Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials

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Summary

Background There is a great unmet need for advanced therapies that provide rapid, robust, and sustained disease control for patients with ulcerative colitis. We assessed the efficacy and safety of upadacitinib, an oral selective Janus kinase 1 inhibitor, as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis.

Methods This phase 3, multicentre, randomised, double-blind, placebo-controlled clinical programme consisted of two replicate induction studies (U-ACHIEVE induction [UC1] and U-ACCOMPLISH [UC2]) and a single maintenance study (U-ACHIEVE maintenance [UC3]). The studies were conducted across Europe, North and South America, Australasia, Africa, and the Asia-Pacific region at 199 clinical centres in 39 countries (UC1), 204 clinical centres in 40 countries (UC2), and 195 clinical centres in 35 countries (UC3). Patients aged 16–75 years with moderately to severely active ulcerative colitis (Adapted Mayo score 5–9; endoscopic subscore 2 or 3) for at least 90 days were randomly assigned (2:1) to oral upadacitinib 45 mg once daily or placebo for 8 weeks (induction studies). Patients who achieved clinical response following 8-week upadacitinib induction were re-randomly assigned (1:1:1) to upadacitinib 15 mg, upadacitinib 30 mg, or placebo for 52 weeks (maintenance study). All patients were randomly assigned using web-based interactive response technology. The primary endpoints were clinical remission per Adapted Mayo score at week 8 (induction) and week 52 (maintenance). The efficacy analyses in the two induction studies were based on the intent-to-treat population, which included all randomised patients who received at least one dose of treatment. In the maintenance study, the primary efficacy analyses reported in this manuscript were based on the first 450 (planned) clinical responders to 8-week induction therapy with upadacitinib 45 mg once daily. The safety analysis population in the induction studies consisted of all randomised patients who received at least one dose of treatment; in the maintenance study, this population included all patients who received at least one dose of treatment as part of the primary analysis population. These studies are registered at ClinicalTrials.gov, NCT02819635 (U-ACHIEVE) and NCT03653026 (U-ACCOMPLISH).

Findings Between Oct 23, 2018, and Sept 7, 2020, 474 patients were randomly assigned to upadacitinib 45 mg once daily (n=319) or placebo (n=155) in UC1. Between Dec 6, 2018, and Jan 14, 2021, 522 patients were randomly assigned to upadacitinib 45 mg once daily (n=345) or placebo (n=177) in UC2. In UC3, a total of 451 patients (21 from the phase 2b study, 278 from UC1, and 152 from UC2) who achieved a clinical response after 8 weeks of upadacitinib induction treatment were randomly assigned again to upadacitinib 15 mg (n=148), upadacitinib 30 mg (n=154), and placebo (n=149) in the primary analysis population. Statistically significantly more patients achieved clinical remission with upadacitinib 45 mg (83 [26%] of 319 patients in UC1 and 114 [34%] of 341 patients in UC2) than in the placebo group (seven [5%] of 154 patients in UC1 and seven [4%] of 174 patients; p<0·0001; adjusted treatment difference 21·6% [95% CI 15·8–27·4] for UC1 and 29·0% [23·2–34·7] for UC2). In the maintenance study, clinical remission was achieved by statistically significantly more patients receiving upadacitinib (15 mg 63 [42%] of 148; 30 mg 80 [52%] of 154) than those receiving placebo (18 [12%] of 149; p<0·0001; adjusted treatment difference 30·7% [21·7–39·8] for upadacitinib 15 mg *vs* placebo and 39·0% [29·7–48·2] for upadacitinib 30 mg *vs* placebo). The most commonly reported adverse events in UC1 were nasopharyngitis (15 [5%] of 319 in the upadacitinib 45 mg group *vs* six [4%] of 155 in the placebo group), creatine phosphokinase elevation (15 [4%] *vs* three [2%]), and acne (15 [5%] *vs* one [1%]). In UC2, the most frequently reported adverse event was acne (24 [7%] of 344 in the upadacitinib 45 mg group *vs* three [2%] of 177 in the placebo group). In both induction studies, serious adverse events and adverse events leading to discontinuation of treatment were less frequent in the upadacitinib 45 mg group than in the placebo group (serious adverse events eight [3%] *vs* nine (6%) in UC1 and 11 [3%] *vs* eight [5%] in UC2; adverse events leading to discontinuation six [2%] *vs* 14 [9%] in UC1 and six [2%] *vs* nine [5%] in UC2). In UC3, the most frequently reported adverse events (≥5%) were worsening of ulcerative colitis (19 [13%] of 148 in the upadacitinib 15 mg group *vs* 11 [7%] of 154 in the upadacitinib 30 mg group *vs* 45 [30%] of 149 in the placebo group), nasopharyngitis (18 [12%] *vs* 22 [14%] *vs* 15 [10%]), creatine phosphokinase elevation (nine [6%] *vs* 13 [8%] *vs* three [2%]), arthralgia (nine [6%] *vs* five [3%] *vs*

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15 [10%]), and upper respiratory tract infection (seven [5%] *vs* nine [6%] *vs* six [4%]). The proportion of serious adverse events (ten [7%] *vs* nine [6%] *vs* 19 [13%]) and adverse events leading to discontinuation (six [4%] *vs* ten [6%] *vs* 17 [11%]) was lower in both upadacitinib groups than in the placebo group. Events of cancer, adjudicated major adverse cardiac events, or venous thromboembolism were reported infrequently. There were no treatment-related deaths.

Interpretation Upadacitinib demonstrated a positive efficacy and safety profile and could be an effective treatment option for patients with moderately to severely active ulcerative colitis.

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Introduction

Ulcerative colitis is a chronic inflammatory bowel disease (IBD) affecting the colon and involves the rectum in approximately 95% of cases.[1] Despite the availability of multiple therapeutic options for patients with ulcerative colitis, achieving short-term and long-term disease control remains challenging, and symptoms negatively impact quality of life (QOL).[1–3] Even with new biological agents, approximately two-thirds of patients with ulcerative colitis do not attain or maintain remission after 1 year.[4–7] Thus, there remains an unmet need for additional therapeutic options for patients with ulcerative colitis.

Janus kinase (JAK) pathways regulate immune signalling and are implicated in IBD pathogenesis.[8,9] Tofacitinib, a nonselective inhibitor of JAK1, JAK2, and JAK3, is approved for the treatment of patients with moderately to severely active ulcerative colitis.[10] Tofacitinib efficacy outcomes are comparable with those reported for currently licensed biological therapies.[4,5,11]

Upadacitinib[12] is an oral, selective, small molecule JAK inhibitor engineered to have greater inhibitory effects for JAK1 than JAK2, JAK3, and tyrosine kinase 2. Upadacitinib selectivity might allow the evaluation of higher doses, potentially providing greater efficacy without increasing some of the reported safety issues associated with JAK2 and JAK3 inhibition.[13] In a phase 2b (U-ACHIEVE substudy 1), dose-ranging, placebo-controlled induction study, patients with moderately to severely active ulcerative colitis received upadacitinib at the following doses: 7·5 mg, 15 mg, 30 mg, and 45 mg once daily.[14] Upadacitinib 45 mg once daily showed an optimal benefit–risk profile with the highest efficacy rates and no clinically relevant increase in safety events compared with lower doses, and was therefore selected for the phase 3 induction dose.[14] Considering a potentially

Research in context

Evidence before this study

We searched PubMed with the terms "ulcerative colitis", "treatment", and "moderate to severe" to identify articles published in English between Oct 1, 2016, and Sept 23, 2021. We retrieved 636 articles describing the treatment of ulcerative colitis. Despite multiple therapeutic options available for patients with ulcerative colitis, achieving both short-term and long-term disease control is challenging, and there remains an unmet medical need for more effective therapies. Upadacitinib is an oral, small molecule Janus kinase (JAK) inhibitor that has been engineered with increased selectivity for JAK1 versus JAK2, JAK3, or tyrosine kinase 2. Upadacitinib is approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and atopic dermatitis, and is currently under investigation for the treatment of ulcerative colitis. In a phase 2b, dose-ranging study in patients with moderately to severely active ulcerative colitis, upadacitinib was found to be more effective than placebo at inducing remission after 8 weeks of treatment and had a tolerable safety profile.

Added value of this study

To our knowledge, U-ACHIEVE and U-ACCOMPLISH were the first randomised, placebo-controlled, phase 3 studies investigating upadacitinib as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis. In two replicate induction studies, a significantly higher proportion of patients receiving upadacitinib 45 mg once daily as induction therapy achieved clinical remission at week 8 compared with placebo. In the maintenance study, a significantly greater proportion of patients achieved clinical remission at week 52 with upadacitinib 15 mg or 30 mg as maintenance therapy than those receiving placebo. In addition, each study met all prespecified secondary endpoints (including the evaluation of disease activity, symptoms, endoscopy, histology, and quality of life). Upadacitinib as induction and maintenance therapy was well tolerated, and no new safety risks were observed compared with its known safety profile.

Implications of all the available evidence

The results of this multicentre, phase 3 study programme demonstrate the potential of upadacitinib as a treatment option for patients with moderately to severely active ulcerative colitis.

more favourable long-term safety profile, two doses (15 mg and 30 mg once daily) lower than the induction dose were selected as the phase 3 maintenance doses; both doses also showed superior efficacy versus placebo in the phase 2b study.[14]

Here we report the phase 3 results from two replicate induction studies and a single maintenance study assessing the efficacy and safety of upadacitinib in patients with moderately to severely active ulcerative colitis. We report the results from the blinded, 8-week treatment period for the induction studies and the protocol prespecified primary analysis population of the first randomised 451 patients for the maintenance study.

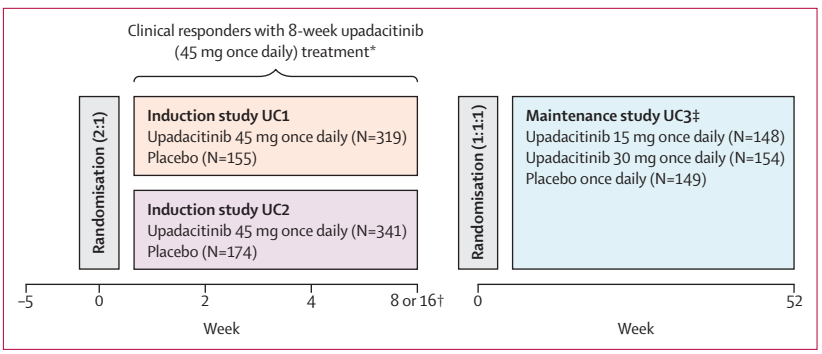


Figure 1: **Study design for two induction studies and a maintenance study**
UC1=U-ACHIEVE substudy 2. UC2=U-ACCOMPLISH. UC3=U-ACHIEVE substudy 3. *Patients who achieved clinical response (per Adapted Mayo score) with 8 weeks of upadacinitib 45 mg once daily induction treatment were eligible to enter UC3. †Patients who did not achieve clinical response at week 8 in UC1 and UC2 continued in an additional 8-week, open-label, induction extension period with upadacitinib 45 mg once daily; patients who achieved clinical response at week 16 were eligible for UC3. ‡In UC3, the primary analysis population included the first 451 randomly assigned patients who achieved clinical response following 8-week upadacitinib 45 mg once daily treatment (including patients who received 8-week upadacitinib treatment in the masked phase 2b [U-ACHIEVE substudy 1] and phase 3 [UC1 and UC2] induction studies and patients who received 8-week blinded placebo treatment followed by 8-week open label upadacitinib in induction extension period in UC1 and UC2). Of these 451 patients, 21 were from phase 2b study, 278 from UC1, and 152 from UC2. For details on the non-primary analysis population of UC3, including the additional 77, 79, and 74 patients enrolled in upadacitinib 15 mg, upadacitinib 30 mg, and placebo treatment groups, respectively, who were responders to 8-week treatment of upadacitinib 45 mg once daily, see appendix (p 18; results not reported in this Article).

Methods

Study design and participants

This phase 3, multicentre, randomised, double-blind, placebo-controlled clinical programme consisted of two replicate induction studies (U-ACHIEVE substudy 2 [UC1] and U-ACCOMPLISH [UC2]) and a maintenance study (U-ACHIEVE substudy 3 [UC3]; figure 1). The studies were conducted across Europe, North and South America, Australasia, Africa, and the Asia-Pacific region at 199 clinical centres in 39 countries (UC1), 204 clinical centres in 40 countries (UC2), and 195 clinical centres in 35 countries (UC3).

In the induction studies, eligible patients were aged 16–75 years with a confirmed ulcerative colitis diagnosis for at least 90 days and active disease (Adapted Mayo score [Mayo score excluding Physician's Global Assessment; PGA] of 5–9; centrally assessed Mayo endoscopic subscore of 2 or 3). Patients had previous inadequate response, loss of response, or intolerance to at least one oral aminosalicylate, corticosteroid, immunosuppressant, or biological therapy (infliximab, adalimumab, golimumab, vedolizumab, or ustekinumab). Enrolment of patients with at least three biological failures was limited to less than 30% of the total population with previous biological failure; patients with previous biologic exposure who discontinued for reasons other than inadequate response or intolerance (eg, change of insurance, well controlled disease), provided their biological exposure duration was less than 1 year, were limited to less than 20% of the total population without previous biological failure. At baseline, a washout period of 8 weeks was required for patients with previous use of antitumour necrosis factor (TNF) drugs and vedolizumab, and 12 weeks for ustekinumab.

Key exclusion criteria included a diagnosis of Crohn's disease, indeterminate colitis, fulminant colitis, toxic megacolon, disease limited to the rectum, active infection, and previous exposure to JAK inhibitors. Full eligibility criteria are shown in the appendix (pp 4–8).

The independent ethics committee or institutional review board at each study site approved the study protocol, informed consent forms, and recruitment materials before patient enrolment. Studies were conducted in accordance with the International Conference for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. Patients provided written informed consent before screening. In response to the COVID-19 pandemic, operational accommodations for clinical trial continuity were incorporated for temporary site disruptions and secure in-place measures, including remote visits, local laboratory collections, courier delivery of treatment to the patient, and indefinite interruption of treatment if no permanent discontinuation criteria were met.

Randomisation and masking

In both induction studies, patients were randomly assigned (2:1) to receive oral upadacitinib (45 mg once daily) or placebo for 8 weeks. Randomisation was stratified by history of biological failure (inadequate response, loss of response, or intolerance to biological therapy [yes *vs* no]), baseline corticosteroid use (yes *vs* no), and baseline Adapted Mayo score (≤7 *vs* >7). Randomisation was further stratified by the number of previous biological treatments received (1 *vs* >1 for patients with biological failure) or by previous biological use (for patients without previous biological failure).

Following 8-weeks induction with upadacitinib 45 mg, patients (from the phase 2b [U-ACHIEVE substudy 1][14] and phase 3 [UC1 and UC2] studies) who achieved clinical response were randomly assigned (1:1:1) to receive upadacitinib 15 mg, upadacitinib 30 mg, or placebo once daily in the UC3 maintenance study. Randomisation was stratified by previous biological failure, clinical remission status post-induction, and corticosteroid use at the

See Online for appendix

beginning of UC3. In UC3, responders to 8-weeks induction with placebo continued to receive placebo whereas responders to 16 week upadacitinib 45 mg once daily were randomly assigned (1:1) to upadacitinib 15 or 30 mg once daily. Because these patients were not included in the primary analysis population, their results are not reported in this Article. Patients who did not achieve clinical response by week 16 of induction were discontinued.

All patients were randomly assigned using web-based interactive response technology using block randomisation methods; block randomisation schedules (block size of 3) were generated by randomisation specialists at AbbVie and then distributed to the interactive response technology vendor for patient randomisation. Study investigators, study site personnel, and patients were masked to treatment allocation throughout the study (except in the open-label extension periods [induction studies]). To maintain masking, the upadacitinib and placebo tablets were identical in appearance.

Procedures

The UC1 and UC2 studies included a 5-week screening period and an 8-week, double-blind treatment period with oral upadacitinib (45 mg once daily) or placebo. Patients from UC1 and UC2 who achieved clinical response (defined as a decrease from baseline in the Adapted Mayo score ≥2 points and ≥30% from baseline, plus a decrease in rectal bleeding score [RBS]≥1 or an absolute RBS≤1) at week 8 (at week 16 for patients who did not achieve clinical response at week 8 and continued in an additional 8 week, open-label, induction extension period with upadacitinib 45 mg once daily) were eligible for enrolment into the 52-week UC3 maintenance study. Patients achieving clinical response in the phase 2b induction study[14] were also eligible to enter UC3 (the phase 2b and phase 3 study designs were operationally seamless).[14] Patients who achieved clinical response following 8-weeks induction with upadacitinib 45 mg once daily were subsequently randomly assigned to receive 52-weeks oral upadacitinib 15 mg, 30 mg, or placebo once daily maintenance treatment (UC3).

During induction, concomitant ulcerative colitis-related medications (oral corticosteroids not exceeding the equivalent dose of prednisone 30 mg daily, antibiotics, aminosalicylates, or methotrexate) were kept at a stable dose. Concomitant use of biologics and immunosuppressants other than methotrexate was prohibited. At week 0 of the maintenance study, corticosteroid was tapered according to a predefined schedule (appendix p 9). During maintenance, rescue therapy could be provided to treat worsening of ulcerative colitis (initiated or increased dose: corticosteroids, aminosalicylates, methotrexate, or antibiotics) at the investigator's discretion. Rescue therapy is summarised in appendix (p 44).

Adapted Mayo score (with centrally assessed endoscopy) was assessed at baseline, weeks 8 and 16 (induction), and week 52 (maintenance). Partial Adapted Mayo (including Mayo stool frequency subscore [SFS], RBS, and Partial Mayo score [Mayo score excluding endoscopy subscore])

Panel: Score components and endpoints definitions

Score components

- Mayo score (score range 0 [normal]–12 [most severe]): RBS (0–3); SFS (0–3); PGA (0–3); endoscopy (0–3)
- Partial Mayo score (score range 0–9): RBS (0–3); SFS (0–3); PGA (0–3)
- Adapted Mayo score (score range 0–9): RBS (0–3); SFS (0–3); endoscopy (0–3)
- Partial Adapted Mayo score (score range 0–6): RBS (0–3); SFS (0–3)

Primary endpoint

- Clinical remission: defined as Adapted Mayo score ≤2, with SFS ≤1 and not greater than baseline, RBS=0, and endoscopic subscore ≤1 without friability

Secondary endpoints

- Endoscopic improvement: endoscopic score ≤1 without friability
- Endoscopic remission: endoscopic score of 0
- Clinical response per Adapted Mayo score: a decrease in Adapted Mayo score of ≥2 points and ≥30% from baseline, and a decrease in the RBS of ≥1 point or an absolute RBS of ≤1
- Clinical response per Partial Adapted Mayo score: a decrease in Partial Adapted Mayo score of ≥1 point and ≥30% from baseline, and a decrease in RBS of ≥1 point or an absolute RBS of ≤1
- Histological-endoscopic mucosal improvement: endoscopic score ≤1 without friability and Geboes score ≤3·1
- Histological improvement: any decrease in Geboes score from baseline
- Mucosal healing: endoscopic score of 0 and a Geboes score <2
- Maintenance of clinical remission: clinical remission per Adapted Mayo score at week 52 in those who achieved clinical remission at the end of the induction studies
- Corticosteroid-free clinical remission: clinical remission per Adapted Mayo score at week 52 and were corticosteroid-free for ≥90 days prior to week 52 in those who achieved clinical remission at the end of the induction studies
- Maintenance of endoscopic improvement: endoscopic improvement at week 52 in those who achieved endoscopic improvement at the end of the induction studies
- Maintenance of clinical response per Adapted Mayo score: clinical response at week 52 in those who achieved clinical response at the end of the induction studies

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

were assessed at baseline and every 2 weeks thereafter during induction; and weeks 4, 8, 12, and every 8 weeks thereafter during maintenance. The Inflammatory Bowel Disease Questionnaire (IBDQ) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) were assessed at baseline and weeks 2 and 8 (induction), and at week 52 (maintenance). Bowel urgency and abdominal pain were assessed via data derived from the patients' electronic diary; patients were asked daily to rate their abdominal pain and confirm bowel urgency in the past 24 h. Stool samples for faecal calprotectin and blood samples were collected throughout for laboratory testing, including assays to measure high sensitivity C-reactive protein (CRP). Major adverse cardiovascular events (MACEs) and venous thromboembolic events (VTEs) were adjudicated by an external adjudication committee. Gastrointestinal perforations were adjudicated by an internal AbbVie adjudication committee. Treatment-related adverse events were coded using the Medical Dictionary for Regulatory Activities (version 23.0).

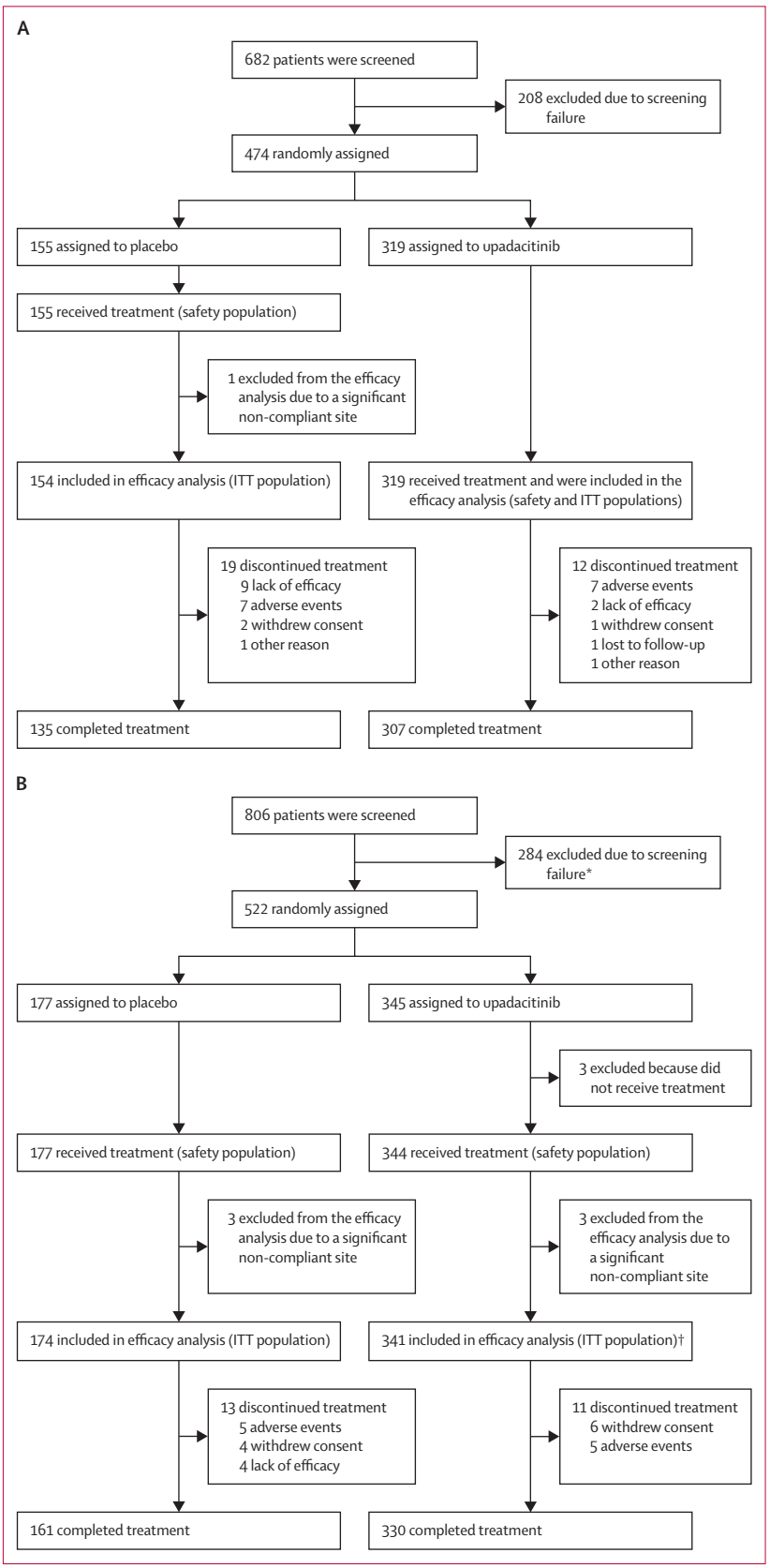
Details of other study procedures are provided in the appendix (pp 14–17).

Outcomes

In the two induction studies, the primary endpoint was clinical remission per Adapted Mayo score at week 8 (efficacy endpoint definitions are shown in the panel). Secondary endpoints evaluated at week 8 (unless otherwise indicated) were endoscopic improvement, endoscopic remission, clinical response per Adapted Mayo score, clinical response per Partial Adapted Mayo score (week 2), histological-endoscopic mucosal improvement (HEMI), no bowel urgency, no abdominal pain, histological improvement, change from baseline in IBDQ score (32-item patient QOL questionnaire), mucosal healing, and change from baseline in FACIT-F score (13 item patient QoL questionnaire).

In the maintenance study, the primary endpoint was clinical remission per Adapted Mayo score at week 52. Secondary endpoints at week 52 were endoscopic improvement, maintenance of clinical remission, corticosteroid-free clinical remission, maintenance of endoscopic improvement, endoscopic remission, maintenance of clinical response per Adapted Mayo score, HEMI, change from baseline in IBDQ score, mucosal healing, no bowel urgency, no abdominal pain, and change from baseline in FACIT-F score.

Safety analyses included adverse events, physical examination, electrocardiograms, and clinical laboratory parameters. Treatment-emergent adverse events were defined as any adverse event that began or worsened in severity after the first dose of treatment, and within 30 days after the last dose or before the first dose of treatment in any additional study the patient continued onto (maintenance study or the long-term extension study [not reported here]). Adverse events of special interest were prespecified based on previous studies in patients treated



(Figure 2 continues on next page)

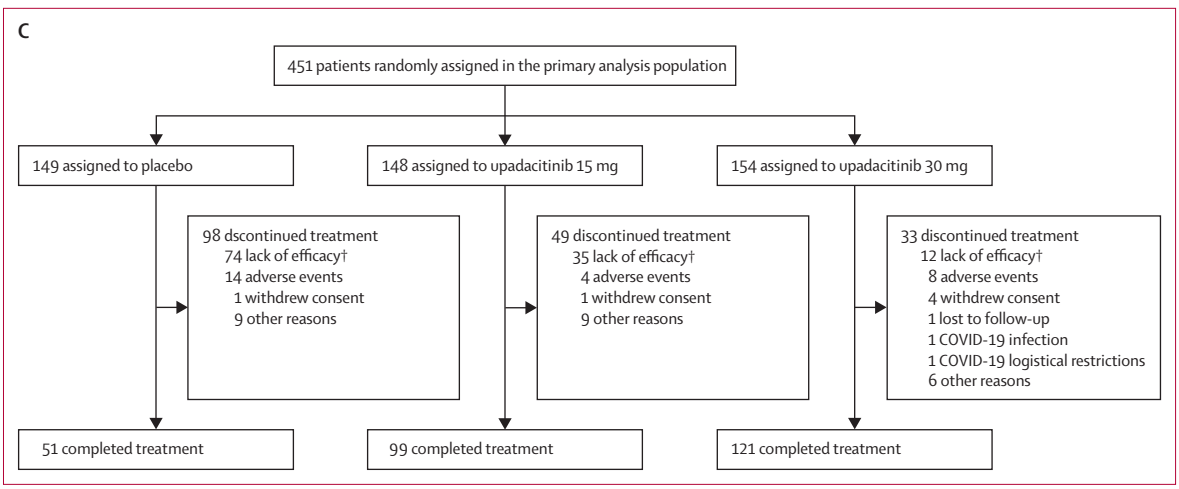


Figure 2: **Trial profiles of the phase 3 induction and maintenance studies**
(A) UC1 induction. (B) UC2 induction. (C) UC3 maintenance (21 patients were from phase 2b U-ACHIEVE substudy 1, 278 from UC1, and 152 from UC2). UC2=U-ACCOMPLISH. UC3=U-ACHIEVE substudy 3. ITT=intention-to-treat population. UC1=U-ACHIEVE substudy 2. *All randomly assigned patients, except one assigned to the upadacitinib 45 mg once daily group, received at least one dose of treatment. †Includes patients who moved to the long-term extension study to receive upadacitinib due to loss of response.

with upadacitinib or other JAK inhibitors (eg, serious infection, herpes zoster, malignancy, MACE, and VTEs).

Statistical analysis

For the two phase 3 induction studies, the sample size was estimated from results of the phase 2b study (11 [19·6%] of 56 patients in the upadacitinib 45 mg group and 0 of 46 patients in the placebo groups achieved the primary endpoint). Considering the small sample size in the phase 2b study, it was assumed that 18% of patients on upadacitinib 45 mg once daily and 5% on placebo would achieve clinical remission in UC1 and UC2. Based on these assumptions, enrolment of 308 patients in the upadacitinib 45 mg once daily group and 154 in the placebo group was expected to provide more than 95% power to detect the 13% target difference in the primary endpoint between treatment groups using the two-sided Fisher's exact test at a 0·05 significance level. The sample size calculation also factored in the need to ensure that a sufficient number of induction clinical responders entered the maintenance study and considered the number of patients required to meet regulatory requirements.

For the maintenance study, the sample size of 450 for the primary analysis was based on the assumption that 40% of patients on upadacitinib 15 mg once daily or 30 mg once daily, and 12% on placebo would achieve clinical remission. Enrolment of 150 patients per treatment group was expected to provide more than 95% power to detect the anticipated 28% treatment difference in the primary endpoint between an upadacitinib dose (15 or 30 mg) and placebo using the two-sided Fisher's exact test at a 0·025 significance level with multiplicity adjustment. The sample size calculation also factored in the need for more than 100 patients in each upadacitinib group with drug exposure for 1 year per regulatory requirements.

Data for the three studies were analysed independently. The efficacy analyses in the two induction studies were based on the intent-to-treat population, which included all randomised patients who received at least one dose of treatment. In the maintenance study, the primary efficacy analyses reported in this manuscript were based on the first 450 (planned) clinical responders to 8-week induction therapy with upadacitinib 45 mg once daily. For multiplicity adjustment for strong overall type I error control within each study, the primary and all secondary endpoints were compared between each of the upadacitinib and placebo groups using a fixed-sequence multiple testing procedure and an iterative graphical testing procedure for the induction and maintenance study, respectively. As the studies were conducted during the COVID-19 pandemic, completion of in-person study visits and sample collection were affected, leading to missing data. Non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) was used for the categorical endpoints (appendix pp 19–22), which were analysed using the Cochran–Mantel–Haenszel test adjusted by stratification factors. Patients who received rescue therapy were classed as non-responders. Continuous endpoints collected longitudinally, including changes from baseline in faecal calprotectin and high sensitivity CRP, were analysed using a mixed-effect model repeated measurement method.[15] Continuous endpoints collected at only one post-baseline visit were analysed using an analysis of covariance model.

We did subgroup analyses for the efficacy endpoints by demographic and baseline characteristics (sex, age, race, biological failure status, baseline corticosteroid use, baseline Adapted Mayo score, baseline Full Mayo score, previous exposure to antitumor necrosis factor, previous

exposure to biological therapy, baseline weight, presence of pancolitis at baseline, disease duration at baseline, baseline high sensitivty CRP, and region). Treatment difference between each upadacitinib treatment group and placebo group were presented with point estimate and 95% CI using normal approximation. The NRI-C approach was used to handle missing data.

The safety analysis population consisted of all randomised patients who received at least one dose of treatment; in the maintenance study, this population included all patients who received ≥1 dose of treatment as part of the primary analysis population.

An independent external Data Monitoring Committee (DMC) reviewed the accumulating safety data (unblinded safety data were analysed by statisticians from an independent vendor to minimise the operational bias) every 6 months and provided recommendations to the sponsor on whether to continue, modify, or terminate the studies.

All statistical analyses were done with SAS (version 9.4 or newer). An external data monitoring committee oversaw the studies. These studies are registered with ClinicalTrials.gov (U-ACHIEVE [UC1, UC3]: NCT02819635; U-ACCOMPLISH [UC2]: NCT03653026).

Role of the funding source

The trials were designed by the sponsor, AbbVie, in collaboration with the investigators. The investigators were responsible for suggesting the patient population to be studied, inclusion and exclusion criteria, details of the study design, and safety and efficacy endpoints. The trial protocols and analysis plans were written by the sponsor with input from the investigators; the sponsor and investigators jointly conducted the trials and gathered data. The data were analysed by statisticians employed by the sponsor and the results were presented to all authors for interpretation. The first draft of the manuscript was written under the guidance of the lead authors (SD, SV, and RP) by medical writers funded by the sponsor. All authors reviewed and provided feedback on all subsequent versions of the manuscript, and along with the sponsor, made the decision to submit the manuscript for publication. The study funder was involved in the study design, data collection, data analysis, data interpretation, and writing of the report.

Results

In UC1, 474 patients were randomly assigned to upadacitinib 45 mg once daily (n=319) or placebo (n=155) between Oct 23, 2018, and Sept 7, 2020. All patients were included in the intention-to-treat population, except one (in the placebo group) who was excluded from a non-compliant site (figure 2A). All patients were included in the safety analysis.

In UC2, 522 patients were randomly assigned to upadacitinib 45 mg once daily (n=345) or placebo (n=177) between Dec 6, 2018, and Jan 14, 2021. 341 patients in the upadacitinib 45 mg group and 174 patients in the placebo group were included in the intention-to-treat population. Six patients from the same non-compliant site as in UC2 were excluded from the efficacy analysis (three per

	UC1		UC2	
	Placebo (n=154)	Upadacitinib 45 mg once daily (n=319)	Placebo (n=174)	Upadacitinib 45 mg once daily (n=341)
Sex				
Female	57 (37%)	121 (38%)	67 (39%)	127 (37%)
Male	97 (63%)	198 (62%)	107 (61%)	214 (63%)
Race				
White	100 (65%)	206 (65%)	124 (71%)	234 (69%)
Black or African American	4 (3%)	12 (4%)	6 (3%)	11 (3%)
Asian	46 (30%)	95 (30%)	41 (24%)	94 (28%)
American Indian or Alaska Native	2 (1%)	0	1 (1%)	0
Native Hawaiian and other Pacific Islander	0	1 (<1%)	1 (1%)	0
Multiple	2 (1%)	5 (2%)	1 (1%)	2 (1%)
Age, years	44·5 (23·0)	43·0 (23·0)	42·0 (24·0)	40·0 (24·0)
Weight, kg	70·0 (26·5)	69·3 (24·6)	71·5 (24·3)	71·2 (21·4)
Disease duration, years	6·0 (10·0)	6·6 (9·6)	4·9 (7·4)	5·6 (7·5)
Disease extent				
Left-sided	74 (48%)	158 (50%)	88 (51%)	164 (48%)
Extensive or pancolitis	80 (52%)	161 (50%)	86 (49%)	176 (52%)
Faecal calprotectin, mg/kg	1902 (2651)	1780 (3728)	1540 (2507)	1655 (2415)
High sensitivity CRP, mg/L	4·7 (12·5)	4·1 (8·1)	4·7 (10·0)	3·8 (8·0)
Immunosuppressant (methotrexate) use	3 (2%)	2 (1%)	3 (2%)	1 (<1%)
Aminosalicylates use	103 (67%)	220 (69%)	120 (69%)	233 (68%)
Corticosteroid use				
Yes	61 (40%)	124 (39%)	72 (41%)	120 (35)
Baseline dose,* mg	20·0 (10·0)	20·0 (12·5)	20·0 (15·0)	20·0 (15)
Previous biological therapy failure				
Yes	78 (51%)	168 (53%)	89 (51%)	172 (50%)
No	76 (49%)	151 (47%)	85 (49%)	169 (50%)
Number of previous biological treatments				
1	29 (19%)	64 (20%)	39 (22%)	64 (19%)
2	31 (20%)	64 (20%)	36 (21%)	67 (20%)
3	18 (12%)	35 (11%)	15 (9%)	34 (10%)
≥4	4 (3%)	11 (3%)	3 (2%)	8 (2%)
Adapted Mayo score				
≤7	94 (61%)	195 (61%)	103 (59%)	205 (60%)
>7	60 (39%)	123 (39%)	71 (41%)	135 (40%)
Mean (SD)	7·0 (1·2)	7·0 (1·2)	7·0 (1·2)	7·0 (1·2)
Endoscopic subscore				
3	104 (68%)	223 (70%)	121 (70%)	233 (68%)
Mean (SD)	2·7 (0·47)	2·7 (0·46)	2·7 (0·46)	2·7 (0·47)

Data are n (%) or median (IQR), unless stated otherwise. UC1=U-ACHIEVE substudy 2. UC2=U-ACCOMPLISH. CRP= C-reactive protein. *Corticosteroids doss are converted to equivalent daily dosage of prednisone in mg; the maximum dose of prednisolone allowed as concomitant therapy was 30 mg, equivalent to prednisone.

Table 1: **Baseline demographics and disease characteristics of patients in induction studies (intention-to-treat population)**

	Placebo (n=149)	Upadacitinib 15 mg once daily (n=148)	Upadacitinib 30 mg once daily (n=154)
Sex			
Female	64 (43%)	53 (36%)	68 (44%)
Male	85 (57%)	95 (64%)	86 (56%)
Race			
White	93 (62%)	97 (66%)	101 (66%)
Black or African American	6 (4%)	7 (5%)	3 (2%)
Asian	42 (28%)	44 (30%)	48 (31%)
American Indian or Alaska Native	0	0	0
Native Hawaiian and other Pacific Islander	1 (1%)	0	1 (1%)
Multiple	7 (5%)	0	1 (1%)
Age, years	40·0 (21·0)	40·0 (22·0)	41·0 (7·0)
Weight, kg	70·0 (21·2)	71·5 (25·6)	68·8 (29·0)
Disease duration, years	6·2 (8·6)	6·4 (10·6)	6·0 (9·7)
Disease extent			
Left-sided	79 (53%)	66 (45%)	68 (44%)
Extensive or pancolitis	70 (47%)	82 (55%)	86 (56%)
Faecal calprotectin, mg/kg	1991 (3193)	1718 (2502)	1465 (1750)
High sensitivity CRP, mg/L	4·3 (8·0)	3·8 (10·0)	4·1 (7·1)
Immunosuppressant (methotrexate) use	0	1 (<1%)	1 (<1%)
Aminosalicylates use	99 (66%)	99 (67%)	106 (69%)
Corticosteroid use			
Yes	60 (40%)	55 (37%)	57 (37%)
Baseline dose†, mg	15·0 (10·0)	15·0 (15·0)	20·0 (10·0)
Previous biological therapy failure			
Yes	81 (54%)	71 (48%)	73 (47%)
No	68 (46%)	77 (52%)	81 (53%)
Number of previous biological treatments			
1	30 (20%)	30 (20%)	34 (22%)
2	34 (23%)	32 (22%)	24 (16%)
3	16 (11%)	10 (7%)	16 (10%)
≥4	4 (3%)	1 (<1%)	3 (2%)
Adapted Mayo score			
≤7	87 (58%)	89 (60%)	88 (58%)
>7	62 (42%)	59 (40%)	64 (42%)
Mean (SD)	7·0 (1·2)	7·0 (1·2)	7·1 (1·3)
Endoscopic subscore			
3	98 (66%)	100 (66%)	108 (70%)
Mean (SD)	2·7 (0·48)	2·7 (0·47)	2·7 (0·48)

Data are n (%) or median (IQR), unless stated otherwise. CRP=high-sensitivity C-reactive protein. UC3=U-ACHIEVE substudy 3. *Patients who achieved clinical response based on Adapted Mayo score following 8-week treatment with upadacitinib 45 mg OD in U-ACHIEVE or UACCOMPLISH. †Corticosteroids doses are converted to equivalent daily dosage of prednisone in mg; the maximum dose of prednisolone allowed as concomitant therapy was 30 mg, equivalent to prednisone.

Table 2: **Baseline demographics and disease characteristics of patients in the maintenance study (intention-to-treat population)**

group) but were included in the safety analysis; another patient (upadacitinib 45 mg once daily) was not included in the efficacy or safety analyses as no treatment was administered (figure 2B).

In UC3, a total of 451 patients (21 from the phase 2b study, 278 from UC1, and 152 from UC2) who achieved a clinical response after 8 weeks of upadacitinib 45 mg induction treatment were randomly assigned again to upadacitinib 15 mg (n=148), upadacitinib 30 mg (n=154), and placebo (n=149) in the primary analysis population (figure 2C). Patient demographics and disease characteristics were generally balanced across treatment groups in both induction studies and the maintenance study (tables 1 and 2).

In UC1, the primary endpoint—clinical remission at week 8—was achieved by 83 (26%) of 319 patients receiving upadacitinib versus seven (5%) of 154 patients receiving placebo (p<0·0001; adjusted treatment difference 21·6% [95% CI 15·8–27·4]; table 3, appendix p 25). In UC2, clinical remission at week 8 was achieved by 114 (33%) of 341 of patients receiving upadacitinib versus seven (4%) of 174 receiving placebo (p<0·0001; adjusted treatment difference of 29·0% [95% CI 23·2–34·7]; table 3; appendix p 25). In both induction studies, clinical remission at week 8 was consistent across all subgroups (appendix pp 31–32), including patient subgroups with or without previous biological failure (appendix p 45).

All secondary endpoints in both induction studies were achieved in the upadacitinib 45 mg once daily group compared with the placebo group (table 3). At week 8, disease activity and symptoms were statistically significantly improved as shown by achievement of clinical response, no abdominal pain, and no bowel urgency. Endoscopic, histological, and QOL (IBDQ and FACIT-F) improvements were also achieved (table 3, appendix pp 25–26). The proportion of patients achieving clinical response at week 2 with upadacitinib was statistically significantly greater than with placebo in both UC1 and UC2 (192 [60%] of 319 *vs* 42 [27%] of 154 and 216 [63%] of 341 *vs* 45 [26%] of 174, respectively; both p<0·0001; table 3).

Consistent with clinical and endoscopic outcomes, more patients treated with upadacitinib achieved faecal calprotectin less than 150 mg/kg at weeks 2 and 8 of induction (appendix p 47). Greater decreases in high sensitivity CRP concentrations were demonstrated with upadacitinib treatment versus placebo (appendix p 40–41).

In UC3, the primary endpoint—clinical remission at week 52—was achieved by 63 (42%) of 149 patients receiving upadacitinib 15 mg once daily, 80 (52%) of 154 receiving upadacitinib 30 mg once daily, and 18 (12%) of 149 receiving placebo (adjusted treatment difference of 30·7% [95% CI 21·7–39·8] for upadacitinib 15 mg *vs* placebo, p<0·0001; 39·0% [29·7–48·2] for upadacitinib 30 mg *vs* placebo, p<0·0001; table 4, appendix p 28). Clinical remission at week 52 was consistent across all subgroups assessed in the maintenance study (appendix pp 33–34), including patient subgroups with or without previous biological failure (appendix pp 45–46). The placebo adjusted rates for the primary endpoint of clinical remission per Adapted Mayo score were 30·7% (15 mg) and 39·0% (30 mg) in overall population, 43·7% (15 mg) and 45·1% (30 mg) in patients with

	UC1				UC2			
	Placebo (n=154)	Upadacitinib 45 mg once daily (N=319)	Adjusted treatment difference, % (95% CI)	p value	Placebo (N=174)	Upadacitinib 45 mg once daily (N=341)	Adjusted treatment difference, % (95% CI)	p value
Primary endpoint								
Clinical remission (Adapted Mayo)	7 (5%)	83 (26%)	21·6% (15·8–27·4)	<0·0001	7 (4%)	114 (33%)	29·0% (23·2–34·7)	<0·0001
Secondary endpoints								
Endoscopic improvement	11 (7%)	116 (36%)	29·3% (22·6–35·9)	<0·0001	14 (8%)	150 (44%)	35·1% (28·6–41·6)	<0·0001
Endoscopic remission	2 (1%)	44 (14%)	12·7% (8·4–17·0)	<0·0001	3 (2%)	62 (18%)	15·9% (11·4–20·3)	<0·0001
Clinical response (Adapted Mayo)	42 (27%)	232 (73%)	46·3% (38·4–54·2)	<0·0001	44 (25%)	254 (74%)	49·4% (41·7–57·1)	<0·0001
Clinical response (Partial Adapted Mayo) at week 2	42 (27%)	192 (60%)	33·3% (24·8–41·8)	<0·0001	45 (26%)	216 (63%)	37·0% (28·8–45·1)	<0·0001
Histological–endoscopic mucosal improvement	10 (6%)	96 (30%)	23·7% (17·5–30·0)	<0·0001	10 (6%)	125 (36%)	30·1% (24·1–36·2)	<0·0001
No bowel urgency	33 (21%)	155 (48%)	27·4% (19·2–35·6)	<0·0001	45 (26%)	183 (54%)	27·1% (19·0–35·3)	<0·0001
No abdominal pain	36 (23%)	149 (47%)	23·6% (15·1–32·1)	<0·0001	42 (24%)	183 (54%)	29·1% (20·9–37·4)	<0·0001
Histological improvement	35 (23%)	175 (55%)	32·2% (23·8–40·7)	<0·0001	43 (25%)	212 (62%)	37·9% (29·8–46·1)	<0·0001
Change from baseline in IBDQ total score, least squares mean (95% CI)	n=125; 21·7 (16·0–27·3)	n=292; 55·3 (51·5–59·2)	33·7 (27·0–40·4)	<0·0001	n=156; 21·1 (16·0–26·2)	n=315; 52·2 (48·6–55·9)	31·2 (25·0–37·4)	<0·0001
Mucosal healing	2 (1%)	34 (11%)	9·7% (5·7–13·7)	<0·0001	3 (2%)	46 (13%)	11·3% (7·2–15·3)	<0·0001
Change from baseline in FACIT-F score, least squares mean (95% CI)	n=125; 2·8 (1·2–4·4)	n=291; 9·5 (8·4–10·6)	6·7 (4·8–8·6)	<0·0001	n=155; 3·5 (2·0–4·9)	n=312; 9·4 (8·4–10·5)	6·0 (4·2–7·7)	<0·0001

Data are n (%) unless stated otherwise. Endpoints are measured at 8 weeks, unless stated otherwise. Results for categorical endpoints are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19. Clinical remission: adapted Mayo score ≤2, with stool frequency score ≤1 and not greater than baseline, RBS=0, and endoscopic subscore ≤1 without friability. Endoscopic improvement: endoscopic score ≤1. Endoscopic remission: endoscopic score of 0. Clinical response per Adapted Mayo score: a decrease in Adapted Mayo score of ≥2 points and ≥30% from baseline, and a decrease in the RBS of ≥1 point or an absolute RBS of ≤1. Clinical response per Partial Adapted Mayo score: a decrease in Partial Adapted Mayo score of ≥1 point and ≥30% from baseline, and a decrease in RBS of ≥1 point or an absolute RBS of ≤1. Histological-endoscopic mucosal improvement: endoscopic score ≤1 without friability and Geboes score ≤3·1.Histological improvement: any decrease in Geboes score from baseline. Mucosal healing: endoscopic score of 0 and a Geboes score <2. FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue. IBDQ=Inflammatory Bowel Disease Questionnaire. RBS=rectal bleeding score. UC1=U-ACHIEVE substudy 2. UC2=U-ACCOMPLISH.

***Table 3*: Primary and secondary endpoints in induction studies (intention-to-treat population)**

moderate disease at baseline (Mayo score ≤9), and 16·4% (15 mg) and 35·6% (30 mg) in patients with severe disease at baseline (Mayo score >9).

All secondary endpoints in the maintenance study were achieved in the upadacitinib 15 mg once daily and 30 mg once daily groups compared with the placebo group (table 4). A sustained treatment effect was demonstrated in both upadacitinib 15 mg and 30 mg once daily groups versus placebo, with more patients achieving the endpoints of maintenance of clinical remission, clinical response, and endoscopic improvement (table 4, appendix pp 28–29). Corticosteroid-free clinical remission was achieved by 27 (57%) of 47 patients in the upadacitinib 15 mg group and 39 (68%) of 58 patients in the upadacitinib 30 mg group versus 12 (22%) of 54 patients receiving placebo (all p<0·0001; appendix p 29). Statistically significantly more patients achieved HEMI (appendix p 30), and improvement in symptoms (no abdominal pain or no bowel urgency) and QOL (IBDQ and FACIT-F) with upadacitinib 15 mg or 30 mg versus placebo (all p<0·0001; table 4).

Consistent with clinical and endoscopic outcomes, more patients treated with upadacitinib achieved faecal calprotectin of less than 150 mg/kg during maintenance (appendix p 47). High sensitivity CRP concentrations maintained stable with upadacitinib maintenance dosing, whereas concentrations increased in patients receiving placebo during maintenance (appendix p 40).

Additional prespecified efficacy endpoints and subgroup analyses from all three phase 3 studies are presented in the appendix (pp 10–13).

The proportion of patients with reported adverse events was similar in the upadacitinib 45 mg group (180 [56%] of 319 patients) and placebo group (93 [60%] of 155; table 5) in UC1; the proportions were higher in the upadacitinib 45 mg group than in the placebo group in UC2 (182 [53%]

	Placebo (N=149)	Upadacitinib 15 mg once daily (N=148)	Adjusted treatment difference, % (95% CI)	p value	Upadacitinib 30 mg once daily (N=154)	Adjusted treatment difference, % (95% CI)	p value
Primary endpoint							
Clinical remission (Adapted Mayo)	18 (12%)	63 (42%)	30·7% (21·7–39·8)	<0·0001	80 (52%)	39·0% (29·7–48·2)	<0·0001
Secondary endpoint							
Endoscopic improvement	22 (14%)	72 (49%)	34·4% (25·1–43·7)	<0·0001	95 (62%)	46·3% (36·7–55·8)	<0·0001
Maintenance of clinical remission (Adapted Mayo)	12/54 (22%)	28/47 (57%)	37·4% (20·3–54·6)	<0·0001	40/58 (68%)	47·0% (30·7–63·3)	<0·0001
Corticosteroid-free clinical remission	12/54 (22%)	27/47 (57%)	35·4% (18·2–52·7)	<0·0001	39/58 (68%)	45·1% (28·7–61·6)	<0·0001
Maintenance of endoscopic improvement	14/74 (19%)	39/63 (62%)	42·0% (27·8–56·2)	<0·0001	55/79 (70%)	48·6% (35·5–61·7)	<0·0001
Endoscopic remission	8 (6%)	36 (24%)	18·7% (11·0–26·4)	<0·0001	40 (26%)	19·4% (11·7–27·2)	<0·0001
Maintenance of clinical response (Adapted Mayo)	25/134 (19%)	85/135 (63%)	44·6% (34·5–54·7)	<0·0001	110/144 (77%)	56·6% (47·2–66·0)	<0·0001
Histological-endoscopic mucosal improvement	18 (12%)	51 (35%)	23·8% (14·8–32·8)	<0·0001	76 (50%)	37·3% (27·8–46·8)	<0·0001
Change from baseline in IBDQ total score, east squares mean (95% CI)	17·9 (10·8–25·0)	49·2 (42·6–55·9)	31·3 (22·0–40·7)	<0·0001	58·9 (52·1– 65·6)	41·0 (31·4–50·6)	<0·0001
Mucosal healing	7 (5%)	26 (18%)	13·0% (6·0–20·0)	0·0003	29 (19%)	13·6% (6·6–20·6)	<0·0001
No bowel urgency	26 (17%)	83 (56%)	38·7% (28·9–48·5)	<0·0001	98 (64%)	45·1% (35·5–54·8)	<0·0001
No abdominal pain	31 (21%)	68 (46%)	24·3% (14·2–34·5)	<0·0001	85 (55%)	33·7% (23·6–43·9)	<0·0001
Change from baseline in FACIT-F score, least squares mean (95% CI)	3·7 (1·9–5·4)	8·7 (7·0–10·5)	5·1 (2·7–7·5)	<0·0001	9·5 (7·8–11·2)	5·9 (3·4–8·3)	<0·0001

Data are n (%) or n/N (%) unless stated otherwise. Endpoints are measured at week 52. Results for categorical endpoints are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; results for continuous endpoints are based on return-to-baseline multiple imputation. Clinical remission: adapted Mayo score ≤2, with stool frequency score ≤1 and not greater than baseline, rectal bleeding score of 0, and endoscopic subscore ≤1 without friability. Endoscopic improvement: endoscopic score ≤1. Maintenance of clinical remission: clinical remission per Adapted Mayo score at week 52 in those who achieved clinical remission at the end of the induction studies. Corticosteroid-free clinical remission: clinical remission per Adapted Mayo score at week 52 and were corticosteroid-free for ≥90 days prior to week 52 in those who achieved clinical remission at the end of the induction studies. Maintenance of endoscopic improvement: endoscopic improvement at week 52 in those who achieved endoscopic improvement at the end of the induction studies. Maintenance of clinical response per Adapted Mayo score: clinical response at week 52 in those who achieved clinical response at the end of the induction studies. Histological-endoscopic mucosal improvement: endoscopic score ≤1 without friability and Geboes score ≤3·1. Mucosal healing: endoscopic score of 0 and a Geboes score <2. FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue. IBDQ=Inflammatory Bowel Disease Questionnaire. UC3=U-ACHIEVE substudy 3.

Table 4: **Primary and secondary endpoints in the maintenance study (intention-to-treat)**

of 344 *vs* 70 [40%] of 177). In UC1, the most commonly reported adverse events were nasopharyngitis (15 [5%] of 319 in the upadacitinib 45 mg group *vs* six [4%] of 155 in the placebo group), creatine phosphokinase elevation (15 [4%] *vs* three [2%]), and acne (15 [5%] *vs* one [1%]). In UC2, the most frequently reported adverse event was acne (24 [7%] of 344 in the upadacitinib 45 mg group *vs* three [2%] of 177 in the placebo group; table 5).

In both induction studies, serious adverse events and adverse events leading to discontinuation of treatment were less frequent in the upadacitinib 45 mg group than in the placebo group (serious adverse events eight [3%] *vs* nine (6%) in UC1 and 11 [3%] *vs* eight [5%] in UC2; adverse events leading to discontinuation six [2%] *vs* 14 [9%] in UC1 and six [2%] *vs* nine [5%] in UC2). No deaths were reported in the induction studies.

Adverse events of special interest were infrequent in both induction studies. No events of active tuberculosis, cancer, renal dysfunction, or adjudicated MACE in any treatment group across the induction studies were reported. In UC2, gastrointestinal perforation (large intestine perforation) and VTE (pelvic venous thrombosis and pulmonary embolism in a patient with a history of smoking and Factor V Leiden mutation) were each reported in the placebo group; both patients withdrew from the study.

In both induction studies, similar proportions of patients reported serious infections across treatment groups. In UC1, one patient had an event of herpes zoster in the upadacitinib 45 mg group (led to treatment discontinuation) followed by post-herpes zoster neuralgia, and another patient had an opportunistic infection (oral fungal infection) in the upadacitinib 45 mg; these were considered non-serious events.

In UC2, herpes zoster (cutaneous only and involving one dermatome) and opportunistic infection (cytomegalovirus colitis and cytomegalovirus infection) were reported in two patients each in the upadacitinib 45 mg group; none were serious or led to treatment discontinuation. Creatine phosphokinase elevation, neutropenia, and lymphopenia were reported more frequently in the upadacitinib 45 mg group than in the placebo group in both induction studies. Most creatine phosphokinase elevations were mild to moderate and asymptomatic, with one patient in UC1 discontinuing treatment. There were no cases of myopathy or rhabdomyolysis. Most cases of neutropenia and lymphopenia were mild to moderate and did not lead to treatment discontinuation. Based on the clinical review,

	UC1			UC2		
	Placebo (N=155)	Upadacitinib 45 mg once daily (N=319)	Treatment difference (95% CI)	Placebo (N=177)	Upadacitinib 45 mg once daily (N=344)	Treatment difference (95% CI)
Adverse events	96 (62%); 883·1	180 (56%); 898·0	−5·5 (−14·9 to 3·9)	70 (40%); 638·5	182 (53%); 738·5	13·4 (4·4 to 22·3)
Serious adverse events	9 (6%); 62·1	8 (3%); 16·3	−3·3 (−7·4 to 0·8)	8 (5%); 45·6	11 (3%); 20·9	−1·3 (−4·9 to 2·3)
Adverse events leading to discontinuation	14 (9·0) [66·6]	6 (2%); 14·3	−7·2 (−11·9 to -2·4)	9 (5%); 57·0	6 (2%); 19·0	−3·3 (−6·9 to 0·2)
Death*	0	0	0	0	0	0
Most frequent adverse events (reported by ≥5% of patients in any treatment group across studies)						
Nasopharyngitis	6 (4%)	15 (5%)	..	4 (2%)	13 (4%)	..
CPK elevation	3 (2%)	16 (5%)	..	2 (1%)	16 (5%)	..
Worsening of ulcerative colitis	21 (14%)	3 (<1%)	..	8 (5%)	6 (2%)	..
URTI	7 (5%)	8 (3%)	..	1 (1%)	7 (2%)	..
Acne	1 (1%)	15 (5%)	..	3 (2%)	24 (7%)	..
Arthralgia	6 (4%)	5 (2%)	..	3 (2%)	5 (1%)	..
Headache	4 (3%)	13 (4%)	..	9 (5%)	8 (2%)	..
Anaemia	9 (6%)	8 (3%)	..	4 (2%)	14 (4%)	..
Adverse event of special interest						
Serious infection	2 (1%); 8·9	5 (2%); 10·2	0·3 (−2·0 to 2·5)	1 (1%); 7·6	2 (1%); 3·8	0 (−1·3 to 1·4)
Opportunistic infection (excluding tuberculosis and herpes zoster)	0	1 (<1%); 2·0	0·3 (−0·3 to 0·9)	0	2 (1%); 3·8	0·6 (−0·2 to 1·4)
Herpes zoster†	0	1 (<1%); 4·1	0·3 (−0·3 to 0·9)	0	2 (1%); 3·8	0·6 (−0·2 to 1·4)
Malignancy excluding NMSC‡	0	0	0	0	0	0
NMSC	0	0	0	0	0	0
Renal dysfunction	0	0	0	0	0	0
Hepatic disorder	7 (5%); 53·2	9 (3%); 30·6	−1·7 (−5·4 to 2·0)	1 (<1%); 11·4	10 (3%); 26·6	2·3 (0·3 to 4·4)
Adjudicated gastrointestinal perforation‡	0	0	0	1 (1%); 3·8	0	−0·6 (−1·7 to 0·5)
Adjudicated MACE‡§	0	0	0	0	0	0
Adjudicated VTE¶	0	0	0	1 (1%); 3·8	0	−0·6 (−1·7 to 0·5)
Anaemia†	14 (9%); 66·6	10 (3%); 22·4	−5·9 (−10·8 to −1·0)	4 (2%); 15·2	15 (4%); 30·5	2·1 (−1·0 to 5·2)
Neutropenia†	1 (1%); 4·4	16 (5%); 34·7	4·4 (1·7 to 7·1)	0	15 (4%); 30·5	4·4 (2·2 to 6·5)
Lymphopenia†	1 (1%); 4·4	10 (3%); 24·5	2·5 (0·2 to 4·8)	1 (1%); 7·6	6 (2%); 15·2	1·2 (−0·6 to 2·9)
CPK elevation	3 (2%); 13·3	16 (5%); 36·7	3·1 (−0·2 to 6·3)	2 (1%); 7·6	16 (5%); 34·3	3·5 (0·8 to 6·2)

Data are n (%); events per 100 person-years or n (%), unless stated otherwise. There were no adverse event of special interest of active tuberculosis or lymphoma in the studies. CPK=creatine phosphokinase. MACE=major adverse cardiovascular event. NMSC=non-melanoma skin cancer. UC1=U-ACHIEVE substudy 2. UC2=U-ACCOMPLISH. URTI=upper respiratory tract infection. VTE=venous thromboembolic event. *Includes non-treatment emergent deaths. †Search criteria were based on Company MedDRA Query. ‡These events were determined on the basis of external adjudication. §MACE is defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. ¶VTE is defined as deep vein thrombosis and pulmonary embolism (fatal and non-fatal).

Table 5: **Overview of treatment-emergent adverse events in the safety analysis set (UC1 and UC2 induction studies)**

patients with neutropenia or lymphopenia did not usually report concurrent infections.

In UC3, the proportions of reported adverse events were similar in the upadacitinib 15 mg (115 [78%] of 148), 30 mg (121 [79%] of 154), and placebo groups (113 [76%] of 148; table 6). The most frequently reported adverse events (≥5%) were worsening of ulcerative colitis (19 [13%] of 148 in the upadacitinib 15 mg group *vs* 11 [7%] of 154 in the upadacitinib 30 mg group *vs* 45 [30%] of 149 in the placebo group), nasopharyngitis (18 [12%] *vs* 22 [14%] *vs* 15 [10%]), creatine phosphokinase elevation (nine [6%] *vs* 13 [8%] *vs* three [2%]), arthralgia (nine [6%] *vs* five [3%] *vs* 15 [10%]), and upper respiratory tract infection (seven [5%] *vs* nine [6%] *vs* six [4%]). The proportion of serious adverse events (ten [7%] *vs* nine [6%] *vs* 19 [13%]) and adverse events leading to discontinuation (six [4%] *vs* ten [6%] *vs* 17 [11%]) was lower in both upadacitinib groups than in the placebo groups. No deaths were reported during the maintenance period.

Serious infections, were similarly reported in the upadacitinib 15 mg, 30 mg, and placebo groups (five [3%] *vs* four [3%] *vs* six [4%]). There were six events of herpes zoster (all non-serious and involved one dermatome; one event led to treatment discontinuation in the upadacitinib 30 mg group) each in the upadacitinib 15 mg (4%) and 30 mg (4%) treatment groups, and one non-serious event of opportunistic infection (cytomegalovirus infection) in the upadacitinib 15 mg group. Herpes zoster or opportunistic infection were not reported in the placebo

	Placebo (n=149)	Upadacitinib 15 mg once daily (n=148)	Treatment difference (95% CI)*	Upadacitinib 30 mg once daily (n=154)	Treatment difference (95% CI)*
Treatment-emergent adverse events					
Adverse events	113 (76%); 492·2	115 (78%); 304·2	2·4 (–7·0 to 11·8)	121 (79%); 304·9	3·1 (–6·2 to 12·3)
Serious adverse events	19 (13%); 27·5	10 (7%); 9·2	–6·1 (–13·0 to 0·7)	9 (6%); 6·7	–6·8 (–13·5 to –0·1)
Adverse events leading to discontinuation	17 (11%); 20·6	6 (4%); 5·9	–7·4 (–13·6 to –1·3)	10 (6%); 7·4	–4·8 (–11·4 to 1·8)
Death†	0	0	0	0	0
Most frequent adverse events (reported by ≥5% of patients in any treatment group across studies)					
Nasopharyngitis	15 (10%)	18 (12%)	..	22 (14%)	..
CPK elevation	3 (2%)	9 (6%)	..	13 (8%)	..
Worsening of ulcerative colitis	45 (30%)	19 (13%)	..	11 (7%)	..
URTI	6 (4%)	7 (5%)	..	9 (6%)	..
Acne	6 (4%)	4 (3%)	..	6 (4%)	..
Arthralgia	15 (10%)	9 (6%)	..	5 (3%)	..
Headache	6 (4%)	4 (3%)	..	5 (3%)	..
Anaemia	6 (4%)	7 (5%)	..	1 (<1%)	..
Adverse event of special interest					
Serious infection	6 (4%); 6·9	5 (3%); 4·2	–0·7 (–5·3 to 3·8)	4 (3%); 3·0	–1·4 (–5·8 to 3·0)
Opportunistic infection (excluding tuberculosis and herpes zoster)	0	1 (1%); 0·8	0·6 (–1·6 to 2·9)	0	0
Herpes zoster‡	0	6 (4%); 5·0	4·2 (0·5 to 7·8)	6 (4%); 4·4	3·8 (0·3 to 7·3)
Malignancy excluding NMSC§	1 (<1%); 1·1	1 (<1%); 0·8	0 (–2·7 to 2·6)	2 (1%); 1·5	0·6 (–2·3 to 3·5)
NMSC	0	0	0	2 (1%); 1·5	1·3 (–1·2 to 3·9)
Renal dysfunction	1 (<1%); 1·1	1 (<1%); 0·8	–0·1 (–2·7 to 2·5)	1 (<1%); 0·7	0 (–2·6 to 2·5)
Hepatic disorder	3 (2%); 5·7	10 (7%); 16·8	4·8 (–0·1 to 9·7)	8 (5%); 7·4	3·2 (–1·3 to 7·8)
Adjudicated gastrointestinal perforation§	1 (1%); 2·3	0	–0·7 (–3·0 to 1·6)	0	–0·7 (–3·0 to 1·6)
Adjudicated MACE§¶	1 (1%); 1·1	0	–0·7 (–2·9 to 1·6)	0	–0·7 (–2·9 to 1·6)
Adjudicated VTE‖	0	0	0	2 (1%); 1·5	1·3 (–1·2 to 3·9)
Anaemia‡	9 (6%); 12·6	7 (5%); 5·9	–1·2 (–6·5 to 4·1)	3 (2%); 2·2	–4·1 (–8·7 to 0·5)
Neutropenia‡	2 (1%); 2·3	4 (3%); 4·2	1·4 (–2·3 to 5·0)	9 (6%); 8·9	4·5 (0·1 to 8·9)
Lymphopenia‡	2 (1%); 3·4	3 (2%); 2·5	0·7 (–2·7 to 4·1)	3 (2%); 3·0	0·7 (–2·7 to 4·0)
CPK elevation	3 (2%); 3·4	9 (6%); 7·3	3·9 (–0·8 to 8·7)	13 (8%); 11·1	6·4 (1·2 to 11·5)

Data are n (%); events per 100 person-years or n (%), unless stated otherwise. There were no adverse event of special interest of active tuberculosis or lymphoma in the study. CPK=creatine phosphokinase. MACE=major adverse cardiovascular event. NMSC=non-melanoma skin cancer. UC3=U-ACHIEVE substudy 3. URTI=upper respiratory tract infection. VTE=venous thromboembolic event. *Study size adjusted risk difference between treatment groups. †Includes non-treatment emergent deaths. ‡Search criteria were based on Company MedDRA Query. §These events were determined on the basis of external adjudication. ¶MACE is defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. ‖VTE is defined as deep vein thrombosis and pulmonary embolism (fatal and non-fatal).

Table 6: **Overview of treatment-emergent adverse events in the safety analysis set (UC3 maintenance study)**

group. Adjudicated gastrointestinal perforation and adjudicated MACE (acute myocardial infarction) were each reported in the placebo group. No events of active tuberculosis were reported in any treatment group in UC3.

One malignancy (excluding non-melanoma skin cancer) was reported both in the placebo (invasive breast cancer) and upadacitinib 15 mg (invasive breast cancer) groups, and two malignancies (colon cancer and prostate cancer) were reported in the upadacitinib 30 mg group. Non-melanoma skin cancer was reported in two patients in the upadacitinib 30 mg group. There were two non-serious events of adjudicated VTE (both deep vein thrombosis) reported in the upadacitinib 30 mg group: a left popliteal vein thrombosis in a 74-year-old man who was obese (the patient discontinued the study due to the event), and a right axillary vein thrombosis in a 64-year-old man with concomitant serious COVID-19 pneumonia, acute respiratory failure, hypoxia, and diastolic congestive heart failure. Both deep vein thrombosis events were assessed by the study investigator as unrelated to study drug. Hepatic disorders were more commonly reported in the upadacitinib 15 mg and 30 mg groups than in the placebo group (ten [7%] of 148 in the upadacitinib 15 mg group *vs* eight [5%] of 154 in the upadacitinib 30 mg

group *vs* three [2%] of 149 in the placebo group; table 6). All hepatic events were mild or moderate and most (86%) were transaminase elevations. None led to treatment discontinuation. No patients had grade 3 or worse alanine transaminase elevations, aspartate transaminase elevations, or both across the treatment groups. In all three studies, total cholesterol concentrations were increased with upadacitinib treatment, whereas the ratio of low-density lipoprotein cholesterol and high-density lipoprotein cholesterol remained stable (appendix p 57).

The proportion of patients with anaemia was highest in the placebo group and lowest in the upadacitinib 30 mg group (seven [5%] of 148 in the upadacitinib 15 mg group *vs* three [2%] of 154 in the upadacitinib 30 mg group *vs* nine [6%] of 149 in the placebo group). More patients had neutropenia in the upadacitinib 30 mg once daily group than in the upadacitinib 15 mg and placebo groups (four [3%] of 148 in the upadacitinib 15 mg group *vs* nine [6%] of 154 in the upadacitinib 30 mg group *vs* two [1%] of 149 in the placebo group); none were serious or led to treatment discontinuation. The number of adverse events of lymphopenia were similarly reported (three [2%] *vs* three [2%] *vs* two [1%]); none were serious or led to treatment discontinuation. Creatine phosphokinase elevations were reported by a larger proportion of patients in the upadacitinib 15 mg and 30 mg groups than in the placebo group (nine [6%] *vs* 13 [8%] *vs* three [2%]); none were serious and were mainly asymptomatic. One patient in the upadacitinib 30 mg group discontinued treatment due to a mild creatine phosphokinase elevation that presented with muscle pain.

Discussion

In this phase 3 programme in patients with moderately to severely active ulcerative colitis, upadacitinib induction and maintenance therapy met the primary endpoint of clinical remission and all secondary endpoints, including clinical, endoscopic, histological, and QOL outcomes. Despite the use of a 45 mg induction dose, which is higher than previous doses evaluated in indications other than IBD, upadacitinib induction (45 mg) followed by upadacitinib maintenance (15 mg or 30 mg) was generally well tolerated, and no new important safety risks were observed compared with its known safety profile.[16–19]

In this programme, we incorporated the definition of clinical remission per Adapted Mayo score which excluded the PGA due to its subjectiveness from Mayo score and used a more stringent criterion RBS of 0, compared with previous studies which used RBS of 1 or less to define clinical remission.[4,5] The criteria for mucosal healing requiring both endoscopic and histological remission were also more stringent compared with previous studies, which used endoscopic measures only or endoscopic and histological evaluation with less stringent criteria.[4,5,20] Bowel urgency and abdominal pain are experienced by approximately 50% of patients with ulcerative colitis and are often important factors in patient treatment decisions.[21–23] Although neither of these symptoms is included in the Mayo score and is not usually measured in ulcerative colitis clinical trials, their impact on patient QOL is becoming increasingly recognised.[4,5,20] In this programme, we included the proportion of patients achieving no bowel urgency and no abdominal pain as secondary endpoints, allowing a better understanding of upadacitinib's effect across the multifaceted disease burden of ulcerative colitis.

In both induction studies, upadacitinib 45 mg onset of action was rapid, with statistically significantly more patients achieving clinical response in this group than in the placebo at week 2. Corresponding decreases in faecal calprotectin and high sensitivity CRP were also observed. In the maintenance study, although the results showed the superiority of both upadacitinib 15 mg and 30 mg versus placebo, the results in the subgroups of patients with moderate or severe disease at baseline (per Mayo score) suggested that upadacitinib 30 mg might be more appropriate for patients with higher disease burden. Of note, the placebo-adjusted treatment differences observed in this study were greater than those reported for other biologics and small molecule therapies in published phase 3 studies of ulcerative colitis.[4,5,20,24,25] In addition, efficacy was achieved in a population of patients who were treatment resistant (approximately 50% had biological failure) with moderately to severely active disease and a long-standing disease duration.

Studies in patients with atopic dermatitis, psoriatic arthritis, or rheumatoid arthritis have shown that upadacitinib (30 mg) is associated with an increased risk of serious infection.[16,17,19,26] In this programme, the frequency of serious infections was similar among all treatment groups, including placebo. Cytomegalovirus infections accounted for most opportunistic infections reported with upadacitinib, which is not unexpected in patients with ulcerative colitis.[27] Consistent with studies of upadacitinib in rheumatoid arthritis,[17–19,28] herpes zoster, neutropenia, and creatine phosphokinase elevation were also more common with upadacitinib treatment in patients with ulcerative colitis.[17–19,28] Increased risk of herpes zoster infections have been observed with JAK inhibitors. In this programme, herpes zoster events were usually non-serious and did not lead to study discontinuation. In general, patients with IBD should be considered for prophylactic herpes zoster vaccination to mitigate these risks. VTEs and malignancies (excluding non-melanoma skin cancer), reported previously in studies of upadacitinib in atopic dermatitis, psoriatic arthritis, or rheumatoid arthritis were reported similarly among the upadacitinib and placebo groups in patients with ulcerative colitis.[16,17,19,26] Patients with IBD are at higher risk than those without IBD to develop thrombosis; thus, it is not unexpected to observe events of VTE in ulcerative colitis studies. In a study of tofacitinib in patients with ulcerative colitis, reports of VTE

were infrequent with long-term treatment up to 7·8 years,[29] suggesting no increased risk of thrombosis with JAK inhibition. Regardless, patients should be informed of the risks of VTE when taking upadacitinib and, if symptoms or signs of VTE appears, evaluated promptly and treated appropriately. Of note, anaemia, a common complication in ulcerative colitis, was reported more often with placebo than upadacitinib treatment, which might reflect the improvement in ulcerative colitis in upadacitinib-treated patients (ie, reduction in gastrointestinal bleeding and inflammation).[30] Lipid increases, another known effect of JAK inhibitors, were also observed in upadacitinib-treated patients in all three phase 3 studies. However, the impact of these changes on cardiovascular morbidity and mortality are yet to be determined.

A limitation of these studies is the restriction to an 8-week induction and 52 week maintenance therapeutic regimen with limited patient exposure, which might limit detection and interpretation of adverse events with low incidences (eg, malignancy). The ongoing long-term extension study will permit further characterisation of the long-term safety profile of upadacitinib in ulcerative colitis. Another limitation was the lack of dose adjustment during maintenance treatment (eg, patients could not return to upadacitinib 45 mg or increase to 30 mg if the 15 mg dose was ineffective).

The efficacy and safety data from this programme support the potential of upadacitinib as a promising treatment option in patients with moderately to severely active ulcerative colitis, where despite the currently available treatments, a large unmet need still persists. As an oral small molecule, upadacitinib might offer various additional benefits to biological therapies including increased treatment adherence and lack of immunogenicity.

Contributors

SD, SV, JS, SG, XH, GD, JP, PDRH, PJ, JOL, EVL, WJS, WR, M-HC, and RP participated in data acquisition. SD, SV, WZ, ALP, WJS, YSG, BH, WX, JL, and RP participated in study design. SD, SV, RP, WZ, and WX assessed and verified the data. BH and WX participated in statistical analysis. All authors participated in data interpretation, critically reviewed this manuscript, and provided final approval for publication. All authors had full access to all data in the study, vouch for the completeness and accuracy of the data and analyses and for the fidelity of the protocol, and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

SD reports consultancy fees from AbbVie, Allergan, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Enthera, Ferring Pharmaceuticals, Gilead, Hospira, Janssen, Johnson & Johnson, Merck Sharp and Dohme (MSD), Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, TiGenix, UCB, and Vifor. SV reports grants from AbbVie, Johnson & Johnson, Pfizer, Galapagos, and Takeda; and consulting or speaking fees from AbbVie, Abivax, Alimentiv (formerly Robarts Clinical Trials), Arena Pharmaceuticals, Avaxia, Boehringer Ingelheim, Celgene, Dr Falk Pharma, Ferring, Galapagos, Genentech-Roche, Gilead, Hospira, Janssen, Mundipharma, MSD, Pfizer, Prodigest, Progenity, Prometheus, Second Genome, Shire, Takeda, Theravance, and Tillots Pharma. WZ, YSG, BH, WX, and JL are full-time employees of AbbVie, and might hold AbbVie stock or stock options. MAW and ALP are former employees of AbbVie, and might hold AbbVie stock or stock options. 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Data sharing

AbbVie is committed to responsible data sharing regarding the clinical trials it sponsors. Sharing includes access to anonymised, individual, and trial-level data (analysis datasets), and other information (eg, protocols, clinical study reports, and analyses plans), as long as the trials are not part of an ongoing or planned regulatory submission, and accepting requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data sharing statement. Data requests can be submitted at any time after approval in the USA and Europe and acceptance for publication, and the data will be accessible for 12 months, with possible extensions considered.

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