = 20.0) E (E/100 PYS)**	**End of OL Extended Induction[b] (Week 0 – Week 16) (PY = 39.1) E (E/100 PYS)**
Any AE	133 (665.0)	259 (662.2)
Blood creatine phosphokinase increased	8 (40.0)	16 (40.9)
Anaemia	10 (50.0)	15 (38.4)
Pyrexia	6 (30.0)	10 (25.6)
Headache	4 (20.0)	9 (23.0)
Acne	7 (35.0)	8 (20.5)
Colitis ulcerative	2 (10.0)	7 (17.9)
Nasopharyngitis	5 (25.0)	7 (17.9)
Herpes zoster	1 (5.0)	6 (15.3)
Abdominal pain	2 (10.0)	5 (12.8)
Neutrophil count decreased	3 (15.0)	5 (12.8)
Hepatic enzyme increased	1 (5.0)	4 (10.2)
Alanine aminotransferase increased	2 (10.0)	3 (7.7)
Chest discomfort	2 (10.0)	3 (7.7)
Gastrooesophageal reflux disease	2 (10.0)	3 (7.7)
Hypertension	2 (10.0)	3 (7.7)
Lymphopenia	2 (10.0)	3 (7.7)
Anxiety	2 (10.0)	2 (5.1)
Constipation	2 (10.0)	2 (5.1)
Folliculitis	2 (10.0)	2 (5.1)
Oropharyngeal pain	2 (10.0)	2 (5.1)
Palpitations	2 (10.0)	2 (5.1)
Pustule	2 (10.0)	2 (5.1)
Urinary tract infection	2 (10.0)	2 (5.1)

a. All events and exposure time from Part 1 of the induction studies (for the EXT_IND Analysis Set).

b. All events and exposure time from Parts 1 and 2 of the induction studies (for the EXT_IND Analysis Set).

Note: EAERs are displayed by decreasing frequency in the End of OL Extended Induction column.

Maintenance phase

In Cohort 1 of the RESP_MAIN Analysis Set, the most frequent TEAEs by SOC (≥ 25 E/100 PY) were infections and infestations, investigations, and GI disorders in the upadacitinib 15 mg group, infections and infestations, investigations, GI disorders, and skin and subcutaneous tissue disorders in the upadacitinib 30 mg group, and GI disorders, infections and infestations, musculoskeletal and connective tissue disorders, and skin and subcutaneous tissue disorders in the placebo group.

The most frequently reported TEAEs (≥ 10 E/100 PY) were nasopharyngitis and worsening of UC in the upadacitinib 15 mg group, nasopharyngitis and blood CPK increased in the upadacitinib 30 mg group, and worsening of UC, arthralgia, nasopharyngitis, and anaemia in the placebo group. In Cohorts 1 and 3 of the RESP_MAIN Analysis Set, the overall pattern observed of most common TEAEs by SOC and by PT for the upadacitinib groups was generally similar to that described above for Cohort 1.

2.6.1.2.3. Adverse events proposed for labelling

Based on the induction data, the MAH proposes to add 2 new ADRs: rash and lymphopenia (Table 55).

Based on the maintenance and long-term data, the MAH proposes to add 2 new ADRs: rash and hyperlipidemia (Table 56).

Table 55. ADRs Identified During the UC Induction Treatment Period (PC_IND Analysis Set)

System Organ Class	Preferred Term or Grouped Term	Upadacitinib 45 mg QD N = 719 n (%)	Placebo N = 378 n (%)
Blood and lymphatic system disorders	Lymphopenia	18 (2.5)	2 (0.5)
	Neutropenia	33 (4.6)	1 (0.3)
Infections and infestations	Folliculitis	16 (2.2)	2 (0.5)
	Herpes simplex	15 (2.1)	1 (0.3)
	Herpes zoster	4 (0.6)	0
	Pneumonia	4 (0.6)	1 (0.3)
	Upper respiratory tract infection	60 (8.3)	26 (6.9)
Skin and subcutaneous tissue disorders	Acne	45 (6.3)	5 (1.3)
	Rash	25 (3.5)	3 (0.8)
General disorders and administration site conditions	Pyrexia	18 (2.5)	6 (1.6)
Investigations	Blood CPK increased	37 (5.1)	5 (1.3)

Table 56. ADRs Identified During the UC Maintenance Treatment Period (RESP_MAIN Analysis Set; Cohort 1)

System Organ Class	Preferred Term or Grouped Term	Upadacitinib 15 mg QD N = 250 n (%)	Upadacitinib 30 mg QD N = 251 n (%)	Placebo N = 245 n (%)
Blood and lymphatic system disorder	Neutropenia	7 (2.8)	15 (6.0)	5 (2.0)
Infections and infestations	Folliculitis	4 (1.6)	9 (3.6)	4 (1.6)
	Influenza	7 (2.8)	8 (3.2)	3 (1.2)
	Herpes simplex	6 (2.4)	8 (3.2)	3 (1.2)
	Herpes zoster	11 (4.4)	10 (4.0)	0
	Upper respiratory tract infection	41 (16.4)	50 (19.9)	44 (18.0)
Metabolism and nutrition disorders	Hypercholesterolaemia	6 (2.4)	10 (4.0)	2 (0.8)
	Hyperlipidaemia	6 (2.4)	6 (2.4)	0
Skin and subcutaneous tissue disorders	Rash	12 (4.8)	13 (5.2)	9 (3.7)
Investigations	Blood CPK increased	14 (5.6)	19 (7.6)	5 (2.0)
	ALT increased	7 (2.8)	6 (2.4)	1 (0.4)
	AST increased	9 (3.6)	4 (1.6)	2 (0.8)

2.6.1.2.4. Adverse events of special interest

An overall summary of the adverse events of special interest is provided below.

Table 57. Key Risks of Upadacitinib in Induction and Maintenance Treatment of Moderately to Severely Active UC

	Induction (Week 8) (PBO-Controlled Period)		Extended Induction (Week 16)	Maintenance (Week 52) (PBO-Controlled Period)			Maintenance + LTE	
	Placebo (N = 378) n (%)	UPA 45 mg QD (N = 719) n (%)	UPA 45 mg QD (N = 127) (PY = 39.1) n (E/100 PY or n/100 PY)	Placebo (N = 245) (PY = 128.1) n (E/100 PY or n/100 PY)	UPA 15 mg QD (N = 250) (PY = 182.4) n (E/100 PY or n/100 PY)	UPA 30 mg QD (N = 251) (PY = 198.7) n (E/100 PY or n/100 PY)	UPA 15 mg QD (N = 285) (PY = 316.9) n (E/100 PY or n/100 PY)	UPA 30 mg QD (N = 291) (PY = 304.0) n (E/100 PY or n/100 PY)
Serious infections	5 (1.3)	9 (1.3)	1 (2.6)	8 (6.2)	9 (4.9)	6 (3.0)	13 (4.1)	12 (3.9)
Herpes zoster	0	4 (0.6)	6 (15.3)	0	11 (6.0)	12 (6.0)	18 (5.7)	19 (6.3)
Malignancies excl NMSC	0	0	0/39.1*	1 (0.8)*	1 (0.5)*	2 (1.0)*	1/316.9 (0.3)*	3/303.9 (1.0)*
NMSC	0	0	0/39.1*	0*	0*	3 (1.5)*	0/316.9*	5/300.3 (1.7)*
MACE	0	0	0/39.1*	1 (0.8)*	0*	1 (0.5)*	0/316.9*	2/301.5 (0.7)*
VTE	1 (0.3)	1 (0.1)	0/39.1*	0*	2 (1.1)*	2 (1.0)*	3/313.3 (1.0)*	2/303.9 (0.7)*

CSR = clinical study report; EAER = exposure-adjusted event rate; EAIR = exposure-adjusted incidence rate; LTE = long-term extension; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; PBO = placebo; PY = patient year; QD = once daily; UC = ulcerative colitis; UPA = upadacitinib; VTE = venous thromboembolic event

* EAIR.

Notes: Subgroup analysis was performed in subjects who received > 1 prior biologic and those who received ≤ 1 prior biologic, but not included here.

Sample Size adjusted rates were similar to EAER or EAIR so not included in table.

Herpes zoster

In the PC_IND Analysis Set, the percentage of subjects with TEAEs of herpes zoster was 0.6% in the upadacitinib 45 mg group; no subject reported a TEAE of herpes zoster in the placebo group. There were 4 cases reported: 3 herpes zoster and 1 disseminated herpes zoster (cutaneous, unknown number of dermatomes, resolved after 12 days while upadacitinib was continued). According to the study physician, none were considered severe or serious.

In the EXT_IND Analysis Set, the EAER of TEAEs of herpes zoster in the upadacitinib 45 mg group increased with longer duration of exposure to study drug (15.3 E/100 PY [6 events cumulative] during 16 weeks of treatment compared with 5.0 E/100 PY [1 event] during the initial 8 weeks of treatment). All events of herpes zoster were reported as involving only 1 dermatome. None of the events were considered severe or serious or led to discontinuation of study drug.

In Cohorts 1 and 3 of the RESP_MAIN Analysis Set, the EAER of herpes zoster was the same in the upadacitinib 15 mg and 30 mg groups; no event was reported in the placebo group (Table 58).

Table 58. Treatment-Emergent Herpes Zoster EAER per 100 PY (RESP_MAIN Analysis Set)

System Organ Class MedDRA 23.0 Preferred Term	M14-234 SS3 (Cohort 1)[a]			M14-234 SS3 (Cohorts 1 and 3)[b]	
	Placebo (N = 245) (PY = 128.1)	Upadacitinib 15 mg QD (N = 250) (PY = 182.4)	Upadacitinib 30 mg QD (N = 251) (PY = 198.7)	Upadacitinib 15 mg QD (N = 285) (PY = 316.9)	Upadacitinib 30 mg QD (N = 291) (PY = 304.0)
	E (E/100 PY) [SSA E/100 PY]				
Any TEAE	0	11 (6.0) [5.8]	12 (6.0) [6.1]	18 (5.7) [5.6]	19 (6.3) [6.0]
Infections and infestations	0	11 (6.0) [5.8]	12 (6.0) [6.1]	18 (5.7) [5.6]	18 (5.9) [5.7]
Herpes zoster	0	10 (5.5) [5.3]	11 (5.5) [5.5]	16 (5.0) [5.0]	17 (5.6) [5.4]
Herpes zoster meningitis	0	0	1 (0.5) [0.5]	0	1 (0.3) [0.3]
Herpes zoster oticus	0	0	0	1 (0.3) [0.3]	0
Varicella zoster virus infection	0	1 (0.5) [0.5]	0	1 (0.3) [0.3]	0
Nervous system disorders	0	0	0	0	1 (0.3) [0.3]
Post herpetic neuralgia	0	0	0	0	1 (0.3) [0.3]

a. Only exposure and events from Study M14-234 Substudy 3 (Cohort 1) are included.

b. All exposure and events from the 45 mg responders who entered into Study M14-234 Substudy 3 and any additional upadacitinib exposure and events for these subjects who rolled over to Study M14-533 while maintaining the same DB dose are included.

Venous thromboembolism

Subjects were excluded from the upadacitinib UC global Phase 2b and Phase 3 studies if they had a prior history of thrombotic events including DVT and PE or known inherited conditions that predispose to hypercoagulability; however, most (> 90%) subjects had already enrolled in the induction studies by the time this exclusion criteria was added to the upadacitinib UC protocols.

In the PC_IND Analysis Set, 2 subjects experienced a TEAE of adjudicated VTE; both subjects experienced events of non-fatal concurrent DVT and PE (1 subject [0.1%] in the upadacitinib 45 mg group and 1 subject [0.3%] in the placebo group).

A summary of the VTE cases in subjects who received upadacitinib 45 mg induction treatment and continued into the maintenance period during the UC clinical studies is shown below.

Table 59. Treatment-Emergent Adjudicated VTE EAER per 100 PY (RESP_MAIN Analysis Set)

Event Category Adjudicated Term	M14-234 SS3 (Cohort 1)[a]			M14-234 SS3 (Cohorts 1 and 3)[b]	
	Placebo (N = 245) (PY = 128.1)	Upadacitinib 15 mg QD (N = 250) (PY = 182.4)	Upadacitinib 30 mg QD (N = 251) (PY = 198.7)	Upadacitinib 15 mg QD (N = 285) (PY = 316.9)	Upadacitinib 30 mg QD (N = 291) (PY = 304.0)
	E (E/100 PY) [SSA E/100 PY]				
VTE (fatal and non-fatal)	0	2 (1.1) [1.1]	2 (1.0) [1.0]	3 (0.9) [0.8]	2 (0.7) [0.6]
VTE (fatal)	0	0	0	0	0
Pulmonary embolism	0	0	0	0	0
Venous thrombosis	0	0	0	0	0
Venous thromboembolic events (non-fatal)*	0	2 (1.1) [1.1]	2 (1.0) [1.0]	3 (0.9) [0.8]	2 (0.7) [0.6]
Deep vein thrombosis	0	0	2 (1.0) [1.0]	1 (0.3) [0.3]	2 (0.7) [0.6]
Pulmonary embolism	0	2 (1.1) [1.1]	0	2 (0.6) [0.5]	0

Event Category Adjudicated Term	M14-234 SS3 (Cohort 1)[a]			M14-234 SS3 (Cohorts 1 and 3)[b]	
	Placebo (N = 245) (PY = 128.1)	Upadacitinib 15 mg QD (N = 250) (PY = 182.4)	Upadacitinib 30 mg QD (N = 251) (PY = 198.7)	Upadacitinib 15 mg QD (N = 285) (PY = 316.9)	Upadacitinib 30 mg QD (N = 291) (PY = 304.0)
Deep vein thrombosis and pulmonary embolism (concurrent)	0	0	0	0	0

a. Only exposure and events from Study M14-234 Substudy 3 (Cohort 1) are included.

b. All exposure and events from the 45 mg responders who entered into Study M14-234 Substudy 3 and any additional upadacitinib exposure and events for these subjects who rolled over to Study M14-533 while maintaining the same DB dose are included.

* VTE (non-fatal) include DVT and PE.

Table 60. Treatment-Emergent Adjudicated VTE EAER per 100 PY (ALL_TRT Analysis Set; ALL_TRT[subj] Categorization)

Event Category Adjudicated Term	Induction Dose UPA 45 mg QD[a]		
	UPA 45 mg/PBO (N = 245) (PY = 358.9)	UPA 45 mg/15 mg (N = 306) (PY = 466.1)	UPA 45 mg/30 mg (N = 307) (PY = 443.4)
	E (E/100 PY)		
VTE (fatal and non-fatal)	0	3 (0.6)	2 (0.5)
VTE (fatal)	0	0	0
Pulmonary embolism	0	0	0
Venous thrombosis	0	0	0
Venous thromboembolic events (non-fatal)	0	3 (0.6)	2 (0.5)
Deep vein thrombosis	0	1 (0.2)	2 (0.5)
Pulmonary embolism	0	2 (0.4)	0
Deep vein thrombosis and pulmonary embolism (concurrent)	0	0	0

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).

2.6.1.3. Serious adverse event/deaths/other significant events

In the ALL_TRT Analysis Set (ALL_TRT[subj] categorization), the EAER of treatment-emergent SAEs was slightly higher in the upadacitinib 45 mg/15 mg compared with the upadacitinib 45 mg/30 mg cohort (Table 61). The most commonly reported SAEs (≥ 1.0 E/100 PY in either the upadacitinib 45 mg/15 mg or upadacitinib 45 mg/30 mg cohort) were worsening of UC in the upadacitinib 45 mg/15 mg cohort and COVID-19 pneumonia in the upadacitinib 45 mg/30 mg cohort.

Table 61. Treatment-Emergent SAEs Reported at ≥ 2 Events in any Upadacitinib 45 mg Induction Dose Cohort by Decreasing Frequency (ALL_TRT Analysis Set; ALL_TRT$_{[subj]}$ Categorization)

MedDRA 23.0 Preferred Term	Induction Dose UPA 45 mg QD[a]		
	UPA 45 mg/PBO (N = 245) (PY = 358.9)	UPA 45 mg/15 mg (N = 306) (PY = 466.1)	UPA 45 mg/30 mg (N = 307) (PY = 443.4)
	E (E/100 PY)		
Any SAE	52 (14.5)	61 (13.1)	49 (11.1)
COVID-19 pneumonia	4 (1.1)	2 (0.4)	6 (1.4)
Colitis ulcerative	8 (2.2)	6 (1.3)	3 (0.7)
Basal cell carcinoma	0	0	2 (0.5)
Cervical dysplasia	0	0	2 (0.5)
COVID-19	0	2 (0.4)	2 (0.5)
Herpes zoster	1 (0.3)	2 (0.4)	2 (0.5)
Hypophosphataemia	0	0	2 (0.5)[b]
Pneumonia	4 (1.1)	0	2 (0.5)
Anxiety	2 (0.6)	1 (0.2)	1 (0.2)
Depression	2 (0.6)	1 (0.2)	1 (0.2)
Abortion induced	0	2 (0.4)	0
Appendicitis	0	3 (0.6)	0
Atrial fibrillation	2 (0.6)	0	0
Chronic obstructive pulmonary disease	0	2 (0.4)	0
Nephrolithiasis	2 (0.6)	0	0
Pulmonary embolism	0	2 (0.4)	0
Suicidal ideation	2 (0.6)	0	0

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. Both events occurred in 1 subject, 8 days apart, and were confounded by recent treatment with ferric carboxymaltose (ISS Table 2.4 4.7.1).

Note: Rates are displayed by decreasing frequency in the upadacitinib 45 mg/30 mg cohort.

There were two deaths reported in the clinical studies in the initial application:

- A subject who received upadacitinib 45 mg as induction treatment, followed by upadacitinib 15 mg as maintenance treatment, and rolled over to LTE Study M14-533 while maintaining the same DB dose. The subject died due to a TEAE of brain injury leading to acute respiratory failure and hypoxia. The subject experienced an opiate overdose 6 days prior to the death. Both events of overdose and brain injury were considered by the investigator to have no reasonable possibility of being related to study drug. The patient had a history of opioid abuse and overdose.
- A subject who received upadacitinib 30 mg as induction therapy, followed by upadacitinib 15 mg as maintenance therapy, and upadacitinib 30 mg in LTE Study M14-533. The subject died due to a TEAE of pancreas adenocarcinoma on Day 862, and the fatal event was considered by the investigator as having no reasonable possibility of being related to study drug.

- One additional death was reported in response to day 120 LoQ, due to COVID-19 and pulmonary embolism in a patient receiving updacitinib 30 mg.

2.6.1.4. Laboratory findings

Hepatic disorders

In the upadacitinib UC global Phase 2b and Phase 3 studies, the inclusion criteria for transaminases were AST and ALT < 2 × ULN at Screening. The protocol mandated interruption of study drug if a subject experienced: a confirmed elevation of ALT or AST > 3 × ULN in combination with either TBL > 2 × ULN or an international normalized ratio > 1.5 or, in combination with relevant clinical symptoms, and/or eosinophilia (> 5%); ALT or AST > 5 × for more than 2 weeks or ALT or AST > 8 × ULN, in which case the subject was to be evaluated for an alternative aetiology and managed medically, as appropriate.

Treatment with upadacitinib is associated with an increased incidence of liver enzyme elevation and both ALT increased and AST increased are included in the product labelling as ADRs.

In the PC_IND Analysis Set, mean increases in ALT and AST at Week 8 from Baseline were observed for the upadacitinib 45 mg group (ALT: 5.6 U/L, AST: 5.8 U/L), while values of ALT and AST generally remained unchanged from Baseline for the placebo group (ALT: –0.1 U/L, AST: –0.4 U/L).

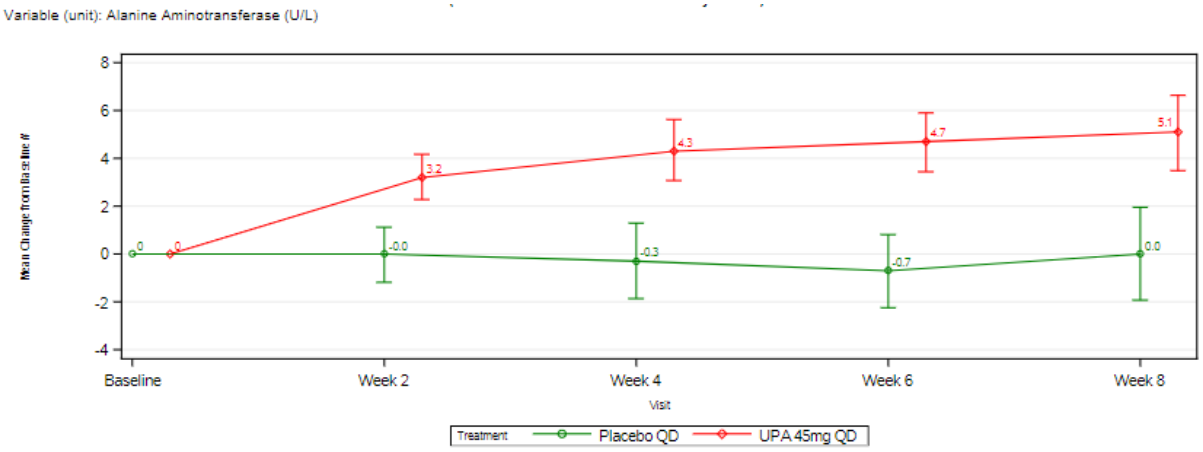


Figure 15. Plot of Mean Change from Baseline in ALT (Placebo-Controlled Induction Analysis Set)

The percentages of subjects with ALT ≥ 5 × ULN and subjects with AST ≥ 5 × ULN were higher in the upadacitinib 45 mg group compared with the placebo group although all percentages were ≤ 1%). No subject treated with upadacitinib 45 mg met biochemical criteria for Hy's Law.

One subject in the upadacitinib 45 mg group receiving treatment for latent TB experienced a nonserious TEAE of liver damage due to isoniazid (PT of drug-induced liver injury [DILI]) on Day 15 (ALT was 117 U/L and AST was 55 U/L). With continued upadacitinib treatment, ALT and AST levels returned to normal on Day 28 and the event resolved on Day 42. The event of DILI was considered by the investigator as having no reasonable possibility of being related to study drug.

In the EXT_IND Analysis Set, mean increases in ALT and AST at Week 8 and Week 16 from Baseline were observed in the upadacitinib 45 mg group (ALT: 7.0 and 7.8 U/L, and AST: 7.5 and 8.6 U/L, respectively). The percentages of subjects with ALT ≥ 5 × ULN and AST ≥ 5 × ULN were 1.6% (2 subjects) each. No subject treated with upadacitinib 45 mg for up to 16 weeks met biochemical criteria for Hy's Law.

In Cohort 1 of the RESP_MAIN Analysis Set, mean increases in ALT and AST at Week 52 from Baseline were observed in all treatment groups, with larger increases occurring in the upadacitinib 15 mg (7.2 U/L and 6.2 U/L, respectively) and 30 mg (9.3 U/L and 9.9 U/L, respectively) groups compared with the placebo group (1.9 U/L and 3.6 U/L, respectively). One subject treated with upadacitinib 30 mg met biochemical criteria for Hy's Law.

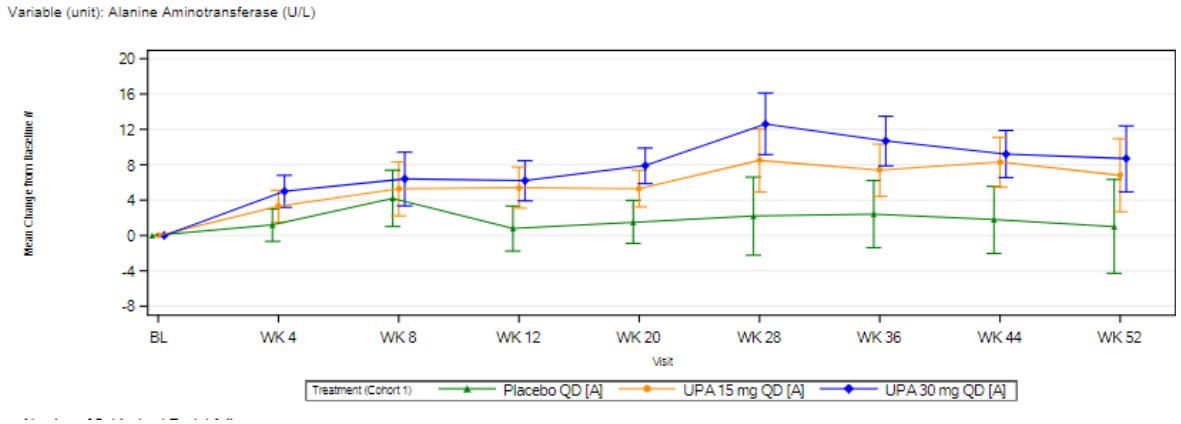


Figure 16. Plot of Mean Change from Baseline in ALT (Responders Maintenance Analysis Set)

In the ALL_TRT Analysis Set, four subjects treated with upadacitinib met biochemical Hy's Law criteria based on elevated ALT and/or AST > 3 × ULN and TBL > 2 × ULN at any post-Baseline visit during upadacitinib dosing. None of the cases were confirmed as true Hy's Law cases.

Anaemia

Anaemia is listed in section 4.8 of the Rinvoq SmPC. In the upadacitinib UC global Phase 2b and Phase 3 studies, all subjects at study entry were required to have a haemoglobin value ≥ 90 g/L. The protocols mandated interruption of study drug if a subject's haemoglobin value (confirmed by repeat testing) was < 80 g/L or decreased ≥ 30 g/L 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 decreases in haemoglobin at Week 8 from Baseline were observed which were numerically greater in the upadacitinib 45 mg group (–1.6 g/L) compared with the placebo group (–0.7 g/L). The percentage of subjects with TEAEs of anaemia was numerically lower in the upadacitinib 45 mg group (3.5%) compared with the placebo group (5.6%).

In the EXT_IND Analysis Set, a mean decrease in haemoglobin from Baseline, observed in the upadacitinib 45 mg group through Week 8 (–3.8 g/L), was maintained through Week 16 (–3.7 g/L).

Neutropenia

Neutropenia is listed in section 4.8 of the Rinvoq SmPC. In the UC studies, Clinical haematology laboratory test results for neutrophil count were evaluated. Subjects with absolute neutrophil count (ANC) < 1,200/µL were excluded from the UC studies. The protocols mandated interruption of study drug if a subject's neutrophil count (confirmed by repeat testing) was < 1000 cells/µL until the neutrophil count returned to the normal reference range or its Baseline value. Study drug discontinuation criterion for confirmed ANC was < 500/µL without an alternative aetiology.

In the PC_IND Analysis Set, a mean decrease in neutrophil count at Week 8 from Baseline were observed for the upadacitinib 45 mg group (–1.172 × 109/L), which was larger than the placebo group (–0.103 × 109/L). The percentage of subjects with TEAEs of neutropenia was higher in the upadacitinib 45 mg group (4.6%) compared with the placebo group (0.3%). According to the MAH, in

the EXT_IND Analysis Set, a mean decrease in neutrophil count from Baseline was generally maintained with extended induction treatment with upadacitinib 45 mg.

Lymphopenia

In the PC_IND Analysis Set, no notable mean changes from Baseline in lymphocyte count over the 8-week induction treatment was observed in both the upadacitinib 45 mg and placebo groups.
The percentage of subjects with TEAEs of lymphopenia was higher in the upadacitinib 45 mg group (2.5%) compared with the placebo group (0.5%).

In Cohorts 1 and 3 of the RESP_MAIN Analysis Set, the percentage of subjects with Grade 3 lymphocyte count decreases was slightly higher in the upadacitinib 15 mg compared with the upadacitinib 30 mg group (Table 62).

In the ALL_TRT Analysis Set, a total of 2 (0.2%) subjects receiving upadacitinib had a Grade 4 lymphocyte count decrease which occurred at a single time point. No SAE of lymphopenia was reported and discontinuation of upadacitinib due to a TEAE of lymphopenia was infrequent (0.1 E/100 PY).

Table 62. Number and Percentage of Subjects Meeting Criteria for Potentially Clinically Significant Values for Lymphocytes (RESP_MAIN Analysis Set)

	M14-234 SS3 (Cohort 1)[a]			M14-234 SS3 (Cohorts 1 and 3)[b]	
Lymphocytes ($\times 10^9$/L)	**Placebo (N = 245)**	**Upadacitinib 15 mg QD (N = 250)**	**Upadacitinib 30 mg QD (N = 251)**	**Upadacitinib 15 mg QD (N = 285)**	**Upadacitinib 30 mg QD (N = 291)**
	n/N_OBS (%)				
Grade 2 (0.5 to < 0.8)	8/244 (3.3)	21/250 (8.4)	24/250 (9.6)	33/285 (11.6)	33/290 (11.4)
Grade 3 (0.2 to < 0.5)	2/244 (0.8)	4/250 (1.6)	2/250 (0.8)	7/285 (2.5)	5/290 (1.7)
Grade 4 (< 0.2)	0/244	0/250	0/250	0/285	0/290
At least Grade 3	2/244 (0.8)	4/250 (1.6)	2/250 (0.8)	7/285 (2.5)	5/290 (1.7)

a. Only exposure and events from Study M14-234 Substudy 3 (Cohort 1) are included.

b. All exposure and events from the 45 mg responders who entered into Study M14-234 Substudy 3 and any additional upadacitinib exposure and events for these subjects who rolled over to Study M14-533 while maintaining the same DB dose are included.

Notes: Toxicity grading scale is based on NCI CTCAE v4.03. Post-Baseline grade must also be worse than the Baseline grade.
N_OBS indicates the number of subjects with non-missing Baseline and at least 1 post-Baseline value.
Maximum grade for each subject was summarized.
Bi-directional parameters higher side lymphocytes was not populated since higher end is not a safety concern.

Creatine Phosphokinase Elevation

CPK increase is an ADR for upadacitinib in the current product labelling.

In the PC_IND Analysis Set, Grade ≥ 3 CPK increases and TEAEs of CPK elevation were reported in a higher percentage of subjects receiving upadacitinib 45 mg treatment compared with placebo. Grade 3 and 4 CPK increases were infrequent.

In the EXT_IND Analysis Set, no Grade 4 CPK increase was reported during the extended induction period with upadacitinib 45 mg treatment.

In the RESP_MAIN Analysis Set, the percentage of subjects with Grade ≥ 3 CPK increases and rate of TEAEs of CPK elevation were higher with upadacitinib in a dose-dependent manner compared with placebo.

In the ALL_TRT Analysis Set, no TEAE of CPK elevation was serious and discontinuation of upadacitinib due to TEAEs of CPK elevation was infrequent (0.2 E/100 PY).

Renal Dysfunction

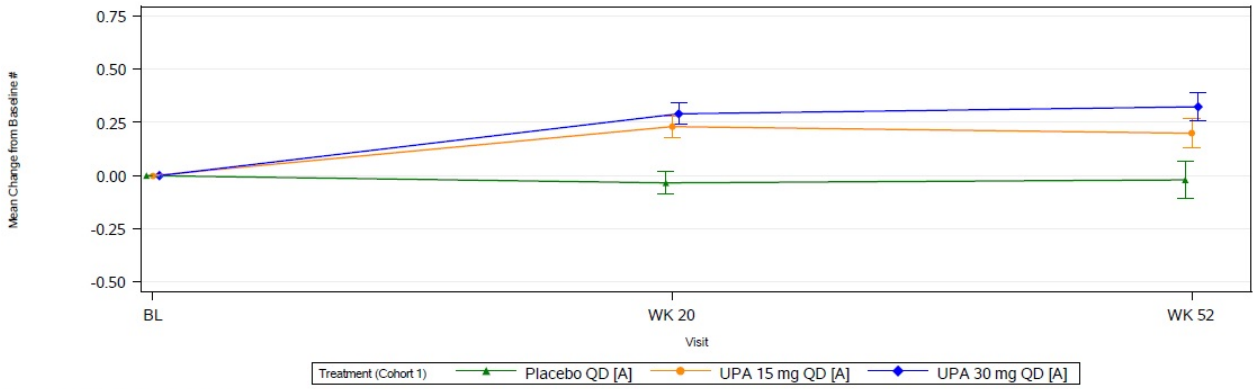
In the PC_IND Analysis Set, a small mean increase at Week 8 from Baseline was observed for creatinine in the upadacitinib 45 mg group (4.6 µmol/L), which was higher than the placebo group (0.8 µmol/L). Grade 2 creatinine increases were reported at similar frequencies in the upadacitinib 45 mg (1.0%) and placebo (1.1%) groups.

In Cohort 1 of the RESP_MAIN Analysis Set, throughout the 52 weeks, increases in creatinine were higher in the upadacitinib 30 mg group compared to the 15 mg group. The highest levels were observed at Week 52, with higher mean increases in creatinine from Baseline for the upadacitinib 15 mg and 30 mg groups (6.9 and 7.4 µmol/L, respectively) compared with the placebo group (2.8 µmol/L).

Lipids

In the RA, PsA, and AD programs, a dose-dependent lipid increase was observed with upadacitinib treatment. However, the impact of increased lipid parameters with JAK inhibitors on CV morbidity and mortality is currently unknown. Information on lipid elevations is included in section 4.8 of the SmPC.

The mean change from baseline in HDL and HDL levels during the maintenance phase is shown below.



Number of Subjects at Each Visit

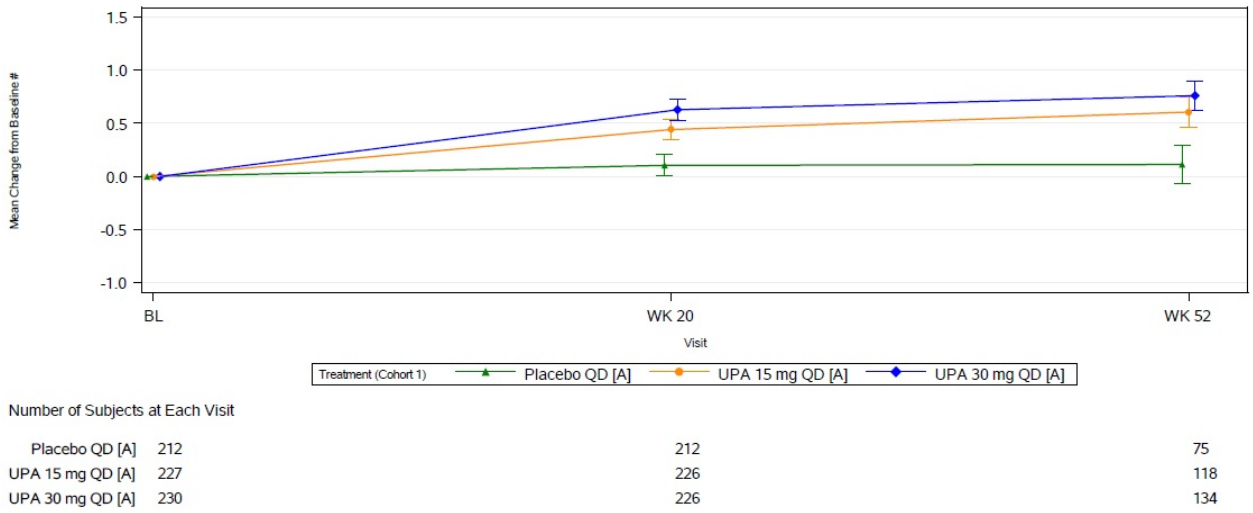
Placebo QD [A]	214	214	75
UPA 15 mg QD [A]	230	229	122
UPA 30 mg QD [A]	236	234	137

A Includes all subjects who responded to upadacitinib 45 mg during induction and were re-randomized to placebo, upadacitinib 15 mg, or upadacitinib 30 mg and entered into Study M14-234 Substudy 3 (Cohort 1).

Least square mean is based on analysis of covariance (ANCOVA) model with treatment as a main factor, and Baseline and study/substudy number as covariates. Error bars are based on the standard error (SE) of the mean.

Note: Baseline mean includes subjects with non-missing Baseline and at least 1 post-Baseline value.

Figure 17. Mean Change from Baseline in HDL-C Over Time (RESP_MAIN Analysis Set; Cohort 1)



Number of Subjects at Each Visit

Placebo QD [A]	212	212	75
UPA 15 mg QD [A]	227	226	118
UPA 30 mg QD [A]	230	226	134

A Includes all subjects who responded to upadacitinib 45 mg during induction and were re-randomized to placebo, upadacitinib 15 mg, or upadacitinib 30 mg and entered into Study M14-234 Substudy 3 (Cohort 1).

Least square mean is based on ANCOVA model with treatment as a main factor, and Baseline and study/substudy number as covariates. Error bars are based on the SE of the mean.

Note: Baseline mean includes subjects with non-missing Baseline and at least 1 post-Baseline value.

Figure 18. Mean Change from Baseline in LDL-C Over Time (RESP_MAIN Analysis Set; Cohort 1)

2.6.1.5. Safety in special populations

Gender

Across the PC_IND, RESP_MAIN, and ALL_TRT Analysis Sets and across treatment groups, the rates of TEAEs overall were higher in females compared with males, while the rates of TEAEs leading to discontinuation of study drug were generally similar. There was no consistent pattern or trend observed for serious TEAEs and severe TEAEs across analysis sets and treatment groups.

Across the PC_IND, RESP_MAIN, and ALL_TRT Analysis Sets and across treatment groups, the rates of most AESIs were generally similar or there was no consistent trend between males and females. The rates of TEAEs of hepatic disorder were higher in males compared with females across analysis sets and upadacitinib treatment groups.

Renal impairment

Due to a very limited number of patients with GFR<40 mL/min/1.73 m2 (n=4), the data presented below are for subjects with screening eGFR ≥ 60 – < 90 mL/min/1.73 m2 (mild renal impairment) and those with eGFR ≥ 90 mL/min/1.73 m2 (normal renal function).

Table 63. TEAEs by GFR (placebo-controlled induction analysis set)

MedDRA 23.0 System Organ Class Preferred Term	>= 90 mL/min/1.73m^2 Placebo (N=208) n (%) [SSA%]	>= 90 mL/min/1.73m^2 UPA 45 mg QD (N=405) n (%) [SSA%]	>= 60 and < 90 mL/min/1.73m^2 Placebo (N=159) n (%) [SSA%]	>= 60 and < 90 mL/min/1.73m^2 UPA 45 mg QD (N=289) n (%) [SSA%]
Any adverse event	105 (50.5) [50.5]	215 (53.1) [53.2]	87 (54.7) [53.5]	164 (56.7) [56.8]

	>= 40 and < 60 mL/min/1.73m^2 Placebo (N=11) n (%) [SSA%]	>= 40 and < 60 mL/min/1.73m^2 UPA 45 mg QD (N=21) n (%) [SSA%]	- Treatment Comparison - (95% CI) [A] UPA 45 mg QD - PBO
Subjects with:			
Any adverse event (AE)	7 (63.6) [62.9]	15 (71.4) [71.3]	

Across the PC_IND, RESP_MAIN, and ALL_TRT Analysis Sets and across treatment groups, there was no consistent pattern or trend observed for TEAEs overall, SAEs, TEAEs leading to study drug discontinuation, and severe TEAEs between subjects with normal renal function and those with renal impairment.

Prior biologic response status

According to the MAH, the safety profile was generally similar between non-Bio-IR and Bio-IR subjects.

Number of prior biologics

Across the PC_IND, RESP_MAIN, and ALL_TRT Analysis Sets and across treatment groups, there was no consistent pattern or trend observed for the rates of TEAEs overall, SAEs, and TEAEs leading to discontinuation of study drug in subjects who received > 1 prior biologic and those who received ≤ 1 prior biologic.

Baseline steroid use

Across the PC_IND, RESP_MAIN, and ALL_TRT Analysis Sets and across treatment groups, there was no consistent pattern or trend observed for TEAEs overall, SAEs, TEAEs leading to study drug discontinuation, and severe TEAEs with respect to Baseline steroid use.

Baseline aminosalicylate use

The majority of subjects in the UC clinical studies were on aminosalicylates at Baseline. Across the PC_IND, RESP_MAIN, and ALL_TRT Analysis Sets and across treatment groups, there was no consistent pattern or trend observed for TEAEs overall, SAEs, TEAEs leading to study drug discontinuation, and severe TEAEs between subjects on aminosalicylates at Baseline and those who were not.

Across the PC_IND, RESP_MAIN, and ALL_TRT Analysis Sets and across treatment groups, the rates of TEAEs of serious infection, neutropenia, and lymphopenia were generally higher in subjects on aminosalicylates at Baseline compared to those who were not.

Use in pregnancy and lactation

Upadacitinib has been shown to be teratogenic in animal studies, and is contraindicated during pregnancy. Neither, upadacitinib should be used during lactation.

As of 31 May 2021, there were a total of 93 pregnancies reported in female subjects in upadacitinib clinical studies. The majority were reported in RA studies. Of the 64 unblinded pregnancies with known exposure to upadacitinib, 8 were from UC studies (Table 64).

Table 64. Maternal Exposure Pregnancy Outcomes in Female Subjects Administered Upadacitinib at Time of Pregnancy

Pregnancy Outcomes for Maternal Exposure Reports	N = 64
Total live births:	**19**
Live birth without congenital anomaly	19[a]
Live birth with congenital anomaly	0
Total fetal deaths:	**28**
Spontaneous Abortion	14
Stillbirth without fetal defects	0
Stillbirth with fetal defects	0
Ectopic pregnancy	1
Elective termination (no fetal defects or unknown)	13
Elective termination (with fetal defects)	0
Ongoing pregnancy	**13**
Lost to follow-up	**4**
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 31 May 2021.

The 14 reports of spontaneous abortion in the upadacitinib clinical program translates to a reporting rate of 22% (14 of 64 pregnancies). Of the 14 pregnancies which resulted in a spontaneous abortion, all had other risk factors contributing to an increased risk of miscarriage, including concomitant MTX use, advanced maternal age, prior history of miscarriage, obesity, current smoking, or poorly controlled diabetes mellitus. The majority of the spontaneous abortion cases were from the RA clinical program and on concomitant MTX at the time of the pregnancy (10 of the 14 spontaneous abortions). Thus, the rate of spontaneous abortion observed in the upadacitinib clinical program was not higher than what was reported in literature in pregnant patients with exposure to MTX or other risk factors.

The 8 pregnancies reported in UC studies included 3 live births without congenital anomaly, 2 elective terminations (no foetal defects or unknown), 2 ongoing, and 1 lost to follow-up. The subject with a pregnancy lost to follow-up received upadacitinib 45 mg while the other 7 subjects received upadacitinib 15 mg.

Age

An overview of AEs in patients >=65 years is presented in Table 65 (induction) and Table 66 (maintenance).

Table 65. Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Age (Placebo-Controlled Induction Analysis Set)

	>= 65 Years		
	Placebo (N=33) n (%) [SSA%]	UPA 45 mg QD (N=62) n (%) [SSA%]	- Treatment Comparison - (95% CI) [A] UPA 45 mg QD - PBO
Subjects with:			
Any adverse event (AE)	23 (69.7) [70.3]	33 (53.2) [53.8]	
COVID-19 infection related AE	0	0	0.0
Any serious AE	2 (6.1) [6.1]	3 (4.8) [5.1]	-1.0 (-12.5, 10.5)
Any AE leading to discontinuation of study drug	3 (9.1) [10.2]	3 (4.8) [5.1]	-5.1 (-17.8, 7.5)
Any severe AE	3 (9.1) [9.3]	1 (1.6) [1.6]	-7.7 (-19.1, 3.6)
Any AE with reasonable possibility of being related to study drug$	9 (27.3) [27.3]	19 (30.6) [31.3]	4.0 (-14.3, 22.3)
Any AE leading to death	0	0	0.0
Deaths#	0	0	0.0
Deaths occurring <= 30 days after last dose of study drug	0	0	0.0
Deaths occurring > 30 days after last dose of study drug	0	0	0.0
COVID-19 infection related deaths	0	0	0.0

Note: Treatment-emergent adverse events are adverse events with an onset date on or after the first dose of study drug and up to 30 days past the last dose of study drug in the 8-week induction period or until one day prior to the first dose of study drug in the Part 2 induction period or any subsequent maintenance or long-term extension period.
SSA = Study-size adjusted.
[A] Study-size adjusted risk difference between treatment groups.
$ As assessed by investigator.
# Includes both treatment-emergent and non-treatment emergent deaths.

Program Source Code: /parepbk/SDA/ABT-494/UC/Integrated_Summaries/ISS/2.4/PCMS_RUN/iss-pcind-aeov1.sas

Table 66.Overview of Treatment-Emergent Adverse Events in Exposure-Adjusted Rate per 100 Patient Years by Age (Responders Maintenance Analysis Set)

	>= 65 Years				
	M14-234 Substudy 3 (Cohort 1) [A]			M14-234 Substudy 3 (Cohorts 1 and 3) [B]	
	Placebo QD (N=21)	UPA 15 mg QD (N=23)	UPA 30 mg QD (N=21)	UPA 15 mg QD (N=26)	UPA 30 mg QD (N=26)
Exposure-adjusted event rate:	(PYs=10.4)	(PYs=19.1)	(PYs=16.3)	(PYs=32.1)	(PYs=27.1)
	Events (E/100 PYs) [SSA E/100 PYs]	Events (E/100 PYs) [SSA E/100 PYs]	Events (E/100 PYs) [SSA E/100 PYs]	Events (E/100 PYs) [SSA E/100 PYs]	Events (E/100 PYs) [SSA E/100 PYs]
Any adverse event (AE)	64 (613.9) [620.6]	82 (429.7) [421.6]	59 (361.0) [341.9]	115 (357.9) [366.1]	103 (380.6) [329.3]
COVID-19 infection related AE	1 (9.6) [10.4]	0	1 (6.1) [5.5]	2 (6.2) [6.7]	1 (3.7) [3.4]
Any serious AE	2 (19.2) [18.7]	3 (15.7) [13.5]	2 (12.2) [10.9]	5 (15.6) [15.5]	6 (22.2) [19.0]
Any AE leading to discontinuation of study drug	3 (28.8) [29.2]	0	3 (18.4) [18.1]	1 (3.1) [3.8]	3 (11.1) [9.5]
Any severe AE	2 (19.2) [18.7]	2 (10.5) [8.0]	3 (18.4) [17.2]	3 (9.3) [8.8]	4 (14.8) [12.9]
Any AE with reasonable possibility of being related to study drug$	15 (143.9) [135.2]	21 (110.0) [110.5]	25 (153.0) [150.3]	33 (102.7) [104.0]	40 (147.8) [125.6]
Any AE leading to death	0	0	0	0	0

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 period or until one day prior to the first dose of study drug in the LTE period (for Cohort 1) and up to 30 days after the last dose of study drug in the maintenance or LTE period or until one day prior to the first dose of study drug in which the subject's dose was changed during the LTE period.
E/100PYs = Number of events per 100 patient-years. n/100PYs = Number of subjects per 100 patient-years.
[A] Includes all subjects who responded to UPA 45 mg QD during induction and were re-randomized to PBO, 15 mg or 30 mg and entered into M14-234 substudy 3 (Cohort 1).
[B] Includes 15 mg and 30 mg subjects from Cohort 1 plus M14-234 substudy 2 (Part 2) and M14-675 (Part 2) 45/45 mg responders who were re-randomized to 15 mg or 30 mg and entered into M14-234 substudy 3 (Cohort 3) and additional time from M14-533 while subject remained on same double-blind dose.
[C] Study-size adjusted risk differences between treatment groups.
SSA = Study-size adjusted.
$ As assessed by investigator.
# Includes both treatment-emergent and non-treatment emergent deaths.

Program Source Code: /parepbk/SDA/ABT-494/UC/Integrated_Summaries/ISS/2.4/PCMS_RUN/iss-rm-aeov1.sas

The MAH concludes that the elderly (≥ 65 years of age) who received upadacitinib 45 mg induction treatment and upadacitinib 30 mg as maintenance treatment showed higher rates of SAEs, TEAEs leading to discontinuation of study drug, and herpes zoster compared to the lower maintenance dose and/or younger population. Only patients aged <75 years were included in the studies.

Table 67 AEs by age

	Upadacitinib 15 mg		Upadacitinib 30 mg	
MedDRA Terms	Age <65 number (E/100PYs)	Age 65-74 number (E/100PYs)	Age <65 number (E/100PYs)	Age 65-74 number (E/100PYs)
Total AEs	517 (316.6)	71 (392.0)	577 (316.4)	59 (411.1)
Serious AEs – Total	21 (12.9)	2 (11.0)	19 (10.4)	2 (13.9)
- Fatal	0	0	0	0
- Hospitalization/prolong existing hospitalization	16 (9.8)	2 (11.0)	18 (9.9)	1 (7.0)
- Life-threatening	1 (0.6)	0	1 (0.5)	0
- Disability/incapacity	1 (0.6)	0	0	0
- Other (medically significant)	7 (4.3)	0	8 (4.4)	1 (7.0)
AE leading to drop-out	6 (3.7)	0	9 (4.9)	3 (20.9)
Psychiatric disorders	5 (3.1)	1 (5.5)	14 (7.7)	1 (7.0)
Nervous system disorders	17 (10.4)	2 (11.0)	18 (9.9)	2 (13.9)
Accidents and injuries	0	0	0	0
Cardiac disorders	1 (0.6)	1 (5.5)	7 (3.8)	1 (7.0)
Vascular disorders	4 (2.4)	5 (27.6)	9 (4.9)	2 (13.9)
Cerebrovascular disorders	0	0	0	0
Infections and infestations	145 (88.8)	11 (60.7)	155 (85.0)	14 (97.5)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	2 (1.2)	1 (5.5)	4 (2.2)	1 (7.0)

Note: There are no data in patients aged 75 or above.

2.6.1.6. 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 (C_{max}) 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.

2.6.1.7. 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 European Union on 25 January 2021 and in additional countries. Through 30 June 2021, the estimated cumulative post marketing exposure is 88,004 patient treatment years.

The overall safety of upadacitinib 15 mg QD therapy was evaluated through review of post marketing reports (spontaneous, solicited, literature) received from 16 August 2019 through 30 June 2021. Search of the AbbVie global safety database retrieved 42,580 reports, which include 4,440 serious reports and 38,140 nonserious reports. Of the 38,140 nonserious reports, 96% (36,699 reports) were from solicited sources.

According to the MAH, review of the post marketing safety data reported for upadacitinib to date demonstrated a similar safety profile as observed in the clinical studies for RA. The most frequently reported AEs were in the SOC of general disorders and administration site conditions. Overall, the most common reported AEs include arthralgia, pain, and RA (4% each); and drug ineffective and pain in extremity (3% each). Most of the post marketing events are either expected for upadacitinib or commonly seen in the general population or patients with RA.

The most common reported SAEs by PT include surgery and hospitalization (3% each); and pneumonia, COVID-19, and cataract (2% each). The reports of COVID-19 infection were reflective of the ongoing COVID-19 pandemic during the review period. 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. Surgery and hospitalization are not unexpected in patients with RA. 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.

Although many of the post marketing 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.

The MAH concludes that analysis of the safety data available from the post marketing experience has not confirmed any new clinically important safety risks for upadacitinib.

2.6.2. 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), ankylosing spondylitis (AS) and atopic dermatitis (AD). The recommended dose in RA, PsA and AS is 15 mg once daily, while in AD the

recommended dose is either 15 or 30 mg once daily. In UC, the proposed induction dose is 45 mg for 8 weeks (with the option to prolong induction for additional 8 weeks) followed by 15 or 30 mg as maintenance treatment. Thus, the induction dose proposed for UC is higher than the recently approved dose.

The main questions for the safety assessment in the present application are as follows:

- whether the safety of the 45 mg induction dose is acceptable, since this is higher than the currently approved doses, and
- whether the use of the 30 mg maintenance dose is sufficiently justified considering that this dose was associated with a less favourable safety outcome in the rheumatoid arthritis studies.

The clinical development program is complex, but the main studies are:

- Two separate 8-week induction studies (M14-234 substudy 2 and M14-675), with the possibility to prolong induction treatment to a total of 16 weeks
- One common 52-week maintenance study (M14-234 substudy 3). The study is currently ongoing, and 445/1046 patients had completed the study at data cut-off for this application.
- One long-term extension (M14-533) for patients who left the maintenance study due to loss of response, or who completed the maintenance study. The long-term extension continues up to 288 weeks. The study is listed as a category 3 study in the RMP, with final study report expected in Q1 2025.

Cut-off date for the maintenance and long-term extension studies is 30 April 2021.

The patients are assigned to the following cohorts based on the treatment they achieved in the induction studies:

- Cohort 1: Responders on 8-week induction with UPA 15 mg, 30 mg, 45 mg, re-randomised to UPA 15 mg, UPA 30 mg or placebo in the maintenance phase
- Cohort 2: Responders on 8-week induction with placebo, continuing placebo in the maintenance phase
- Cohort 3: Responders on 16-week induction with upadacitinib 45 mg, re-randomised to UPA 15 mg or UPA 30 mg in the maintenance phase
- Cohort 4: Responders on 8-week induction with UPA 7.5 mg, continuing UPA 7,5 mg in the maintenance phase

The following datasets have been used for the safety assessment:

- Placebo-Controlled Induction (PC_IND) Analysis Set: to evaluate induction dosing in subjects who received up to an 8-week treatment with upadacitinib 45 mg or placebo;
- Extended Induction (EXT_IND) Analysis Set: to evaluate induction dosing in subjects who received up to a 16-week treatment with upadacitinib 45 mg; and
- Responders Maintenance (RESP_MAIN) Analysis Set: to evaluate maintenance dosing in subjects who responded to upadacitinib 45 mg 8-week induction treatment and were re-randomized to upadacitinib 15 mg or 30 mg or placebo during the maintenance period. This set also evaluates long-term data of maintenance dosing with continuous exposure to upadacitinib 15 mg and 30 mg during the maintenance period through the LTE period in subjects who responded to either upadacitinib 45 mg 8-week or 16-week induction treatment for which data were censored at dose switching.

- All Treated UC (ALL_TRT) Analysis Set: to evaluate the safety of treatment regimens over the entire treatment course (induction, maintenance, and LTE) in subjects who received at least 1 dose of study drug in the clinical trials. This analysis set contains the largest subject numbers and PY of upadacitinib exposure. Safety data were not censored at treatment switching and thus, all events, including rare and uncommon events in upadacitinib exposed subjects, are captured in this analysis set. However, because dose switching is part of the study design of this clinical program, certain cohorts, as defined for this dataset, contain data from subjects who may have been exposed to various doses during the treatment course. Therefore, this analysis set is complementary or supportive to the findings in the other datasets as well as aids in detection of potential rare events.

The total exposure in the RESP_MAIN analysis set is 316.9 PYs for UPA 15 mg (n=285, mean treatment duration 58 weeks) and 304.0 PYs for UPA 30 mg (n=291, mean treatment duration 54.5 weeks).

Overview of adverse events

During the placebo-controlled 8-week induction period, the frequency of adverse events (AEs) was 52.6% in the placebo group and 55.4% in the UPA group. SAEs occurred in 5.8% in the placebo group and 3.1% in the UPA group. The frequency of patients with AEs leading to discontinuation was higher in the placebo group. There were no deaths in either group.

In patients who received an additional 8-week induction, the exposure-adjusted incidence rates of AEs, SAEs and SAEs were similar as during the first 8 weeks of induction.

In cohort 1 in the maintenance phase, the exposure-adjusted incidence rate (EAIR) of AEs was lower in both UPA groups (UPA 15 mg: 328.4 E/100PYs and UPA 30 mg: 320 E/100PYs) than in the placebo group (509E/100PYs). Also SAEs and AEs leading to study drug discontinuation were less frequent in the UPA arms than for placebo. AEs and serious adverse events were more frequent in the UPA 15 mg group (AE: 328.4E/100PYs, SAE: 13.2E/100PYs) than in the UPA 30 mg group (AE: 320 E/100PYs, SAE:10.6 E/100PYs). Thus, no clear dose-dependency was observed.

In the combined cohorts 1 and 3 (including also patients who underwent a 16-week induction period), a dose-dependency was observed for AEs and SAEs although the differences between the groups was quite small. When making a direct comparison of AEs in the maintenance phase between patients receiving 8-week induction and 16-week induction, the EAIR of AEs were equally frequent in the 15 mg group (294.4E/100PYs) and 30 mg group (297.3E/100 PYs) among patients receiving 8-week induction, however AEs were less frequent in the 15 mg group (231.2E/100PYs) than in the 30 mg group (337.8E/100 PYs) among patients receiving 16-week induction. It should be noted though, that only 35 patients in the 15 mg group and 40 patients in the 30 mg group who needed a prolonged induction were included in the maintenance phase and the results should therefore be interpreted with caution.

In the all analysis set, the EAIR of AEs was slightly lower for the UPA 15 mg group (323.3E/100PYs) than for the UPA 30 mg group (364E/100PYs), but SAEs were not more frequent in the higher dose group. Although the overall risk for AEs was not higher for UPA 30 mg than for the lower 15 mg dose, a dose-dependent increase in the risk for CPK increase, neutropenia and folliculitis was observed.

Common adverse events

Frequent AEs reported more frequently in the UPA than in the placebo group during the induction phase were acne, increased CPK, nasopharyngitis, neutropenia, pyrexia, rash, folliculitis and upper

respiratory tract infection. These are all listed in section 4.8 of the SmPC and does not constitute any new safety signals.

Three new AEs have been included in the table of adverse reactions in Section 4.8 of the SmPC with a frequency “common”: lymphopenia, hyperlipidaemia, and rash.

The following summary has been included in section 4.8 of the SmPC:

In the placebo-controlled ulcerative colitis 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%), blood CPK increased (7.6%), acne (6.3%), neutropaenia (6.0%), rash (5.2%), herpes zoster (4.4%), hypercholesterolemia (4.0%), 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 which was considered acceptable.

Prolonged induction

In patients receiving a prolonged induction, the rates of herpes zoster and increased liver enzymes was higher during week 0-16 than during week 0-8. These are the most serious concerns with the prolonged induction, in the short term.

The prolonged induction should only be used for patients who do not achieve adequate therapeutic benefit by week 8, i.e., where there is a clear clinical need for more intense treatment. In these patients, the safety of this regimen can be considered acceptable and guidance is adequately reflected in the SmPC.

Deaths and serious adverse events

There were two deaths reported in the original submission, one in the UPA 15 mg arm and one in the UPA 30 mg arm. The first case (opioid overdose with anoxic brain injury) is considered unrelated to upadacitinib treatment. In the other case (pancreatic cancer), causality is possible but cannot be firmly concluded. Malignancy is listed as important potential risk in the RMP and will be further studied with the data from the ongoing PASS studies (see 2.7.).

In the all-treated dataset, the frequency of SAEs was higher in the placebo group than in the upadacitinib groups. SAEs reported as infections were more frequent in the upadacitinib arms. These include COVID-19 and herpes zoster. There were 4 cases of malignancy reported in the UPA 30 mg group: 2 basal cell carcinoma and 2 cervical dysplasia. Malignancies are further discussed below.

At CHMP’s request, the MAH presented un update of the available safety data from study M14-234 to date. This include one new death due to COVID-19 and pulmonary embolism reported in a patient receiving updacitinib 30 mg. Apart from this, there were no new safety signals identified.

Adverse events of special interest

During the induction phase, serious infections occurred with a similar frequency in the placebo and UPA 45 mg groups. During the maintenance phase, the frequency of serious infections was similar in UPA 15 mg and 30 mg groups, and more frequent in the placebo group. In the all-treated dataset, the EAIR of serious infections was slightly higher in the upadacitinib groups, but no dose-dependency was observed. No new safety signals were observed.

There were no reports of hepatitis B reactivation in the UC studies. Patients with hepatitis B infection were excluded from the study. There is a recommendation in section 4.4 of the SmPC to screen for hepatitis B before start of Rinvoq treatment. This is acceptable.

Opportunistic infections excluding TB and herpes zoster occurred with a similar frequency in the upadacitinib and placebo groups during the induction phase, and were more frequent in the placebo group during the maintenance phase. No dose-dependent risk was observed.

In the upadacitinib UC studies, herpes zoster vaccination was not mandatory and 3.7% of subjects who received at least 1 dose of upadacitinib indicated a prior history of zoster vaccination. During the induction phase, there were 4 cases of herpes zoster, all in the UPA 45 mg arm. Among these was one case of disseminated herpes zoster. Of concern, during the prolonged induction phase, the EAIR increased from 5.0 E/100PYs to 15.3E/100PYs. All events involved only 1 dermatome, and none were serious. The increased risk for herpes zoster is considered manageable through herpes zoster vaccination as recommended in the SmPC.

During the maintenance phase, there were five serious cases of HZ reported, all in the upadacitinib arms. These include Bell's palsy and HZ meningitis. Section 4.8 of the SmPC has been updated to reflect this information.

One case of active TB was reported in a patient switching from placebo to upadacitinib 15 mg in the long-term extension phase. Of note, he was found to have latent TB but did not receive TB treatment as recommended. Although it is a serious case, the SmPC includes clear recommendations for TB screening and treatment of latent TB before initiating upadacitinib treatment. This is considered sufficient.

There were 3 gastrointestinal perforations reported, 2 in subjects receiving placebo and 1 in a subject receiving upadacitinib 15 mg (due to a complication of a routine study colonoscopy). No SmPC updates were considered needed.

The EAIR for malignancies excluding non-melanoma skin cancer (NMSC) was lower in the UPA 15 mg group than in the placebo group. Of some concern, there is a dose-dependent increase in EAIR; however, the number of malignancies were few hampering firm conclusions. It is agreed with the MAH that the there is no specific pattern observed with regards to type of malignancy. Also regarding NMSC, it is of concern that the EAIR is higher for the UPA 30 mg group. The SmPC includes the following text in section 4.4: *NMSCs have been reported in patients treated with upadacitinib. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.* This is considered acceptable.

There were no cases of MACE reported in the UPA 15 mg group, and 3 cases in the UPA 30 mg group. A dose-dependency is observed; however, the total number of cases are few (n=3 in the UPA 30 mg group) hampering firm conclusions.

Regarding venous thromboembolism (VTE), there is a current class effect warning in section 4.4. During the induction phase, there was one VTE case reported in the placebo and UPA 15 mg arms, respectively. Throughout the whole study, the EAIR for VTE was slightly higher for the UPA 15 mg (0.6E/100PYs) and UPA 30 mg groups (0.5E/100PYs) than for the placebo group (0 cases).

The MAH argues that no upadacitinib dose relationship in the rates of adjudicated VTE and patterns in the time to onset of the events was observed, and that all subjects who experienced VTE receiving upadacitinib had at least 1 risk factor identified for thrombosis (e.g., including underlying UC or other risk factors). The argumentation is followed, but not completely supported. UC as a risk factor applies to all patients in the studies and should not explain the difference between the UPA and placebo arms in a randomised trial. When looking at the narratives, there are also cases without underlying risk factors. At the CHMP's request, the MAH presented a thorough discussion on the need to update section 4.8 to include VTE as an adverse event for Rinvoq, and concluded that an update was not warranted. The MAH clarified that in most cases, there were risk factors for VTE other than UC, and that the overall rates of adjudicated VTE in the upadacitinib UC program did not appear higher than the

anticipated background rate in the UC population. The observed difference in frequency between Rinvoq and placebo was based on very few cases. Further, no dose dependency was observed. The CHMP agreed that the inclusion of VTE as an adverse drug reaction is not warranted at present. However, this risk will be further assessed within the on-going JAK inhibitor referral procedure (EMEA/H/A-20/1517).

In the latest PSUR, there were higher number of PTs reporting various fractures with upadacitinib in comparison with active comparator or placebo in clinical trials. At CHMP's request, the MAH presented all cases of fractures occurring in the UC studies, including frequencies and exposure-adjusted incidence rates for upadacitinib and placebo respectively. Furthermore, exposure-adjusted incidence rates in pooled data from all upadacitinib clinical studies was requested. When assessing the risk for fractures, the following needs to be taken into consideration:

- The risk for fractures might differ across indications, with patients with high inflammatory burden and/or concomitant use of steroids (i.e. RA and PsA populations) are at high risk for fractures. While the AS population might possibly be less confounded by concomitant corticosteroid treatment, on the other hand the more fragile RA and PsA population might be more sensitive to detect possible differences in fracture rates.
- The placebo-controlled period of the studies were normally around 3 months, and the risk for fractures might increase over time since entry of the study. Therefore, comparisons with this short placebo-controlled period, even if using exposure adjusted figures, are not the most reliable comparisons in this case but rather the active comparator data which is obtained during longer time periods within the studies (i.e. MTX in study M13-545 and adalimumab in study M14-465 and M14-572).

When looking at these studies with active comparators throughout the full study, it is noted that in RA study M13-545, the risk for fractures was higher for MTX than for upadacitinib (both 15 and 30 mg). In RA study M14-465, on the other hand, the risk was higher for upadacitinib 15 mg than for adalimumab. A similar pattern was observed in PsA study M14-572, where a dose-dependent increase in the risk for fracture was observed for upadacitinib, with EAIRs for both strengths of upadacitinib being higher than the EAIR for adalimumab.

Although there are some signals from the RA and PsA data indicating a higher risk for fractures for upadacitinib compared to adalimumab, the increased risk is not consistent across indications and compared to other comparators (placebo in the UC study and MTX in the RA study). It should be noted that stress fractures are included in section 4.8 of the SmPC of methotrexate-containing products which adds some uncertainty to the reliability of this comparison. Overall, the CHMP concluded that there is not enough evidence to conclude on a causal relation between upadacitinib and fractures. However, fracture has been added to the list of important potential risk in the RMP. Furthermore, additional data will be gained from the proposed post-authorization safety study for AD aiming to investigate growth in adolescents receiving upadacitinib. See 2.7.

Laboratory findings

Liver transaminases increased more in the upadacitinib arms than in the placebo arms. According to the MAH, few events were serious and led to study drug discontinuation. Both ALT and AST increases are included in the SmPC sections 4.4 and 4.8. Also, monitoring recommendations (although not very specific) are included in section 4.2. This is considered acceptable.

Anaemia is a known AE for upadacitinib, and monitoring recommendation and dose interruption recommendations are included in the SmPC. A decrease in neutrophil levels was observed during the first 4 weeks of the study, with quite stable levels thereafter. Neutropenia is a known risk with Rinvoq

treatment, and no SmPC updates are considered needed. The MAH proposed to add lymphopenia to section 4.8 of the SmPC. This was considered acceptable (see above).

According to the MAH, small mean increases in serum creatinine, which were not considered clinically meaningful, were observed with upadacitinib treatment, while grade 3 increases in serum creatinine and TEAEs of renal dysfunction were infrequent. The CHMP agreed that no SmPC updates are needed.

Regarding lipids, the MAH proposed to include additional text in the SmPC section 4.8 which was accepted by the CHMP after some modifications in the wording.

Vital signs

Increased diastolic blood pressure was observed in a higher percentage of subjects with upadacitinib 45 mg (3.1%) vs. placebo (1.9%) during induction. With maintenance treatment, both systolic and diastolic blood pressure increases were observed in a higher percentage of subjects with upadacitinib 30 mg, while no difference was seen between upadacitinib 15 mg and placebo.

ECG

In the concentration-QTc analysis from the original MAA, the exposures are limited with respect to the subpopulation with moderate HI (2.4.4.). However, overall the preclinical, PK and clinical data do not raise any concern that Rinvoq would have a QT prolongating effect with the exposures reached with a 45 mg QD ER treatment.

Safety in special populations

Elderly patients (≥ 65 years of age) who received upadacitinib 45 mg induction treatment and upadacitinib 30 mg as maintenance treatment showed higher rates of SAEs, TEAEs leading to discontinuation of study drug, and herpes zoster compared to the lower maintenance dose and/or younger population. Therefore, a 15 mg dose is recommended in this population which was considered acceptable. Section 4.2 of the SmPC states that, for ulcerative colitis, doses higher than 15 mg once daily for maintenance therapy are not recommended in patients aged 65 years and older. In addition, Sections 4.4 and 4.8 of the SmPC reflect that there is an increased risk of adverse reactions with the upadacitinib dose of 30 mg once daily in patients aged 65 years and older. At the CHMP's request, it is also reflected in this section that the safety and efficacy of upadacitinib in patients aged 75 and older have not yet been established.

In patients with renal impairment, the proportion of patients with AEs increased with decreasing GFR during the induction phase, both in the upadacitinib and placebo groups. No specific pattern was observed during the maintenance phase. For patients with severe renal impairment, a 30 mg induction dose and a 15 mg maintenance dose is recommended. This is acceptable and adequately reflected in the SmPC.

Upadacitinib is contraindicated during pregnancy. As of 31 May 2021, there were a total of 93 pregnancies reported in female subjects in upadacitinib clinical studies. No congenital anomalies were identified.

15 vs 30 mg as maintenance dose

In the RA studies which led to the approval of upadacitinib 15 mg, a less favourable safety profile was observed for the 30 mg dose (n=1204 patients) than for the 15 mg dose (n=1213 patients). This included serious infections, opportunistic infections, herpes zoster, malignancy, MACE, and deaths.

In the UC studies, it is not obvious that the 30 mg dose is associated with a less favourable safety outcome. Although the frequency of overall AEs was higher for the 30 mg dose, SAEs occurred more frequently in the 15 mg arm. There was one death in each of the 15 and 30 mg arms. With regards to

adverse events of special interest, the frequency of serious infections and opportunistic infections were similar in both groups, while the frequencies of herpes zoster, malignancy, MACE, and increased liver enzymes were higher in the 30 mg group. Thus, in some aspects the 30 mg dose seems less favourable, although the trend is not consistent for all safety outcomes. Although it is acknowledged there are significant differences between the RA and UC population regarding for example age and concomitant medication, safety data from the RA studies are important for this assessment because of a larger sample size (~2400 patients in the RA program vs ~600 patients in the pooled "all treated" UC population).

Given the recent concern on potential dose-dependent class effects of the JAK inhibitors which is currently being assessed as part of the referral (EMEA/H/A-20/1517), the MAH was requested to further justify why the observed effects for the 30 mg dose outweighs the potential risks and to provide a clearer guidance in section 4.2 to include a more detailed description on which patients that might benefit from the higher 30 mg dose. In their response, the MAH clarified that patients with high disease burden (severe disease, pancolitis or extra-intestinal manifestations) as well as patients who needed a prolonged induction might benefit from a higher 30 mg maintenance dose, Section 4.2 of the SmPC was revised accordingly. This was considered acceptable to the SmPC, see also 2.6.6.

The safety of upadacitinib 15 and 30 mg has been characterised in previous studies in the RA, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis indications. Safety data for the 45 mg induction dose is more limited, since it is currently not approved for any indication and data are limited to the 719 upadacitinib-treated patients in the UC inductions studies. Safety data for the prolonged 16-week induction is even more scarce, since only 127 patients received this regimen in the UC studies.

Overall, long-term data for upadacitinib are still limited, since upadacitinib was first approved in 2019. Interim long-term data through Week 156 from the RA studies have recently been assessed within variation II/14. Long-term data from the UC studies needs to be submitted post approval. This is particularly important with regards to the risk for malignancy, since patients with UC are at increased risk for malignancy. The long-term extension study M14 533 is included in the RMP with final report in 2026, as well as an observational long-term safety study of upadacitinib use in UC patients.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.3. Conclusions on the clinical safety

In the placebo-controlled ulcerative colitis 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%), blood CPK increased (7.6%), acne (6.3%), neutropaenia (6.0%), rash (5.2%), herpes zoster (4.4%), hypercholesterolemia (4.0%), folliculitis (3.6%), herpes simplex (3.2%), and influenza (3.2%).

The overall safety profile observed in patients with ulcerative colitis was generally consistent with that observed in patients with rheumatoid arthritis.

A higher rate of herpes zoster was observed with an induction treatment period of 16 weeks vs 8 weeks.

Based on the limited data in ulcerative colitis patients aged 65 years and older, there was a higher rate of overall adverse reactions with the upadacitinib 30 mg dose compared to the 15 mg dose with maintenance treatment.

Long-term data from the UC studies needs to be submitted post approval. This is particularly important with regards to the risk for malignancy, since patients with UC are at increased risk for malignancy. The long-term extension study M14 533 is included in the RMP with final report in 2026, as well as an observational long-term safety study of upadacitinib use in UC patients.

Based on the safety data submitted as part of this application, the CHMP concluded that the safety of upadacitinib 45 mg as induction and 15 mg or 30 mg as maintenance treatment in the ulcerative colitis population is considered acceptable.

2.7. Risk Management Plan

The CHMP endorsed the Risk Management Plan version 6.2 with the following content:

2.7.1. Safety concerns

Summary of Safety Concerns	
Important identified risks	• Serious and opportunistic infections including TB • Herpes zoster
Important potential risks	• Malignancies • MACE • VTEs (deep venous thrombosis and pulmonary embolus) • GI perforation • 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

AD = atopic dermatitis; GI = gastrointestinal; DILI = drug-induced liver injury; MACE = major adverse cardiovascular event; TB = tuberculosis; VTE = venous thromboembolic event

2.7.2. 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 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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; and 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 • 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 • 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, 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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; and fractures Missing information: use in very elderly (≥ 75 years of age); long-term safety	• Draft protocol • 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 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 13 years post-approval (31 March 2033) • 30 June 2033

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 • Final study report • Targeted submission of final study report to EMA	• Submitted 16 March 2020) • 30 September 2024 • 31 December 2024 (estimated)
Study P20-390 Prospective Cohort Study of Long-term Safety of Upadacitinib in the Treatment of AD in Denmark and Sweden/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, eczema herpeticum/Kaposi's varicelliform	Important identified risks: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTE; GI perforation; DILI; and 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	• Final Study Report	• Estimated Q4 2033

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	eruption, active TB, GI perforations, evidence of DILI, and fractures. To describe the incidence of the above adverse events in patients who receive upadacitinib 15 mg and 30 mg. To describe the incidence of the above adverse events 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.	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 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 Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P21-825 Effectiveness Evaluation of aRMMs for Upadacitinib in the Treatment of 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.	Important identified risks: serious and opportunistic infections including TB; herpes zoster Important potential risks: MACE; VTEs; 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
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 versus 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	Missing information: long-term safety in adolescents with AD	• Final study report	• Estimated Q4 2030
Study P23-480 Long-term Safety Study of Upadacitinib	To compare, where possible, the incidence of malignancy (excluding NMSC), NMSC, MACE, VTE, serious	Important identified risk: serious and opportunistic infections including TB; herpes zoster	• Final study report	• Estimated Q3 2034

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Use in UC Patients in Sweden and Denmark/Planned	infections, herpes zoster, opportunistic infections, active TB, GI perforations, DILI, and fractures in adults with UC who receive upadacitinib relative to those who receive a biologic comparator therapy for the treatment of UC. 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.	Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; and 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 of initiation of upadacitinib or other systemic drug therapies.		

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P23-479 Drug Utilization Study to Evaluate the Effectiveness 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; 5. To describe prescribing physicians' adherence to recommendations for patient screening and laboratory monitoring.	Important identified risk: serious and opportunistic infections including TB; herpes zoster Important potential risks: MACE; VTEs; 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
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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and 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
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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and 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
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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and 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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and 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
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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and 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
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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and 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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and 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
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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and 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
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 DB Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and 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 topical corticosteroids in adolescent and adult subjects with AD who have completed the DB Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and foetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents with AD	• Final study report	• 04 April 2026
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 DB Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and foetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents with AD	• Final study report	• 21 April 2026
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 non-responders 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 Important potential risks: malignancies; MACE; VTEs; GI perforation; DILI; fractures; and foetal malformation following exposure in utero Missing Information: long-term safety	• Final study report	• Q1 2025

AD = atopic dermatitis; aRMMs = additional risk minimization measures; AS = ankylosing spondylitis; bDMARDs = biologic disease-modifying anti-rheumatic drugs; DB = double blind; DILI = drug-induced liver injury; EMA = European Medicines Agency; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; PsA = psoriatic arthritis; PSUR = periodic safety update report; QD = once daily; RA = rheumatoid arthritis; SDS = standard deviation score; TB = tuberculosis; UC = ulcerative colitis; US = United States; VTE = venous thromboembolic event

2.7.3. 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. • 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 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 active, chronic, or recurrent infections. o 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	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 • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation • P20-390: Long-term Safety Study of Upadacitinib use in AD Patients in Denmark and Sweden • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P23-480: Long-Term Safety Study of Upadacitinib Use in UC Patients in Sweden and Denmark • P23-479: Drug Utilization Study to Evaluate the Effectiveness 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 AS trial (Study M16-098) • 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
	monitored, and upadacitinib should be interrupted if the patient is not responding to therapy. o 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. Additional risk minimization measures: • HCP educational brochure • PAC Other routine risk minimization measures: Prescription only medicine.	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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 if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Additional risk minimization measures: • HCP educational brochure • PAC 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 in Denmark and Sweden • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P23-480: Long-Term Safety Study of Upadacitinib Use in UC Patients in Sweden and Denmark • P23-479: Drug Utilization Study to Evaluate the Effectiveness 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 AS trial (Study M16-098) • 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)
Malignancies	Routine risk minimization measures: • SmPC Section 4.4 describes the risk in patients with RA and indicates that upadacitinib clinical data are currently limited and long-term studies are ongoing. • The PL warns that patients who have cancer, develop a new lesion or any	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	change in the appearance of an area on the skin, or are at high risk of developing skin cancer should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 advises that periodic skin examination is recommended for patients who are at increased risk for skin cancer. 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 in Denmark and Sweden • P23-480: Long-Term Safety Study of Upadacitinib Use in UC Patients 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 AS trial (Study M16-098) • 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)
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 contains a section on CV risk including a statement on increased CV risk in RA patients and need for management of CV risk factors as part of usual standard care. • SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • The PL warns that patients who have heart problems, high blood pressure, or high cholesterol should consult their doctor or pharmacist before and during treatment with Rinvoq. Additional risk minimization measures: • HCP educational brochure	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 in Denmark and Sweden • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• PAC Other routine risk minimization measures: Prescription only medicine.	• P23-480: Long-Term Safety Study of Upadacitinib Use in UC Patients in Sweden and Denmark • P23-479: Drug Utilization Study to Evaluate the Effectiveness 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 AS trial (Study M16-098) • 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)
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 patients receiving JAK inhibitors including upadacitinib. • The PL warns that patients who have had blood clots in the veins of the legs (deep vein thrombosis) or lungs (pulmonary embolism) should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get a painful swollen leg, chest pain, or shortness of breath. • SmPC Section 4.4 advises that upadacitinib should be used with caution in patients at high risk for deep vein thrombosis/pulmonary embolism. Risk factors that should be considered in determining the patient's risk for deep venous thrombosis/pulmonary embolism include older age, obesity, a medical history of deep venous thrombosis/pulmonary embolism, patients undergoing major surgery, and prolonged immobilisation. • SmPC Section 4.4 advises that if clinical features of deep vein thrombosis/pulmonary embolism	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 in Denmark and Sweden • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P23-480: Long-Term Safety Study of Upadacitinib Use in UC Patients in Sweden and Denmark • P23-479: Drug Utilization Study to Evaluate the Effectiveness of aRMMs

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment. Additional risk minimization measures: • HCP educational brochure • PAC Other routine risk minimization measures: Prescription only medicine.	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 AS trial (Study M16-098) • 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)
GI perforation	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 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 in Denmark and Sweden • P23-480: Long-Term Safety Study of Upadacitinib Use in UC Patients 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 AS trial (Study M16-098) • 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
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: 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 in Denmark and Sweden • P23-480: Long-Term Safety Study of Upadacitinib Use in UC Patients 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 AS trial (Study M16-098) • 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)
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.	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: Drug Utilization Study to Evaluate the Effectiveness of aRMMs for Upadacitinib in UC in Sweden and Denmark • Long-term extension portion of Phase 3 RA trials (Studies M13-542,

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• 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 brochure • PAC Other routine risk minimization measures: Prescription only medicine.	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 AS trial (Study M16-098) • 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)
Fractures	Routine risk minimization measures: Routine risk communication: 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 in Denmark and Sweden • P21-824: A Study of Growth in Adolescents With AD Who Receive Upadacitinib • P23-480: Long-Term Safety Study of Upadacitinib Use in UC Patients 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 AS trial (Study M16-098) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• Long-term extension Phase 3 UC trial (Study M14-533)
Use in very elderly (≥ 75 years of age)	Routine risk minimization measures: • SmPC Section 4.2 states that there are limited data in patients aged 75 years and older. • SmPC Section 4.4 states that as there is a higher incidence of infections in the elderly ≥ 65 years of age, caution should be used when treating this population. 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 • 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 in Denmark and Sweden • P23-480: Long-term Safety Study of Upadacitinib Use in UC Patients in Sweden and Denmark
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 in Denmark and Sweden • P23-480: Long-term Safety Study of Upadacitinib Use in UC Patients in Sweden and Denmark
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 use in patients with severe hepatic impairment. • The PL advises that patients do not take Rinvoq if they have severe liver	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 in Denmark and Sweden

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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.	• P23-480: Long-term Safety Study of Upadacitinib Use in UC Patients in Sweden and Denmark
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, and AD, the recommended dose is 15 mg QD for patients with severe renal impairment and that for UC, 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 in Denmark and Sweden • P23-480: Long-term Safety Study of Upadacitinib Use in UC Patients in Sweden and Denmark
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 • P20-390: Long-term Safety Study of Upadacitinib use in AD Patients in Denmark and Sweden

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• P23-480: Long-term Safety Study of Upadacitinib Use in UC Patients 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 AS trial (Study M16-098) • 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 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): • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • P20-390: Long-term Safety Study of Upadacitinib use in AD Patients in Denmark and Sweden • P21-824: A Study of Growth in Adolescents With AD Who Receive Upadacitinib

2.7.4. Conclusion

The CHMP considered that the risk management plan version 6.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

As a consequence of the extension of indication sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC and the Additional risk minimisation measures in the Annex II are updated. The Package Leaflet is updated accordingly.

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to RINVOQ 15 mg prolonged-release tablets and RINVOQ 30 mg prolonged-release tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

UC is a chronic, relapsing inflammatory disease of the large intestine characterized by diffuse and continuous inflammation and ulceration of mainly the innermost lining of the colon starting from the rectum. Subjects are typically diagnosed with UC in their 20s or 30s during prime productivity years. The hallmark clinical symptoms include abdominal pain, bloody diarrhoea associated with rectal urgency and tenesmus with moderate to severe UC having at least 5 bowel movements per day frequently associated with blood. The clinical course is marked by exacerbation and remission. Without appropriate treatment UC results in profound clinical symptoms requiring physician visits, hospitalizations, surgery, all resulting in a decreased quality of life.

The most severe intestinal manifestations of UC which are life threatening and can be fatal are toxic megacolon and perforation. Extraintestinal complications include arthritis (peripheral or axial involvement), dermatological conditions (erythema nodosum, aphthous stomatitis, and pyoderma gangrenosum), inflammation of the eye (uveitis), and liver dysfunction (primary sclerosing cholangitis). Subjects with UC have a modest increased risk of cancer overall and are at an increased risk for colon cancer during the first year after diagnosis.

Medical therapy is used initially however about 15% of subjects still require surgery due to failure of medical therapy to control the disease or development of colonic dysplasia. Subjects with newly diagnosed UC have a 5-year colectomy risk of approximately 10 – 35%. The burden of UC on the patient and healthcare system remains high (physician visits and hospitalization) reflecting the need for better management of this disease.

3.1.2. Available therapies and unmet medical need

The therapeutic goal in UC is to induce and maintain a long-term corticosteroid-free remission. Corticosteroids while effective for induction cannot be used long-term due to toxicities, thus as new systemic therapies are developed, they should be effective without the need for long-term

corticosteroids. Conventional therapies such as immunomodulators may be effective for maintenance but have no role in induction and may require monitoring of leucocytes and hepatic function. TNF inhibitors are effective for both induction and maintenance; however, have been associated with serious infections and malignancies. Over the past decade, there is an emerging need for new therapies for subjects who have previously experienced inadequate efficacy or intolerance to TNF inhibitors. Recently approved therapies for moderate to severe UC have incorporated study populations including subjects with inadequate response to TNF inhibitors and/or inadequate response to conventional therapies.

- Vedolizumab is an anti-integrin recommended by American Gastroenterological Association (AGA) for subjects naïve to biologic agents. GEMINI included a population of approximately 1/3 previously treated with anti-TNFs. Clinical remission (rate of 41.8% for vedolizumab) and endoscopic improvement rates (rate of 52% for vedolizumab) for vedolizumab were 26% and 32% higher than placebo at Week 52.
- Ustekinumab is an inhibitor of IL-12 and IL-23 and recommended by AGA following infliximab failure. UNIFI included a population of approximately 50% who failed at least 1 biologic. Clinical remission (rate of 43.8% for ustekinumab) and endoscopic improvement rates (rate of 51.1% for ustekinumab) for ustekinumab were 19% and 20% higher than placebo at Week 44.
- Tofacitinib (JAK inhibitor) is indicated in the EU after failure or intolerance to conventional therapy or biologics, whereas in the US it is indicated after failure of TNF inhibitors. OCTAVE included a population of approximately 50% who previously failed or were intolerant to TNF blockers. Clinical remission (rate of 34% for tofacitinib) and endoscopic improvement rates (rate of 37% for tofacitinib) for tofacitinib (5 mg twice daily) were 23% and 24% higher than placebo at Week 52.
- Filgotinib is an oral JAK1 inhibitor with high in vitro functional specificity for kinases 1 over 2 and is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.
- Ozanimod (sphingosine 1-phosphate receptor modulator) is currently approved in the US only, for the treatment of moderate to severe UC. The Phase 3 study population included 30% of subjects who had previously failed or were intolerant to TNF blockers and of these subjects, 63% received at least two biologics including TNF blockers. Clinical remission (rate of 37% for ozanimod) and endoscopic improvement rates (rate of 46% for ozanimod) for ozanimod were 19% and 19% higher than placebo at Week 52.

While the recent approvals of multiple therapies for UC (vedolizumab, ustekinumab, tofacitinib, etc.) are encouraging, clinical trial remission rates for both induction and maintenance treatment in UC remain limited with up to 18% of subjects achieving clinical remission during induction and up to 44% achieving clinical remission during maintenance. In addition, each has risks and challenges for some patients. Therefore, additional therapeutic options are needed.

3.1.3. Main clinical studies

The global clinical development program includes a Phase 2b dose-ranging induction study (Study M14-234 Substudy 1), two Phase 3 induction studies (Study M14-675 and Study M14-234 Substudy 2), a Phase 3 maintenance study (Study M14 234 Substudy 3), and a Phase 3 long-term extension study (Study M14-533).

The dose finding study (M14-234 Substudy 1) was designed to evaluate the efficacy and safety of 4 oral doses of upadacitinib (7.5 mg, 15 mg, 30 mg and 45 mg) compared to placebo as 8-week induction therapy in subjects with moderately to severely active UC. The study duration included a Screening Period of up to 5 weeks and an 8-week double-blind (DB) Induction Period.

The pivotal induction studies (Study M14-675 and Study M14-234 Substudy 2) were phase 3, randomized, double-blind, parallel-group, placebo controlled, multicenter studies designed to evaluate the efficacy and safety of oral administration of upadacitinib 45 mg compared to placebo as induction therapy for up to 16 weeks. The studies included a Screening Period of up to 5 weeks followed by a placebo controlled part with a duration of 8 weeks where patients were randomized in a 2:1 ratio to receive Upadacitinib 45 mg once daily or placebo. The studies also included a second part were patients who did not achieve a clinical response at week 8 received Upadacitinib 45 mg open label for additional 8 weeks.

Subjects who completed either one of the three studies (M14-234 substudy 1, M14-234 substudy 2 or study M14-675) and achieved a clinical response per adapted mayo score at week 8 (or week 16) were rerandomized into the Maintenance Study (Study M14 234 Substudy 3). Clinical response per adopted mayo score was defined as a decrease from baseline in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1. The subjects were randomized into four different cohorts depending on the treatment received in the induction studies, however the primary analysis for the main result were conducted in a subgroup of these patients who were randomized to either 15 mg or 30 mg upadacitinib or placebo.

Eligible subjects in the study were 16-75 years old with an active UC with an Adapted Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3. The patients should have demonstrated an inadequate response, loss of response, or intolerance to at least one of the following treatments including, oral aminosalicylates, corticosteroids, immunosuppressants and/or biologic therapies.

Primary efficacy endpoint was clinical remission per adapted mayo score, a composite endpoint. To achieve the primary endpoint “clinical remission per adapted mayo score” the patient must have a stool frequency score (SFS) ≤1 and not greater than baseline, a rectal bleeding score (RBS) of 0, and endoscopic subscore ≤ 1 (with no friability).

A total of 988 patients were included in the analysis of the induction studies (319 and 341 Upadacitinib 45 mg patients and 154 respective 174 placebo patients. In the maintenance study 451 patients were included in the analysis (148 upadacitinib 15 mg, 154 Upadacitinib 30 mg and 149 placebo). Prior treatment failure to at least 1 biologic therapy was seen in around 50% of the patients.

3.2. Favourable effects

In the induction studies, the primary endpoint clinical remission per adapted mayo score at week 8 was reached in 83/319 (26.1%) and 114/341 (33.5%) in the Upadacitinib 45 mg groups and 7/154 (4.8%) and 7/174 (4.1%) in the placebo groups. The between group difference was 21.6 % (95% CI 15.8, 27.4 p<0.001) and 29.0% (95% CI 23.2, 34.7, p<0.001) in the M14-234 substudy 2 and the M14-675 study respectively.

All ranked key secondary endpoints were significantly in favour of Upadacitinib 45 mg (p<0.001).

- Endoscopic improvement at week 8

Upadacitinib 36.3% vs placebo 7.4% (difference 29.3%, CI 22.6, 35.9, p<0.001) study M14-234 SS2

Upadacitinib 44.0% vs placebo 8.3% (difference 35.1%, CI 28.6,41.6, p<0.001) study M14-675

- Endoscopic remission at week 8

Upadacitinib 13.7% vs placebo 1.3% (difference 12.7%, CI 8.4, 17.0, p<0.001) study M14-234 SS2

Upadacitinib 18.2% vs placebo 1.7% (difference 15.9%, CI 11.4, 20.3, p<0.001) study M14-675

- Clinical Response per adapted mayo score at week 8

Upadacitinib 72.6% vs placebo 27.3% (difference 46.3%, CI 38.4, 54.2, p<0.001) study M14-234 SS2

Upadacitinib 74.5% vs placebo 25.4% (difference 49.4%, CI 41.7,51.7, p<0.001) study M14-675

- Clinical response per partial adapted mayo score at week 2

Upadacitinib 60.1% vs placebo 27.3% (difference 33.3%, CI 24.8, 41.8, p<0.001) study M14-234 SS2

Upadacitinib 63.3% vs placebo 25.9% (difference 37.0%, CI 28.8, 45.1, p<0.001) study M14-675

- Histologic improvement at week 8

Upadacitinib 55.0% vs placebo 22.5% (difference 32.2%, CI 23.8, 40.7, p<0.001) study M14-234 SS2

Upadacitinib 62.2% vs placebo 24.5% (difference 37.9%, CI 29.8, 46.1, p<0.001) study M14-675

- Mucosal healing at week 8

Upadacitinib 10.7% vs placebo 1.3% (difference 9.7%, CI 5.7, 13.7, p<0.001) study M14-234 SS2

Upadacitinib 13.5% vs placebo 1.7% (difference 11.3%, CI 7.2, 15.3, p<0.001) study M14-675

Also, all other ranked secondary endpoints Histologic-Endoscopic mucosal improvement at week 8, No reported abdominal pain at week 8, No reported bowel urgency at week 8, Change from baseline in IBDQ total score at week 8, Change from baseline in FACIT-F score at week 8, Histologic-Endoscopic mucosal improvement at week 8 were significantly in favour of Upadacitinib 45 mg (p<0.001).

In the maintenance study, the primary endpoint clinical remission per adapted mayo score at week 52 was achieved as follow:

Upadacitinib 15 mg 42.3% vs placebo 12.1% (difference 30.7%, CI 21.7, 39.8, p<0.001)

Upadacitinib 30 mg 51.7% vs placebo 12.1% (difference 39.0%, CI 29.7, 48.2, p<0.001)

All ranked key secondary endpoints were significantly in favour of both Upadacitinib 15 and 30 mg (p<0.001).

- Maintenance of clinical remission

Upadacitinib 15 mg 59.2% vs placebo 22.2% (difference 37.4%, CI 20.3, 54.6, p<0.001)

Upadacitinib 30 mg 69.7% vs placebo 22.2% (difference 47.0%, CI 30.7, 63.3, p<0.001)

- Corticosteroid-free clinical remission

Upadacitinib 15 mg 57.1% vs placebo 22.2% (difference 35.4%, CI 18.2, 52.7, p<0.001)

Upadacitinib 30 mg 68.0% vs placebo 22.2% (difference 45.1%, CI 28.7, 61.6, p<0.001)

- Endoscopic improvement

Upadacitinib 15 mg 48.7% vs placebo 14.5% (difference 34.4%, CI 25.1, 43.7, p<0.001)

Upadacitinib 30 mg 61.6% vs placebo 14.5% (difference 46.3%, CI 36.7, 55.8, p<0.001)

- Endoscopic remission

Upadacitinib 15 mg 24.2% vs placebo 5.6% (difference 18.7%, CI 11.0, 26.4, p<0.001)

Upadacitinib 30 mg 25.9% vs placebo 5.6% (difference 19.4%, CI 11.7, 27.2, p<0.001).

3.3. Uncertainties and limitations about favourable effects

The study uses an Adapted Mayo Score (Adapted Mayo Score of 5 to 9 and endoscopy subscore of 2 to 3), excluding the PGA to define patients with moderately to severely active ulcerative colitis for inclusion in the study. Although this can be acceptable, no minimal level of symptom burden was defined in the study and the relation to the full mayo score previous used in clinical studies are not fully explored. Upon request the MAH provided additional information confirming that >99% of the patients also fulfilled the full mayo score definition of moderately to severe active disease and that the result is valid also in the populations with a clinically relevant symptom burden at baseline. This was considered acceptable to the CHMP.

With respect to concomitant UC medications use, the proportions of subjects taking immunosuppressive treatment at baseline were few (<2%), and thiopurines (eg azathioprine and 6-MP) were not allowed during the studies. In addition, the doses of 5-ASA and thiopurines acceptable for the patient to have tried before inclusion were low, and no doses for concomitant medication were reported, raising a concern of undertreatment in the placebo population. However, upon request additional information were provided confirming that baseline concomitant treatment were similar in the treatment groups and the SmPC was updated to inform that thiopurine were not allowed during the studies.

The primary endpoint used in the studies “clinical remission per adapted mayo score” is a composite endpoint evaluating symptoms and endoscopic features of UC, using 3 parts of the well-known Mayo Score, however with exclusion of the Physician global scale. Similar (but not identical) endpoints have been used in other studies of approved treatments for UC, however a composite endpoint such as this is not in line with the EMA UC GL (CHMP/EWP/18463/2006 rev 1), which states that clinical (symptoms) and endoscopic remission should be evaluated as co-primary endpoints to ensure a beneficial effect over placebo in both parts. Additional information provided by the MAH confirmed that a clinically relevant effect was seen in both clinical symptoms and healing of the mucosa.

The MAH also suggests additional 8 weeks of 45 mg induction treatment for patients who have not achieve a clinical response at week 8. This suggestion is based on the results from the second part of the induction studies, were 125 patients who did not achieve a clinical response at week 8 on 45 mg Upadacitinib continued to receive the same dose open label for in total 16 weeks. Integrated data from the two pivotal induction studies showed that 48.3% of these patients achieved a clinical response per Adapted Mayo at Week 16 although only 5.6% achieved clinical remission per adapted Mayo score at week 16. Endoscopic response at week 16 were seen in only 14.3% patients. Of the 45 patients that continued to the maintenance phase, 8/24 (33.3%) of the patients randomised to 30mg upadacitinib and 4/21 (19%) of the patients randomised to 15 mg were in clinical remission at week 52. A majority of the patients in need of a prolonged treatment represented a difficult to treat patient population, with 66.4% of patients previous failed biologics. Since no relevant clinical features could identify the patients more likely to respond after a prolonged induction treatment, the MAH’s suggestion to provide this for all patients who may require it per the physician's judgment based on the condition of each patient was agreed with a cross-reference to available efficacy and safety data in sections 4.8 and 5.1 of the SmPC.

Also, although both maintenance doses of Upadacitinib were statistically significantly better than placebo, the proportion of patients achieving mucosal healing and endoscopic remission at week 52 were similar between the two Upadacitinib doses (24.2% and 25.9% in endoscopic remission).

Additional information regarding corticosteroid free symptomatic remission and corticosteroid free endoscopic remission confirmed efficacy in both doses. The MAH clarified that patients with high disease burden (severe disease, pancolitis or extra-intestinal manifestations) as well as patients who needed a prolonged induction might benefit from a higher 30 mg maintenance dose. At the CHMP request, this was adequately reflected in the section 4.2 of the SmPC with a statement that the lowest effective dose should be considered.

3.4. Unfavourable effects

Overview of adverse events

During the placebo-controlled 8-week induction period, the frequency of AEs was 52.6% in the placebo group and 55.4% in the UPA 45 mg group. SAEs occurred in 5.8% in the placebo group and 3.1% in the UPA group. There were no deaths in either group.

During the maintenance phase, the EAIR of AEs was lower in both UPA groups (UPA 15 mg: 328.4 and UPA 30 mg: 320 E/100PYs) than in the placebo group (509E/100PYs). AEs and serious adverse events were more frequent in the UPA 15 mg group (AE: 328.4E/100PYs, SAE: 13.2E/100PYs) than in the UPA 30 mg group (AE: 320 E/100PYs, SAE:10.6 E/100PYs).

When comparing patients receiving 8-week induction and 16-week induction, the EAIR of AEs were equally frequent during the maintenance phase in the 15 mg group (294.4E/100PYs) and 30 mg group (297.3E/100 PYs) among patients receiving 8-week induction, however AEs were less frequent in the 15 mg group (231.2E/100PYs) than in the 30 mg group (337.8E/100 PYs) among patients receiving 16-week induction.

In the all analysis set, the EAIR of AEs was slightly lower for the UPA 15 mg group (323.3E/100PYs) than for the UPA 30 mg group (364E/100PYs), but SAEs were not more frequent in the higher dose group.

Three new AEs have been included in the table of adverse reactions in Section 4.8 of the SmPC with a frequency “common”: lymphopenia, hyperlipidaemia, and rash.

Common adverse events

Frequent AEs reported more frequently in the UPA than in the placebo group during the induction phase were acne, increased CPK, nasopharyngitis, neutropenia, pyrexia, rash, folliculitis and upper respiratory tract infection. These are all listed in section 4.8 of the SmPC and does not constitute any new safety signals.

Deaths and serious adverse events

There were two deaths reported, one in the UPA 15 mg arm (opioid overdose with anoxic brain injury) and one in the UPA 30 mg arm (pancreatic cancer). One additional death was reported due to COVID-19 and pulmonary embolism in a patient receiving updacitinib 30 mg.

Adverse events of special interest

During the induction phase, serious infections occurred with a similar frequency in the placebo and UPA 45 mg groups. During the maintenance phase, the frequency of serious infections was similar in UPA 15 mg and 30 mg groups, and more frequent in the placebo group. In the all-treated dataset, the EAIR of serious infections was slightly higher in the upadacitinib groups, but no dose-dependency was observed.

Opportunistic infections excluding TB and herpes zoster occurred with a similar frequency in the upadacitinib and placebo groups during the induction phase, and were more frequent in the placebo group during the maintenance phase. No dose-dependent risk was observed.

During the induction phase, there were 4 cases of herpes zoster, all in the UPA 45 mg arm. Among these was one case of disseminated herpes zoster. During the prolonged induction phase, the EAIR increased from 5.0 E/100PYs to 15.3E/100PYs. During the maintenance phase, there were five serious cases of HZ reported, all in the upadacitinib arms. These include Bell's palsy and HZ meningitis. A higher rate of herpes zoster was observed with an induction treatment period of 16 weeks vs 8 weeks. This is adequately reflected in the SmPC.

The EAIR for malignancies excluding non-melanoma skin cancer (NMSC) was lower in the UPA 15 mg group than in the placebo group. A dose-dependent increase in EAIR is observed, however the number of malignancies were few. Also regarding NMSC, the EAIR is higher for the UPA 30 mg group. Malignancy is listed as important potential risk in the RMP and will be further studied with the data from the ongoing PASS studies (see 2.7.).

There were no cases of MACE reported in the UPA 15 mg group, and 3 cases in the UPA 30 mg group. A dose-dependency is observed; however, the total number of cases are few (n=3 in the UPA 30 mg group) hampering firm conclusions.

There were 3 gastrointestinal perforations reported, 2 in subjects receiving placebo and 1 in a subject receiving upadacitinib 15 mg (due to a complication of a routine study colonoscopy).

During the induction phase, there was one case of venous thromboembolism (VTE) reported in the placebo and UPA 15 mg arms, respectively. Throughout the whole study, the EAIR for VTE was slightly higher for the UPA 15 mg (0.6E/100PYs) and UPA 30 mg groups (0.5E/100PYs) than for the placebo group (0 cases).

Laboratory findings

Liver transaminases increased more in the upadacitinib arms than in the placebo arms. In patients receiving a prolonged induction, the rate of hepatic disorders was higher during week 0-16 than during week 0-8.

A decrease in neutrophil levels was observed during the first 4 weeks of the study, with quite stable levels thereafter. The percentage of subjects with TEAEs of lymphopenia was higher in the upadacitinib 45 mg group (2.5%) compared with the placebo group (0.5%).

According to the MAH, small mean increases in serum creatinine, which were not considered clinically meaningful, were observed with upadacitinib treatment, while grade 3 increases in serum creatinine and TEAEs of renal dysfunction were infrequent. The CHMP agreed that no SmPC updates are needed.

Regarding lipids, an increase in LDL and HLD levels were observed during upadacitinib treatment.

The CHMP concluded that the overall safety profile observed in patients with ulcerative colitis was generally consistent with that observed in patients with rheumatoid arthritis.

3.5. Uncertainties and limitations about unfavourable effects

The safety of upadacitinib 15 and 30 mg has been characterised in previous studies in the RA, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis indications. Safety data for the 45 mg induction dose is more limited, since it is currently not approved for any indication and data are limited to the 719 upadacitinib-treated patients in the UC inductions studies. Safety data for the prolonged 16-week induction is even more scarce, since only 127 patients received this regimen in the UC studies.

Overall, long-term data for upadacitinib are still limited, since upadacitinib was first approved in 2019. Interim long-term data through Week 156 from the RA studies have recently been assessed within variation II/14. Long-term data from the UC studies needs to be submitted post approval. This is particularly important with regards to the risk for malignancy, since patients with UC are at increased risk for malignancy. The long-term extension study M14 533 is included in the RMP with final report in 2026, as well as an observational long-term safety study of upadacitinib use in UC patients.

Based on the limited data in ulcerative colitis patients aged 65 years and older, there was a higher rate of overall adverse reactions with the upadacitinib 30 mg dose compared to the 15 mg dose with maintenance treatment. Therefore, a 15 mg dose is recommended in this population which was considered acceptable.

There are no data in UC patients aged 75 years and above. This is adequately reflected in the SmPC.

Although there are some signals from the RA and PsA data indicating a higher risk for fractures for upadacitinib compared to adalimumab, the increased risk is not consistent across indications and compared to other comparators (placebo in the UC study and MTX in the RA study). It should be noted that stress fractures are included in section 4.8 of the SmPC of methotrexate-containing products which adds some uncertainty to the reliability of this comparison. Overall, the CHMP concluded that there is not enough evidence to conclude on a causal relation between upadacitinib and fractures. However, fracture has been added to the list of important potential risk in the RMP. Furthermore, additional data will be gained from the proposed post-authorization safety study for AD aiming to investigate growth in adolescents receiving upadacitinib. See 2.7.

3.6. Effects Table

Table 68. Effects Table for Rinvoq and Ulcerative Colitis (data cut-off: 30 April 2021)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Clinical Remission per aMS at week 8	Proportion of patients with SFS≤1 and not greater than baseline, RBS)=0, and ES≤ 1 without friability	N (%)	Upa 45 mg 83/319 (26.1) 114/341 (33.5)	7/154 (4.8) 7/174 (4.1)	P<0.001 P<0.001	M14-234 SS2 M14-675
Endoscopic improvement at week 8	ES≤1 without friability	N (%)	116/319 (36.3) 150/341 (44.0) (	11/154 (7.4) 14/174 (8.3)	P<0.001 P<0.001	M14-234 SS2 M14-675
Endoscopic remission at week 8	ES=0	N (%)	44/319 (13.7) 62/341 (18.2)	2/154 (1.3) 3/174 (1.7)	P<0.001 P<0.001	M14-234 SS2 M14-675

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Clinical response per aMS at week 8	A decrease in the Adapted Mayo score ≥ 2 points and ≥ 30% from baseline, and a decrease in RBS ≥ 1 from baseline or an absolute RBS ≤ 1	N (%)	232/319 (72.6) 254/341 (74.5)	42/154 (27.3) 44/174 (25.4)	P<0.001 P<0.001	M14-234 SS2 M14-675
Clinical response per Partial Adapted Mayo Score at Week 2	A decrease in partial aMS ≥ 1 points and ≥ 30% from baseline, and a decrease in RBS≥ 1 from baseline or an absolute RBS ≤ 1		192/319 (60.1) 216/341 (63.3)	42/154 (27.3) 45/174 (25.9)	P<0.001 P<0.001	M14-234 SS2 M14-675
Mucosal Healing at Week 8	ES=0 and Geboes score <2	N (%)	34/319 (10.7) 46/341 (13.5)	2/154 (1.3) 3/174 (1.7)	P<0.001 P<0.001	M14-234 SS2 M14-675
Clinical Remission per aMS at week 52		N (%)	15 mg 63/148 (42.3) 30 mg 80/154 (51.7)	18/149 (12.1)	P<0.001 P<0.001	M14-234 SS3
Maintenance of clinical remission at Week 52	Clinical remission at Week 52 among subjects who have achieved clinical remission in the end of the induction treatment	N (%)	15 mg 28/47 (59.2) 30 mg 40/58 (69.7)	12/54 (22.2)	P<0.001 P<0.001	M14-234 SS3
Maintenance of corticosteroid-free clinical remission at Week 52	Clinical remission per aMS at Week 52 with corticosteroid free at least 90 days prior to the Week 52 visit among subjects who have achieved clinical remission in the end of the induction treatment	N (%)	15 mg 27/47 (57.1) 30 mg 39/58 (68.0)	12/54 (22.2)	P<0.001 P<0.001	M14-234 SS3

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Endoscopic remission at Week 52	ES=0	N (%)	15 mg 36/148 (24.2) 30 mg 40/154 (25.9)	8/149 (5.6)	P<0.001 P<0.001	M14-234 SS3
Unfavourable Effects						
Adverse event	AEs during 8-week induction	N (%)	398/719 (55.4)	199/378 (52.6)		Table 47
Serious adverse event	SAEs during 8-week induction	N (%)	22/719 (3.1)	22/378 (5.8)		Table 47
Adverse event	AEs during maintenance (cohort 1)	N (E/100 PYs)	15 mg: 599/250 (328.4) 30 mg: 636/251 (320.0)	652/245 (509.0)		Table 51
Serious adverse event	SAEs during maintenance (cohort 1)	N (E/100 PYs)	15 mg: 24/250 (13.2) 30 mg: 21/251 (10.6)	28/245 (21.9)		Table 51
Serious infections	Serious infections during maintenance (cohort 1)	N (E/100 PYs)	15 mg: 9/250 (4.9) 30 mg: 6/251 (3.0)	8/245 (6.2)		Table 57
Herpes zoster	HZ during maintenance (cohort 1)	N (E/100 PYs)	15 mg: 11/250 (6.0) 30 mg: 12/251 (6.0)	0		Table 57

Abbreviations:
Notes: Cohort 1: Placebo-controlled 52-week maintenance phase, in responders on 8-week induction with UPA 15 mg, 30 mg, 45 mg, re-randomised to UPA 15 mg, UPA 30 mg or placebo in the maintenance phase.

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 remission in patients with moderate to severe ulcerative colitis. A superior efficacy was seen in symptomatic relieve already at week 2, and after 8 weeks of induction treatment, >70% of the patients in the Upadacitinib group had achieved a clinical response. Also, when assessing endoscopic and histologic features of the mucosa at this early timepoint, Upadacitinib provided a beneficial effect compared to placebo regarding the strictest endpoint, mucosal healing (endoscopic and histologic remission) in a few patients and 36%

respectively 44% of the Upadacitinib treated patients had evidence of an endoscopic improvement (endoscopic subscore of ≤1), compared with less than 10% of the placebo treated patients. This is an important finding.

In the maintenance study statistically significant (<0.001) and clinically relevant treatment differences between both Upadacitinib doses (15 mg and 30 mg) and placebo were observed for the primary and all key secondary endpoints. Clinical remission, maintenance of remission and endoscopic improvement were achieved by around 42%, 59% and 49% of the upadacitinib 15 mg treated patients at week 52, with a treatment difference compared to placebo of >30% in these endpoints. This treatment effect is clearly clinically relevant and in line with other approved products with the same indication, although it is acknowledged that a formal comparison between products are not possible. In the patients treated with 30 mg upadacitinib, clinical remission, maintenance of remission and endoscopic improvement were achieved by an even higher proportion of patients, around 52%, 70% and 62%, however the proportion of patients achieving endoscopic remission at week 52 were similar between the two upadacitinib doses (24.2% and 25.9%). 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 safety profile of Rinvoq has been well characterised through studies in the currently approved indications. Also the safety profile of the recently proposed 45 mg induction dose is considered acceptable, since during the placebo-controlled induction phase the frequency of AEs and SAEs were less frequent among upadacitinib-treated patients than among placebo-treated patients. There are some concerns on the prolonged 16-week induction, primarily because an increased short-term risk for herpes zoster, and an increased long-term risk for serious infections, CPK elevation and anaemia. At CHMP's request, adequate guidance and information were provided in the SmPC.

Regarding the long-term risks, special attention is needed regarding the risk for malignancy since patients with UC are at increased risk for malignancy. Long-term data will be important for further understanding of this risk. This is adequately captured in the RMP.

The trade-off between the benefits and the risks with the 30 mg maintenance dose was discussed during the assessment. Although this dose is currently approved for the treatment of atopic dermatitis, there were concerns that the additional benefits gained with the 30 mg dose compared to the 15 mg dose in the current indication did not outweigh the potential risks with this higher dose. Previous experience from the RA studies have shown a dose-dependent risk for serious infections, opportunistic infections, herpes zoster, malignancy, MACE, and deaths. Since then, we have gained more knowledge on the safety of JAK inhibitors, indicating a possible dose-dependent risk for in particular MACE. With that data at hand, it seems reasonable to strive for the lowest effective dose. Although the 30 mg dose might be acceptable in certain selected patients, the 15 mg dose is probably sufficient for most patients. At the CHMP's request, the SmPC has been updated to indicate that the lowest effective dose for maintenance should be considered and that the 30 mg dose once daily may be appropriate for some patients, such as those with high disease burden or requiring 16-week induction treatment or patients who do not show adequate therapeutic benefit to 15 mg once daily.

3.7.2. Balance of benefits and risks

The two pivotal induction studies demonstrated a clinically relevant and statistically significant superiority of Upadacitinib 45 mg compared to placebo in inducing remission in patients with moderate to severe ulcerative colitis after 8 weeks of induction treatment. A prolonged induction for additional 8 week (in total 16 week) may be useful for patients without an initial response, but the safety concerns

regarding e.g. herpes zoster should be taken into consideration and the treatment should be stopped if no response is seen at week 16.

In the maintenance study statistically significant (<0.001) and clinically relevant treatment differences between both Upadacitinib doses (15 mg and 30 mg) and placebo were observed for the primary and all key secondary endpoints at week 52. The additional beneficial effect seen with the higher 30 mg dose could be of clinical importance in some patients, and the SmPC has been updated to include a statement that the lowest effective dose for maintenance should be considered.

The CHMP concluded that the efficacy data was adequate to support the new strength of 45mg and the new indication in the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

The following dosing recommendations were endorsed by the CHMP:

Induction

The recommended induction dose of upadacitinib is 45 mg once daily for 8 weeks. For patients who do not achieve adequate therapeutic benefit by week 8, upadacitinib 45 mg once daily may be continued for an additional 8 weeks (see sections 4.8 and 5.1). Upadacitinib should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

Maintenance

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

- A dose of 30 mg once daily may be appropriate for some patients, such as those with high disease burden or requiring 16 week induction treatment.
- A dose of 30 mg once daily may be appropriate for patients who do not show adequate therapeutic benefit to 15 mg once daily.
- The lowest effective dose for maintenance should be considered.

The overall safety profile observed in patients with ulcerative colitis was generally consistent with that observed in patients with rheumatoid arthritis.

Long-term data from the UC studies needs to be submitted post approval. This is particularly important with regards to the risk for malignancy, since patients with UC are at increased risk for malignancy. The long-term extension study M14-533 is included in the RMP with final report in 1Q 2025 , as well as an observational long-term safety study of upadacitinib use in UC patients.

3.7.3. Additional considerations on the benefit-risk balance

EMA's safety committee, PRAC, has started a review of the safety of Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis). Rinvoq is part of the products reviewed in the on-going referral. The review of JAK inhibitors in the treatment of inflammatory disorders has been initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004.

The recommendation on the present application is without prejudice to the final conclusions of the ongoing referral procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data.

3.8. Conclusions

The overall benefit/risk balance of RINVOQ is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, RINVOQ new strength is favourable in the following indication(s):

"Ulcerative colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent."

The CHMP therefore recommends the extension(s) of the marketing authorisation for RINVOQ subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- Additional risk minimisation measures

Prior to launch of RINVOQ in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The objective of the programme is to increase awareness of HCPs and patients on the risks of serious and opportunistic infections including TB, herpes zoster, foetal malformation (pregnancy risk), MACE, and VTEs and how to manage these risks.

The MAH shall ensure that in each Member State where RINVOQ is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use RINVOQ have access to/are provided with the following educational package:

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient Alert Card (PAC)

The Guide for healthcare professionals shall contain the following key elements:

- General introductory language that the HCP measure contains important information to assist the discussion with patients when prescribing upadacitinib. The brochure also informs on steps which can be taken to reduce a patient's risk for key safety aspects of upadacitinib.
- Language for HCPs to inform patients of the importance of the PAC
- *Risk of serious and opportunistic infections including TB*
    - Language on the risk of infections during treatment with upadacitinib
    - Language on increased risk of serious infections in patients ≥ 65 years of age
    - Details on how to reduce the risk of infection with specific clinical measures (what laboratory parameters should be used to initiate upadacitinib, screening for tuberculosis (TB), and getting patients immunised as per local guidelines, and interruption of upadacitinib if an infection develops)
    - Language on avoidance of live vaccines (i.e., Zostavax) prior to and during upadacitinib treatment
    - Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.
- *Risk of herpes zoster*
    - Language on the risk of herpes zoster during treatment with upadacitinib
    - Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.
- *Risk of foetal malformation*
    - Language on teratogenicity of upadacitinib in animals
    - Details on how to reduce the risk of exposure during pregnancy for women of childbearing potential based on the following: upadacitinib is contraindicated during pregnancy, women of childbearing potential should be advised to use effective contraception both during treatment and for 4 weeks after the final dose of upadacitinib treatment, and to advise patients to inform their HCP immediately if they think they could be pregnant or if pregnancy is confirmed.
- *Risk of MACE*
    - Language on the increased risk of major adverse cardiovascular event (MACE) in patients with immune-mediated inflammatory diseases and the need to consider typical CV risk factors (e.g., hypertension, hyperlipidaemia) when treating patients
    - Language on the risk of MACE during treatment with upadacitinib
    - Language on the risk of hyperlipidaemia during upadacitinib therapy
    - Details on monitoring of lipid levels and management of elevated lipid levels per clinical guidelines

- *Risk of VTE*
    - Examples of the risk factors which may put a patient at higher risk for venous thromboembolic events (VTE) and in whom caution is needed when using upadacitinib.
    - Language on the risk of VTE during treatment with upadacitinib
    - Language on need for discontinuation of upadacitinib, evaluation, and appropriate treatment for VTE if clinical features of deep venous thrombosis or pulmonary embolism develop

- Information for upadacitinib use in moderate to severe AD

- The 30 mg upadacitinib dose in atopic dermatitis
    - Language on dose-dependent increase in serious infections and herpes zoster with upadacitinib.
    - Language on dose-dependent increase in plasma lipids with upadacitinib.
    - Language that eczema herpeticum occurred in both placebo and upadacitinib-treated subjects with similar rates in the 30 mg and 15 mg groups.
    - Language that the 30 mg dose is not recommended in certain populations (patients with severe renal impairment and patients taking strong CYP3A4 inhibitors).
    - Reminder that the 15 mg dose is the recommended dose in patients ≥ 65 years of age.

- Upadacitinib use in adolescents 12 years and older
    - Reminder that live, attenuated vaccines (ie. varicella, MMR, BCG) which depending on local guidelines may be considered in adolescents. Language not to administer these vaccines immediately prior to or during upadacitinib treatment.
    - Language to remind adolescents of the potential pregnancy risks and on the appropriate use of effective contraception.
    - Language if their adolescent patient has not experienced menarche, to inform their adolescent patient or caregiver to let them know when they do.

- Information for upadacitinib use in ulcerative colitis
    - Reminder to review induction and maintenance dosing in product labeling.
    - Reminder that the 15 mg dose is the recommended maintenance dose in patients aged 65 and older.
    - Reminder about induction and maintenance dose in certain populations (patients taking strong CYP3A4 inhibitors and severe renal impaiment).

Instructions for how to access digital HCP information
Instructions on where to report AEs

The patient information pack should contain:
- Patient information leaflet
- A patient alert card

- The patient alert card shall contain the following key messages:
    - Contact details of the upadacitinib prescriber
    - Language that the PAC should be carried by the patient at any time and to share it with HCPs involved in their care (i.e., non-upadacitinib prescribers, emergency room HCPs, etc.)
    - Description of signs/symptoms of infections the patient needs to be aware of, so that they can seek attention from their HCP:
        - Language to advise patients and their HCPs about the risk of live vaccinations when given during upadacitinib therapy. Examples of live vaccines are provided.

- Description of targeted risks for awareness by the patient and for HCPs involved in their care including:
  - Elevations in plasma lipids and the need for monitoring and lipid lowering treatment
  - A reminder to use contraception, that upadacitinib is contraindicated during pregnancy, and to notify their HCPs if they become pregnant while taking upadacitinib
- Description of signs/symptoms of deep venous thrombosis or pulmonary embolism which the patient needs to be aware of, so that they can seek attention from an HCP

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		Type	Annexes affected
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A
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, II, IIIA and IIIB

Extension application to add a new strength (45 mg) of the prolonged-release tablets, grouped with a type II variation (C.I.6.a) for the existing 15mg and 30mg strengths to include the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent. As a consequence of the extension of indication sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC and the Additional risk minimisation measures in the Annex II are updated. The Package Leaflet is updated accordingly. The RMP (version 6.2) is adopted.

This recommendation is without prejudice to the final conclusions of the ongoing referral procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data.