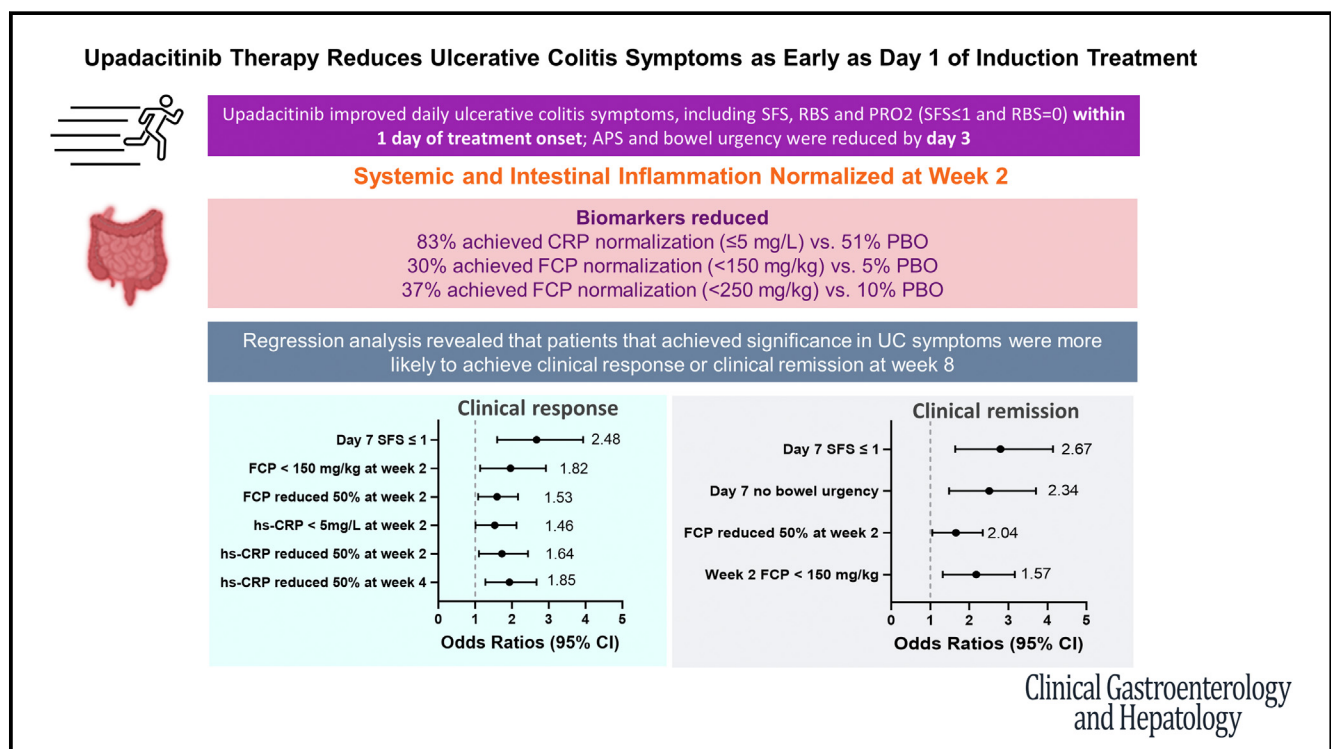# Upadacitinib Therapy Reduces Ulcerative Colitis Symptoms as Early as Day 1 of Induction Treatment

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Upadacitinib Therapy Reduces Ulcerative Colitis Symptoms as Early as Day 1 of Induction Treatment

Upadacitinib improved daily ulcerative colitis symptoms, including SFS, RBS and PRO2 (SFS≤1 and RBS=0) **within 1 day of treatment onset**; APS and bowel urgency were reduced by **day 3**

Systemic and Intestinal Inflammation Normalized at Week 2

Biomarkers reduced
83% achieved CRP normalization (≤5 mg/L) vs. 51% PBO
30% achieved FCP normalization (<150 mg/kg) vs. 5% PBO
37% achieved FCP normalization (<250 mg/kg) vs. 10% PBO

Regression analysis revealed that patients that achieved significance in UC symptoms were more likely to achieve clinical response or clinical remission at week 8

Clinical response
Day 7 SFS ≤ 1 — 2.48
FCP < 150 mg/kg at week 2 — 1.82
FCP reduced 50% at week 2 — 1.53
hs-CRP < 5mg/L at week 2 — 1.46
hs-CRP reduced 50% at week 2 — 1.64
hs-CRP reduced 50% at week 4 — 1.85
Odds Ratios (95% CI)

Clinical remission
Day 7 SFS ≤ 1 — 2.67
Day 7 no bowel urgency — 2.34
FCP reduced 50% at week 2 — 2.04
Week 2 FCP < 150 mg/kg — 1.57
Odds Ratios (95% CI)

Clinical Gastroenterology and Hepatology

BACKGROUND & AIMS: We evaluated the efficacy of once-daily (QD) upadacitinib 45 mg, an oral, reversible Janus kinase inhibitor, on early symptomatic improvement for ulcerative colitis (UC). Post hoc analyses

were performed on pooled data from 2 replicate, phase 3, multicenter induction trials, U-ACHIEVE Induction and U-ACCOMPLISH, to determine the earliest time point of efficacy onset.

METHODS: Diary entry data through 14 days from the first dose of placebo or upadacitinib 45 mg QD were analyzed for daily improvement in UC symptoms (stool frequency, rectal bleeding, abdominal pain, and bowel urgency). Changes in inflammatory markers, high-sensitivity C-reactive protein (hs-CRP), and fecal calprotectin (FCP) were assessed at week 2 and quality of life (QoL) at weeks 2 and 8. Regression analysis determined the association between changes in UC symptoms and the likelihood of achieving clinical remission/response per Adapted Mayo score at week 8.

RESULTS: Overall, 988 patients (n = 328 placebo, n = 660 upadacitinib) were analyzed. Patients treated with upadacitinib demonstrated significant improvements vs placebo in all UC symptoms between days 1 and 3 and maintained through day 14. A >50% reduction from baseline in hs-CRP and FCP levels was achieved by 75.7% and 48.2% of patients, respectively (*P* < .001 vs placebo). Increased rates of clinical remission/response per Partial Mayo score from week 2 (26.9%/59.4% upadacitinib 45 mg QD vs 4.3%/22.3% placebo, *P* < .001) and significant improvements in QoL at weeks 2 and 8 were observed. Early improvement in stool frequency and bowel urgency by day 3 and reductions in hs-CRP and FCP by week 2 were significantly associated with clinical remission/response at week 8.

CONCLUSIONS: Upadacitinib 45 mg QD provided rapid relief of UC symptoms from day 1. Clinicaltrials.gov: U-ACHIEVE Induction (NCT02819635) and U-ACCOMPLISH (NCT03653026).

U lcerative colitis (UC) is a chronic and unpredictable inflammatory bowel disease affecting the rectum and colon, which is characterized by recurring diarrhea, bowel urgency, rectal bleeding, and abdominal pain.[1] Corticosteroids may provide rapid and effective symptom improvement in patients requiring hospitalization. However, there remains an unmet need for therapies that provide rapid improvements in ambulatory patients with moderate-to-severe UC where reliance on corticosteroids still remains a challenge because of requirements of relief of high symptom burden during disease flare.[2,3] Response times for the majority of available treatments such as immunosuppressants and biologics vary between a few weeks to months, whereas some patients exhibit loss of response or failure to respond to biologics or conventional therapies.[4,5] The lack of effective, quick-acting therapies may lead patients to experience prolonged relapses, reduced quality of life (QoL), and a significant burden of illness.[6]

The Janus kinase (JAK) family (JAK1, JAK2, JAK3, and tyrosine kinase 2) are intracellular proteins that regulate signal transduction pathways, with their activation implicated in UC.[7] Tofacitinib, a pan-JAK inhibitor, achieved the primary endpoint of clinical remission at week 8 in OCTAVE trials 1 and 2 and at week 52 in the OCTAVE Sustain trial and is approved for the treatment of moderate-to-severe UC.[8] Similarly, filgotinib, a JAK1 preferential inhibitor, also achieved the primary endpoint (clinical remission) in the SELECTION trial, a phase 2b/3, double-blind study, and is approved for the treatment of moderate-to-severe UC in the European Union.[9]

Upadacitinib is an oral, once daily (QD), reversible JAK inhibitor engineered for increased selectivity for JAK1 over JAK2, JAK3, or tyrosine kinase 2, that was recently approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of adult patients with moderate to severely active UC.[7,10,11] In two phase 3, 8-week induction trials, U-ACHIEVE Induction and U-ACCOMPLISH, significantly more patients who received upadacitinib 45 mg QD met the primary endpoint, clinical remission (per Adapted Mayo score), and all ranked secondary endpoints.[12]

The aims of this study were 2-fold: first, to assess how rapidly upadacitinib 45 mg QD can improve UC symptoms, reduce inflammatory biomarkers, high-sensitivity C-reactive protein (hs-CRP) and fecal calprotectin (FCP), and improve QoL within the first 14 days of treatment onset compared with placebo during U-ACHIEVE Induction and U-ACCOMPLISH. Second, we assessed the association between early improvement of stool frequency subscore (SFS), rectal bleeding subscore (RBS), bowel urgency, abdominal pain, hs-CRP, and FCP with the achievement of clinical remission and response at week 8.

Methods

Study Design and Patients

Data from two phase 3 induction trials, U-ACHIEVE Induction (NCT02819635) and U-ACCOMPLISH (NCT03653026), were pooled for these post hoc

analyses. A full description of the eligibility criteria and study designs have been recently published. Briefly, U-ACHIEVE Induction and U-ACCOMPLISH were 2 identical, randomized, placebo-controlled, double-blind trials that evaluated the safety and efficacy of upadacitinib 45 mg QD in patients with moderately to severely active UC. Patients were randomized 2:1 for 8 weeks of therapy with upadacitinib 45 mg QD or placebo. Randomization was stratified by history of biologic failure (yes or no), corticosteroid use (yes or no) at baseline, and Adapted Mayo score at baseline (composed of Mayo SFS, RBS, and endoscopic subscore) (≤7 or >7). All patients were randomized using web-based Interactive Response Technology; randomization schedules were generated by randomization specialists at AbbVie and then distributed to the Interactive Response Technology vendor for subject randomization. Permitted concomitant UC treatment included stable doses of corticosteroids, antibiotics, or aminosalicylates. For U-ACHIEVE Induction, patients (n = 474) were enrolled from October 2018 to September 2020, whereas for U-ACCOMPLISH, patients (n = 522) were enrolled from December 2018 to January 2021. Eligible participants were between 16 and 75 years of age with moderately to severely active UC, defined as Adapted Mayo score ranging from 5 to 9 and centrally reviewed endoscopic subscore of 2–3. Patients included those who had demonstrated inadequate response to, loss of response to, or intolerance to biologic therapies or to aminosalicylates, immunosuppressants, or corticosteroids. About half of the enrolled patients had a history of failure to respond or inadequate response to biologic treatment (biologic-IR), and the other half had no history of such response.

Efficacy analyses were based on the intent-to-treat population, which included all randomized patients who received ≥1 dose of study drug, except for 7 patients who were excluded because of non-compliance issues related to informed consent or treatment not being administered. All authors had access to the study data and reviewed and approved the manuscript.

The Independent Ethics Committee or Institutional Review Board at each study site approved the study protocol, informed consent forms, and recruitment materials before patient enrollment. The studies were conducted in accordance with the International Conference for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. All patients provided written informed consent before screening.

Diary Assessments

Patients were instructed to use a provided electronic diary to record daily symptoms during the studies, including stool frequency, rectal bleeding frequency, bowel urgency (yes or no), and abdominal pain (0, no abdominal pain; 1, mild pain; 2, moderate pain; 3, severe pain). Mayo SFS and RBS were determined as follows:

What You Need to Know

Background

An urgent need exists to develop a convenient, well-tolerated therapy that offers rapid relief of symptoms in patients with moderate-to-severe ulcerative colitis.

Findings

Upadacitinib 45 mg once daily (QD) exhibited superior efficacy compared with placebo, providing patients with rapid symptomatic relief from ulcerative colitis symptoms within 1–3 days, reducing systemic and intestinal inflammatory markers, and improving quality of life by week 2. Patients who achieved early symptom improvement had a greater chance of achieving clinical remission or response at week 8.

Implications for patient care

These results demonstrate that upadacitinib 45 mg QD is an immediate and effective option for quickly providing symptom relief during induction treatment.

SFS 0, normal number of stools for subject; 1, 1–2 stools more than normal; 2, 3–4 more stools than normal; and 3, 5 or more stools than normal. Scoring for rectal bleeding was as follows: 0, no blood seen; 1, streaks of blood with stool less than half the time; 2, obvious blood with stool most of the time; and 3, blood alone passed.

Study Outcomes

On the basis of daily diary entry data, the following endpoints were evaluated for the first 14 days of induction treatment, with the first dose of study drug administration defined as day 0: percentage of patients who achieved SFS ≤1, SFS = 0, RBS = 0, two-item patient-reported outcome (PRO2 [SFS ≤1 and RBS = 0]), abdominal pain = 0, and bowel urgency absent. Subgroup analyses were also conducted to evaluate for the first 14 days of induction treatment: percentage of patients who achieved SFS ≤1, SFS = 0, RBS = 0, abdominal pain = 0, and bowel urgency absent, grouped by the following baseline clinical characteristics: corticosteroid use (yes or no), disease severity (Adapted Mayo score ≤7 or >7), biologic-IR status (biologic-IR or non–biologic-IR), and disease extent (presence of pancolitis at baseline [yes or no]). The hs-CRP and FCP levels were measured at week 2 in all patients and in subsets of patients with elevated levels of hs-CRP (≥5 mg/L) and FCP (≥150 mg/kg or ≥250 mg/kg) at baseline. The percentages of patients who achieved clinical remission or clinical response per Partial Mayo score were monitored every other week from 2 to 8 weeks. Clinical remission per Partial Mayo score was

defined as Partial Mayo score ≤ 2 with no subscore >1. Clinical response per Partial Mayo score was defined as decrease in Partial Mayo score ≥ 2 points and $\geq 30\%$ from baseline plus a decrease in RBS ≥ 1 or an absolute RBS ≤ 1. Clinical remission per Adapted Mayo score was defined as an Adapted Mayo score ≤ 2 with SFS ≤ 1 and not greater than baseline, RBS $= 0$, and endoscopic subscore ≤ 1 without friability, whereas clinical response per Adapted Mayo score was identified as a decrease in Adapted Mayo score of ≥ 2 points, $\geq 30\%$ from baseline, and a decrease in RBS of ≥ 1 point or an absolute RBS of ≤ 1. Partial Mayo score included SFS, RBS, and physician's global assessment subscore, whereas Adapted Mayo score included SFS, RBS, and endoscopic subscore per central reading (Supplementary Table 1). Subgroup analysis was performed for clinical remission PRO2 and clinical response per Partial Adapted Mayo score every other week from 2 to 8 weeks, stratifying by baseline characteristics, including corticosteroid use (yes or no), Adapted Mayo score (≤ 7 or > 7), prior biologic failure experience (yes or no), and presence of pancolitis (yes or no). Clinical remission PRO2 was defined as a 2-item patient-reported outcome (PRO2 [SFS ≤ 1 and RBS $= 0$]). Clinical response per Partial Adapted Mayo score was defined as decrease in Partial Adapted Mayo score ≥ 1 point and $\geq 30\%$ from baseline plus a decrease in RBS ≥ 1 or an absolute RBS ≤ 1.

Health-related QoL Assessments

The percentages of patients who achieved a clinically meaningful within-patient change (MWPC) from baseline at weeks 2 and 8 were calculated for the following health-related QoL (HRQoL) analyses: Functional Assessment of Chronic Illness Therapy–Fatigue, Ulcerative Colitis Symptoms Questionnaire, Inflammatory Bowel Disease Questionnaire, Work Productivity and Activity Impairment (WPAI) questionnaire, Short Form 36, and European Quality of Life-5 Dimensions 5 Levels Index Score. The percentage of patients with MWPC was calculated by dividing the number of patients who met or exceeded the threshold at that time by the total number of patients. For each parameter, MWPC was defined as the following: Functional Assessment of Chronic Illness Therapy–Fatigue, ≥ 5-point increase; Ulcerative Colitis Symptoms Questionnaire, ≥ 10-point decrease; Inflammatory Bowel Disease Questionnaire, ≥ 16-point increase; WPAI overall, ≥ 7.3-point decrease; WPAI absenteeism, ≥ 6.5-point decrease; WPAI presenteeism, ≥ 6.1-point decrease; WPAI activity impairment, ≥ 8.5-point decrease; Short Form 36 physical or mental component score, ≥ 4.1-point decrease; and European Quality of Life-5 Dimensions 5 Levels, ≥ 0.076-point increase.[13]

Statistical Analyses

All binary endpoints were analyzed using the Cochran–Mantel–Haenszel test stratified by study (U-ACHIEVE Induction, U-ACCOMPLISH), baseline corticosteroid use (yes or no), baseline Adapted Mayo score (≤ 7 or >7), and previous response to biologics (yes or no) to compare the 2 treatment groups. For endpoints related to systemic and intestinal inflammatory markers (hs-CRP and FCP, respectively), clinical remission and clinical response were evaluated at each protocol-defined visit, and all intent-to-treat patients were included in the analyses. For by-visit endpoints, missing data were handled by non-responder imputation while incorporating multiple imputation for missing data due to coronavirus disease 2019 (COVID-19), ie, patients with missing data were imputed as non-responders, unless the missing data were due to COVID-19, in which case the subjects were handled by multiple imputations. Patients were considered non-responders at and after the UC-related corticosteroids censoring time point through week 8. For rapid onset endpoints such as the first 14 days of SFS ≤ 1, as observed analysis was used. Patients with missing evaluations were excluded from the as observed analysis. All values collected were used for the as observed approach regardless of UC-related corticosteroids censoring.

In addition, logistic regression models were built to determine the association between the percentages of patients who achieved clinical remission or response per Adapted Mayo score at week 8 and the following independent variables: day 3 SFS ≤ 1, day 3 SFS $= 0$, day 3 RBS $= 0$, day 3 bowel urgency absent, day 3 abdominal pain $= 0$, day 7 SFS ≤ 1, day 7 SFS $= 0$, day 7 RBS $= 0$, day 7 abdominal pain $= 0$, day 7 no bowel urgency, week 2 FCP <150 mg/kg, week 2 FCP <250 mg/kg, week 2 hs-CRP ≤ 5 mg/L, week 2 FCP reduction $>50\%$, or week 2 or week 4 hs-CRP reduction $>50\%$. Multivariable logistic correlation analysis was performed according to the backward selection, ie, with all independent variables included in the initial step, with redundant steps eliminated until the model fit well; this helped to reduce the multicollinearity between predictors. The sign of the coefficient estimate showed the negative or positive correlation between the independent variable and the week 8 outcome, and its absolute value indicates the magnitude of impact. Odds were defined as the probability of achieving the week 8 endpoint divided by the probability of not achieving it.

Results

Patients

Patients (N $= 996$) were randomized to placebo (n $= 332$) or upadacitinib 45 mg QD (n $= 664$). A total of 8 patients were randomized but excluded from efficacy analysis because of non-compliant sites (n $= 7$) or not receiving a dose of study drug (n $= 1$) (Supplementary Figure 1). Baseline characteristics and demographics are described in Table 1; the groups were well-balanced across all variables.

Table 1. Baseline Characteristics and Demographics

Variable	Placebo (n = 328)	Upadacitinib 45 mg QD (n = 660)
Female	124 (37.8)	248 (37.6)
Race, white	224 (68.3)	440 (66.7)
Age (y), median (range)	42.0 (17–76)	41.0 (17–76)
Weight (kg), mean (SD)	73.9 (19.7)	72.7 (18.1)
Disease duration (y), mean (SD)	8.2 (8.0)	7.9 (6.8)
Disease extent		
Left-sided	162 (49.4)	322 (48.8)
Extensive/pancolitis	166 (50.6)	337 (51.1)
Concomitant immunosuppressant use	6 (1.8)	3 (0.5)
Concomitant aminosalicylates use	223 (68.0)	453 (68.6)
Concomitant corticosteroid use	133 (40.5)	244 (37.0)
Previous biologic treatment failure	167 (50.9)	340 (51.5)
Baseline Partial Mayo Score[a]		
Mean (SD)	6.7 (1.4)	6.6 (1.4)
Baseline Adapted Mayo Score[a]		
Mean (SD)	7.0 (1.2)	7.0 (1.2)
Baseline hs-CRP (mg/L)		
Median (range)	4.7 (0.2–179.0)	4.0 (0.2–107.0)
≤5 mg/L	169 (51.5)	371 (56.2)
>5 mg/L	159 (48.5)	289 (43.8)
Baseline fecal calprotectin (mg/kg)		
Median (range)[b]	1771.0 (30–28,800)	1734.0 (30–28,800)
≤150 mg/kg	17 (5.9)	40 (7.0)
>150 mg/kg	272 (94.1)	533 (93.0)
≤250 mg/kg	31 (10.7)	57 (9.9)
>250 mg/kg	258 (89.3)	516 (90.1)
Baseline stool frequency score		
≤1	15 (4.6)	39 (5.9)
>1	313 (95.4)	619 (94.1)
=0	1 (0.3)	2 (0.3)
>0	327 (99.7)	656 (99.7)
Baseline rectal bleeding score		
=0	27 (8.2)	52 (7.9)
>0	301 (91.8)	606 (92.1)
Baseline abdominal pain score		
=0	35 (10.8)	65 (10.0)
>0	290 (89.2)	582 (90.0)
Presence of bowel urgency		
Yes	299 (92.0)	598 (92.4)

Table 1. Continued

Variable	Placebo (n = 328)	Upadacitinib 45 mg QD (n = 660)
No	26 (8.0)	49 (7.6)
FACIT-F[c]		
Mean (SD)	31.5 (11.8)	30.1 (11.7)
UC-SQ[d]		
Mean (SD)	31.4 (10.9)	32.3 (11.2)
IBDQ[e]		
Mean (SD)	122.2 (34.7)	122.5 (35.5)
Overall WPAI[f]		
Mean (SD)	52.8 (29.6)	53.8 (28.4)
WPAI Absenteeism[f]		
Mean (SD)	19.2 (29.4)	19.6 (31.1)
WPAI Presenteeism[g]		
Mean (SD)	43.5 (26.0)	44.6 (23.6)
WPAI Activity Impairment[h]		
Mean (SD)	49.5 (26.3)	51.6 (25.7)
SF-36 (PCS)[h]		
Mean (SD)	43.1 (8.0)	42.8 (7.8)
SF-36 (MCS)[h]		
Mean (SD)	40.6 (11.0)	40.6 (10.6)
EQ-5D-5L[h]		
Mean (SD)	0.7 (0.21)	0.7 (0.20)

NOTE. Data are represented as n (%) unless otherwise noted. Percentages were calculated on non-missing values.

EQ-5D-5L, European Quality of Life-5 Dimensions 5 Levels; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FCP, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, mental component score; PCS, physical component score; QD, once daily; RBS, rectal bleeding score; SD, standard deviation; SF-36, Short Form 36; SFS, stool frequency score; UC-SQ, Ulcerative Colitis Symptoms Questionnaire; WPAI, Work Productivity and Activity Impairment.

[a]n = 328 placebo, n = 658 upadacitinib 45 mg QD.
[b]n = 289 placebo, n = 573 upadacitinib 45 mg QD.
[c]n = 321 placebo, n = 646 upadacitinib 45 mg QD.
[d]n = 319 placebo, n = 642 upadacitinib 45 mg QD.
[e]n = 322 placebo, n = 649 upadacitinib 45 mg QD.
[f]n = 197 placebo, n = 408 upadacitinib 45 mg QD.
[g]n = 182 placebo, n = 372 upadacitinib 45 mg QD.
[h]n = 321 placebo, n = 647 upadacitinib 45 mg QD.

Improvement in Daily UC Symptoms Indicates Rapid Efficacy Onset

A significantly higher percentage of patients achieved SFS ≤1, SFS = 0, RBS = 0, and PRO2 (SFS ≤1 and RBS = 0) as early as day 1 after treatment initiation among patients receiving upadacitinib 45 mg QD compared with placebo. This difference increased and was maintained through day 14 (Figure 1). The percentages of upadacitinib-treated patients achieving the absence of abdominal pain or bowel urgency were significantly higher vs placebo beginning at day 3 and each day thereafter through day 14 (P < .05 or better for all endpoints). In the baseline clinical characteristics subgroup analyses, the response rate differences vs placebo
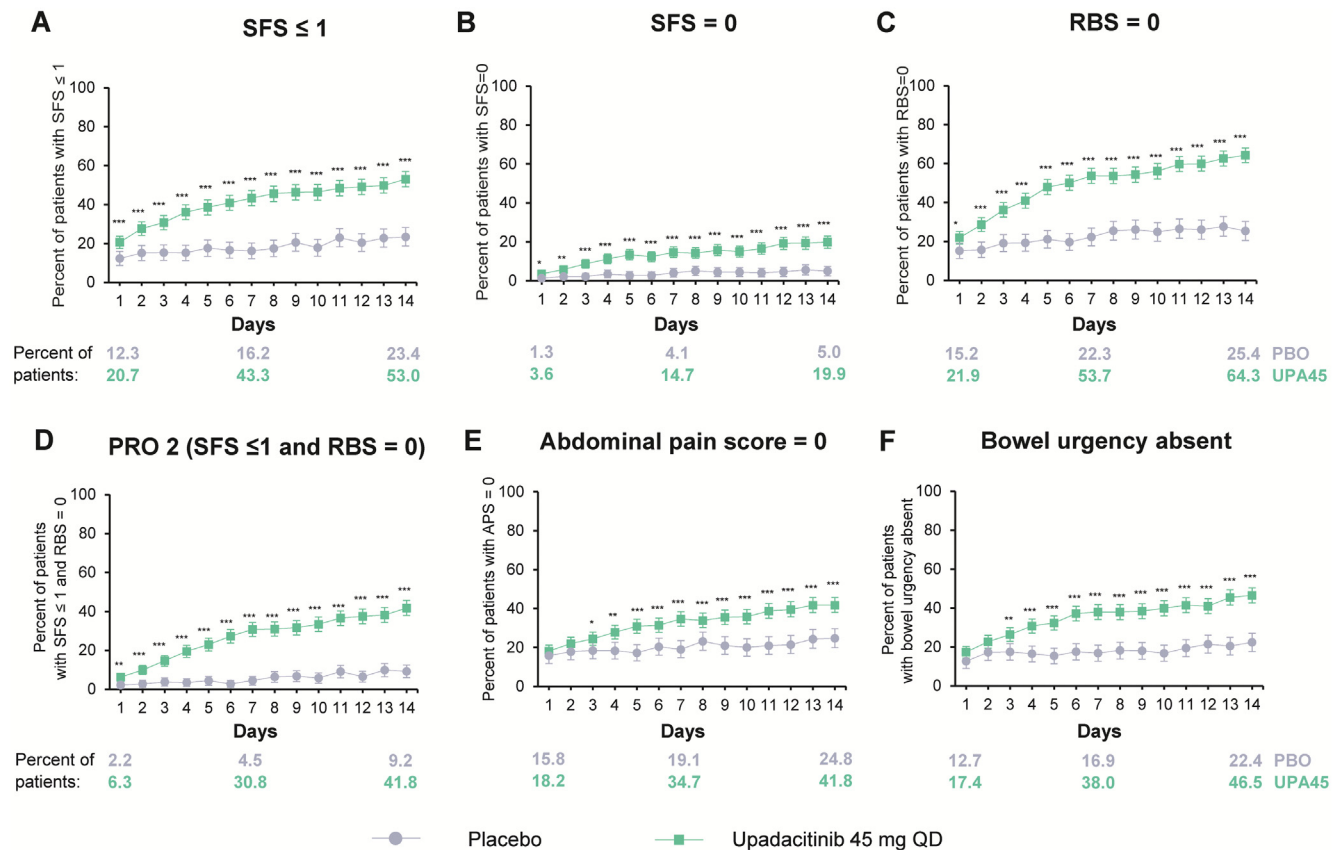
Figure 1. Upadacitinib 45 mg QD improves daily abdominal symptoms early during the induction phase. Percentage of patients with symptomatic improvement in (A) SFS ≤1, (B) SFS = 0, (C) RBS = 0, (D) PRO2 (SFS ≤1 and RBS = 0), (E) abdominal pain score = 0, and (F) bowel urgency absent for first 14 days of treatment. Day 0 represents first day of randomization and first day of treatment. Shown below the x-axis are percentages for each symptom in placebo- (*gray*) and upadacitinib 45 mg QD- (*green*) treated patients at days 1, 7, and 14. Patient numbers for all parameters were n = 303–319 placebo and n = 616–634 upadacitinib 45 mg QD. Error bars are ± 95% CI. 95% CI for adjusted difference and *P* values were calculated according to the CMH test adjusted for strata. *P ≤ .05; **P ≤ .01; ***P < .001 vs placebo. CI, confidence interval; CMH, Cochran–Mantel–Haenszel; PRO 2, two-item patient-reported outcome; QD, once daily; RBS, rectal bleeding score; SFS, stool frequency score.

for SFS ≤1, SFS = 0, RBS = 0, abdominal pain = 0, and bowel urgency absent were similar through day 14 irrespective of corticosteroid use, disease severity, biologic-IR status, and disease extent at baseline (Supplementary Figure 2).

Upadacitinib 45 mg QD Induces Clinical Remission and Clinical Response as Early as Week 2, Continuing Through Week 8 of Induction Phase

The earliest time point for evaluation of clinical response and clinical remission per Partial Mayo score was at week 2. Patients treated with upadacitinib 45 mg QD had a higher rate of clinical remission beginning at week 2 (Figure 2; upadacitinib 45 mg QD, 26.9%; 95% confidence interval [CI], 23.5%–30.3% vs placebo, 4.3%; 95% CI, 2.1%–6.5%; P < .001). Moreover, an even more robust rate was found at week 2 for clinical response

(upadacitinib 45 mg QD, 59.4%; 95% CI, 55.6%–63.1% vs placebo, 22.3%; 95% CI, 17.8%–26.8%). Notably, this was maintained through week 8 for both endpoints, with 39% difference at week 8 for clinical remission and 46% difference at week 8 for clinical response (P < .001).

Stratified analysis was performed for clinical remission PRO2 beginning at week 2. Response rate differences were similar when stratified by baseline corticosteroid use, Adapted Mayo score, prior biologic experience, and disease severity, indicating that these factors did not influence clinical remission rates between upadacitinib 45 mg QD and placebo-treated patients (Supplementary Figure 3). Similarly, subgroup analysis was also performed for clinical response per Partial Adapted Mayo score, stratifying by the same factors, with no difference between rates, because some were beginning to plateau by week 2 (Supplementary Figure 4). This was not surprising because patients normally reach clinical response earlier during treatment, often before clinical remission.
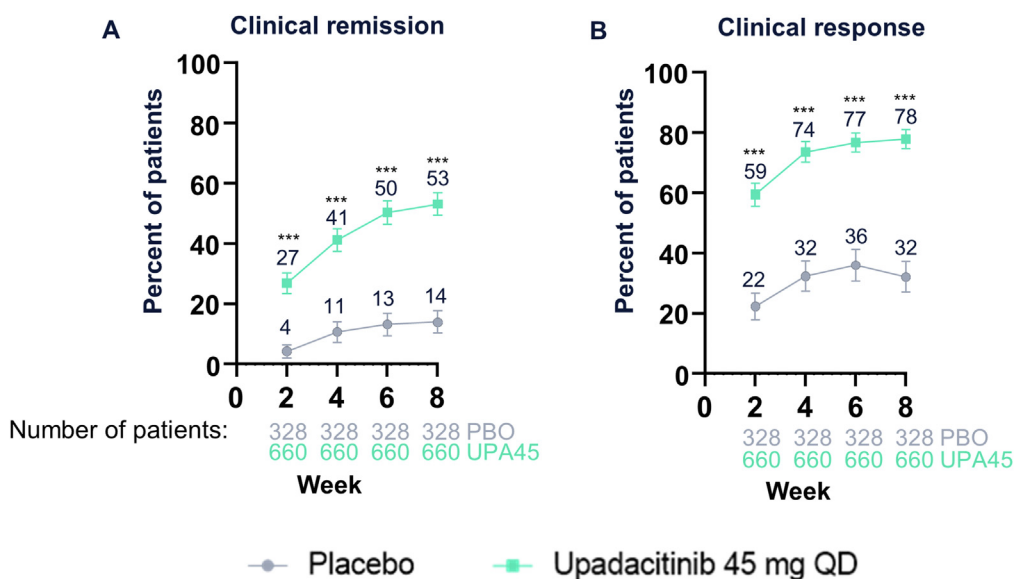
Figure 2. Upadacitinib 45 mg QD induces clinical remission and clinical response at week 2 through week 8 of the induction phase. Shown are percentages of patients who achieved (A) clinical remission and (B) clinical response per Partial Mayo score beginning at week 2 through week 8. For all time points, total numbers of patients analyzed per group were 328 placebo and 660 upadacitinib 45 mg QD. Comparisons were made with 95% CI for response rate as the synthetic result based on normal approximation to binomial distribution. 95% CI for adjusted difference and P values were calculated according to the CMH test adjusted for strata. Error bars are ± 95% CI. ***P < .001 vs placebo. CI, confidence interval; CMH, Cochran–Mantel–Haenszel; QD, once daily.

Early Improvement in Systemic and Intestinal Inflammatory Biomarkers Including hs-CRP and FCP

Serum (hs-CRP) and fecal (FCP) biomarkers, which correlate with the presence of systemic and intestinal inflammation, were first measured at week 2 in all patients. The percentage of patients with hs-CRP response >50% reduction from baseline was significantly higher in patients who received upadacitinib (75.7%) than those who received placebo (21.9%), with a 54% treatment difference (Figure 3, P < .001). Normalization of hs-CRP ≤5 mg/L was seen in 83.1% of patients randomized to upadacitinib 45 mg QD compared with 51.1% of placebo-treated patients (P < .001). Similarly, administration of upadacitinib 45 mg QD reduced intestinal inflammation, with an increase in the percentage of patients who achieved a reduction in FCP >50% from baseline levels compared with placebo (48.2% vs 20.2%, P < .001). In patients treated with upadacitinib 45 mg QD, there was a significant increase in the percentage of patients who attained FCP levels below 150 mg/kg (30% upadacitinib 45 mg QD vs 5% placebo) and 250 mg/kg (37% upadacitinib 45 mg QD vs 10% placebo), compared with those who received placebo (P < .001 for both cutoff values). Similar results were observed when analyses were performed for patients with elevated hs-CRP (≥5 mg/L) and FCP (≥150 mg/kg or ≥250 mg/kg) at baseline (Supplementary Figure 5).

Regression Analysis of Clinical Remission and Clinical Response Based on Changes in Daily Abdominal Symptoms, hs-CRP, and FCP Within the First 14 Days

Odds ratios (ORs) and correlation coefficients were used to express associations between changes in daily abdominal symptoms, hs-CRP and FCP levels within the first 2 weeks of treatment and achievement of clinical remission at week 8. Patients who achieved SFS ≤1 (OR, 2.61; 95% CI, 1.64–4.15) or the absence of bowel urgency (OR, 2.34; 95% CI, 1.48–3.70) at day 7 were significantly more likely to attain clinical remission per Adapted Mayo score at week 8 (Figure 4). Patients with FCP <150 mg/kg (OR, 2.04; 95% CI, 1.32–3.16) or those who achieved a reduction in FCP of >50% (OR, 1.57; 95% CI, 1.05–2.34) at week 2 also had a significantly greater chance of attaining clinical remission.

Similar to clinical remission, multivariate regression analysis was used to assess potential associations between achieving clinical response per Adapted Mayo score at week 8 and changes in patients' daily abdominal symptoms, hs-CRP, and FCP within the first 2 weeks. Patients who achieved SFS ≤1 at day 7 (OR, 2.48; 95% CI, 1.56–3.93) had an increased chance of achieving clinical response. Patients with a reduction in hs-CRP >50% at week 2 (OR, 1.64; 95% CI, 1.10–2.44) or week 4 (OR, 1.85; 95% CI, 1.28–2.67) had greater odds of reaching a clinical response. Similarly, patients with hs-CRP levels ≤5 mg/L at week 2 (OR, 1.46; 95% CI,
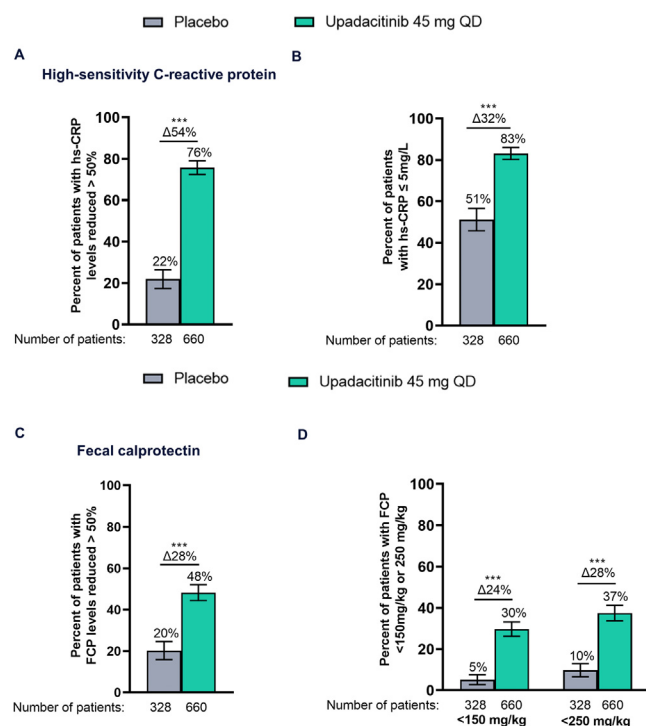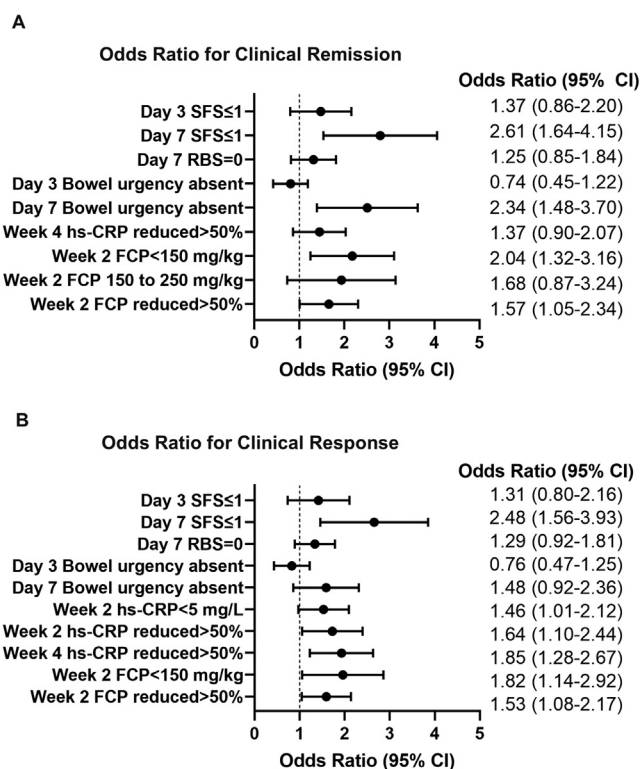
Figure 3. Upadacitinib 45 mg QD promotes reduction in systemic and intestinal inflammatory markers, high-sensitivity C-reactive protein, and fecal calprotectin at week 2. Shown are percentages of patients with (A) hs-CRP reduced >50%, (B) hs-CRP ≤5 mg/L, (C) FCP reduced >50%, and (D) FCP levels <150 mg/kg and 250 mg/kg. FCP was expressed in mg/kg of fecal matter. 95% CI for response rate is the synthetic result based on Student t distribution from the PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on normal approximation to binomial distribution if there are no missing data due to COVID-19. Error bars are ± 95% CI. ***$P < .001$ vs placebo. CI, confidence interval; FCP, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; QD, once daily.

Figure 4. Odds ratios for clinical remission and clinical response. Logistic models were built to determine the association between (A) clinical remission or (B) clinical response per Adapted Mayo score at week 8 and independent variables listed on the y-axes. Model fitting was performed starting by including all independent variables listed in the Methods and then eliminating those that were redundant until the model fit well. Odds were defined as the probability of achieving the week 8 endpoint divided by the probability of not achieving it. Odds ratios (95% CI) corresponding to each variable are listed on the right of each graph. CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; RBS, rectal bleeding score; SFS, stool frequency score.

1.01–2.12) had a greater chance of achieving clinical response. Patients who reduced intestinal inflammation at week 2 by lowering FCP levels to <150 mg/kg (OR, 1.82; 95% CI, 1.14–2.92) or had >50% reduction (OR, 1.53; 95% CI, 1.08–2.17) were more likely to reach a clinical response. The coefficients of prediction for clinical remission and response agree with the OR results (Supplementary Tables 2 and 3).

Upadacitinib 45 mg QD Improves QoL in Patients With UC at Weeks 2 and 8

Patients who received upadacitinib 45 mg QD exhibited improvements in a broad range of HRQoL assessments, including Functional Assessment of Chronic Illness Therapy–Fatigue, Inflammatory Bowel Disease Questionnaire, Ulcerative Colitis Symptoms Questionnaire, overall WPAI, absenteeism, presenteeism, activity impairment, Short Form 36, and European Quality of Life-5 Dimensions 5 Levels at weeks 2 and 8 (Figure 5 and Supplementary Figure 6).

Discussion

In these post hoc analyses of two phase 3 induction trials, upadacitinib 45 mg QD provided rapid relief from UC symptoms as early as day 1 after the first dose. By day 3, all patient-reported UC symptoms that were assessed were significantly improved compared with placebo, including stool frequency, rectal bleeding, abdominal pain, and bowel urgency. The differences between upadacitinib 45 mg QD and placebo continued to increase, with significance maintained through day 14.

Bowel urgency and abdominal pain are experienced by approximately 50% of patients with UC and are often important factors in patient treatment decisions.[14] Although neither of these symptoms are included in the Mayo score and are not usually measured in UC clinical trials, their impact on patient HRQoL is becoming increasingly recognized, because patients experiencing these symptoms have significantly impaired HRQoL, limiting their ability to work and participate in society. For these reasons, patients need a convenient therapy
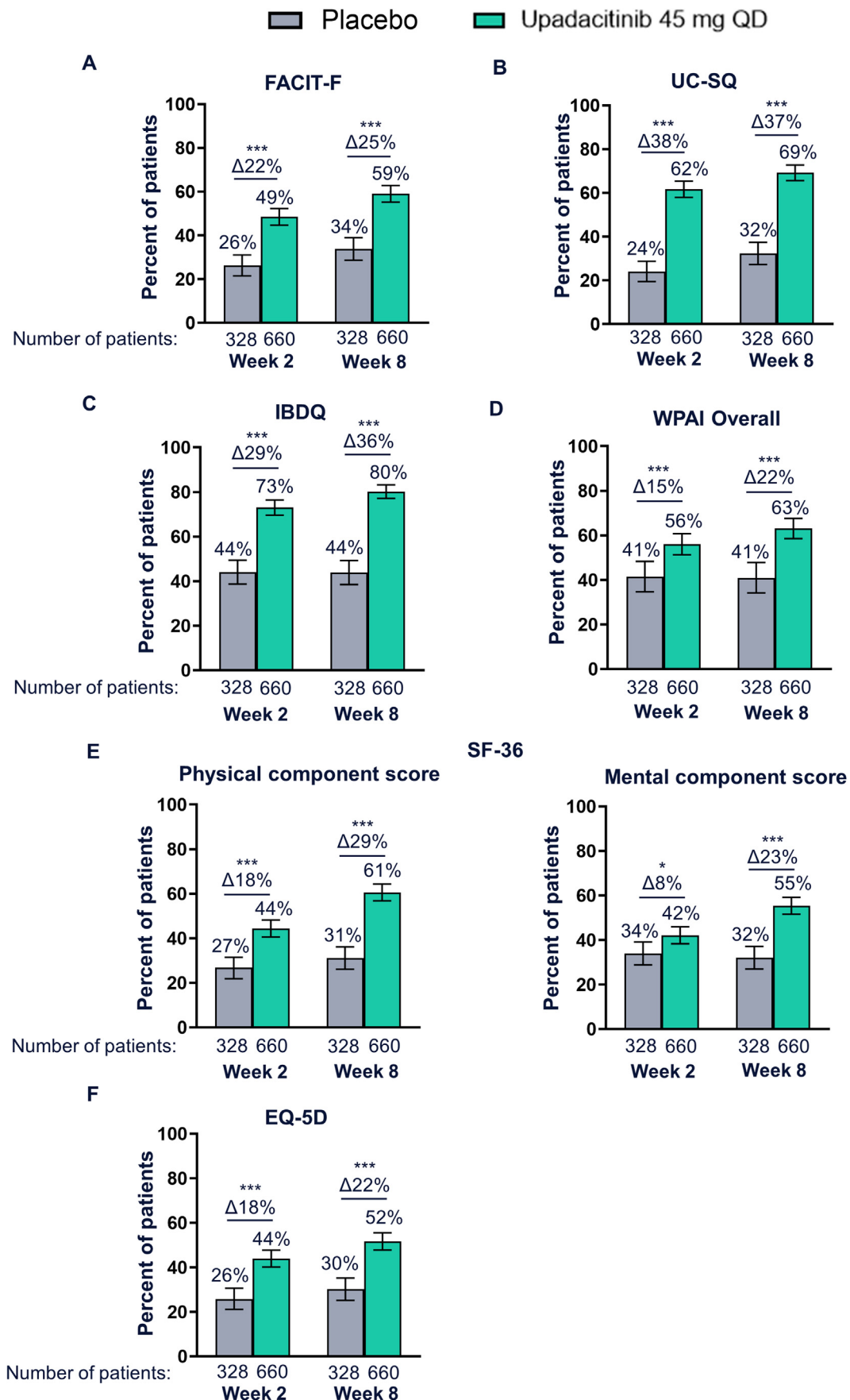
that provides quick resolution of their symptoms. In this study, upadacitinib led to absence of rectal bleeding by day 1 and absence of abdominal pain and bowel urgency by day 3 in a significant proportion of patients vs placebo (all $P < .05$).

Rapid onset of efficacy and control of inflammatory activity were also demonstrated by significant reductions vs placebo in hs-CRP and FCP at week 2, even in patients with elevated hs-CRP and FCP levels at baseline. Because this was the first time point that these biomarkers were collected, it is difficult to know whether these differences could have occurred earlier. Not surprisingly, patients who received upadacitinib 45 mg QD also experienced improvements in HRQoL at weeks 2 and 8.

According to STRIDE II, symptomatic relief and normalization of hs-CRP serum levels were identified as short-term treatment targets, whereas FCP and symptomatic relief were intermediate treatment targets, and endoscopic remission along with normalization of HRQoL were long-term treatment targets.[15] Here, clinical remission and response (per Partial Mayo score) were achieved by week 2 and maintained through week 8, with a large margin of difference maintained between upadacitinib 45 mg QD and placebo-treated patients. Although the Mayo score captures symptoms of stool frequency and rectal bleeding, additional symptoms negatively impair HRQoL, including abdominal pain, bowel urgency, and fatigue. Patients who achieved significant improvements in daily abdominal symptoms, including day 7 SFS ≤1, day 7 absence of bowel urgency, and FCP reductions at week 2, were more likely to reach clinical remission (per Adapted Mayo score) at week 8. Patients who achieved day 7 SFS ≤1, reductions in hs-CRP at week 2 or 4, and reductions in FCP at week 2 were more likely to reach clinical response (per Adapted Mayo score) at week 8.

Because of the HRQoL and psychosocial impact of symptoms experienced by patients with moderate-to-severe UC, rapid control of symptoms is one of the biggest unmet needs and a critical factor when choosing a therapy.[6] This unmet need is likely highlighted by the repeated and overuse of corticosteroids to achieve this rapid control, even during the onset of the biologic era.[2] Monoclonal antibodies including anti-tumor necrosis factor, anti-integrin therapy, or anti-interleukin 12/23 agents may take 1–4 weeks to induce a response.[5] Clinical trials comparing anti-tumor necrosis factor agent infliximab and golimumab found that PRO2 remission was achieved at weeks 2 and 6 by a significantly greater proportion of patients treated with infliximab compared with golimumab.[16] Ustekinumab targeting interleukin 12/23 (p40 subunit) led to a clinical benefit by week 1, with improvement in stool frequency beginning at day 7 and clinical remission at week 2.[17] The anti-$\alpha4\beta7$-integrin agent vedolizumab also reduced UC symptoms by 2 weeks in the GEMINI trials.[18] In our study, upadacitinib demonstrated significant improvements in all UC symptoms vs placebo between days 1 and 3 in this study. Similarly, a pan-JAK inhibitor, tofacitinib, has been shown to have rapid onset of efficacy in the OCTAVE trials, providing patients with significant improvements in stool frequency and rectal bleeding as early as day 3 of treatment.[19] The proportion of patients with RBS = 0 at day 3 was significantly greater with tofacitinib vs placebo. Both upadacitinib and tofacitinib produced early symptomatic improvements that corresponded with clinical response at week 8, irrespective of prior biologic failure.

Overall, this demonstrates that upadacitinib may provide patients with a rapid-acting therapeutic alternative for the management of important UC symptoms as early as 1 day after the first dose of induction treatment.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.11.029.

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Figure 5. Upadacitinib 45 mg QD improves quality of life at weeks 2 and 8. Shown are percentages of patients who achieved MWPC for (A) FACIT-F, (B) UC-SQ, (C) IBDQ, (D) WPAI overall, (E) SF-36 (physical and mental component scores), and (F) EQ-5D-5L. 95% CI for adjusted difference and P values were calculated according to the CMH test adjusted for strata for comparison of 2 treatment groups. Error bars are ± 95% CI. *$P \le .05$; ***$P < .001$ vs placebo. CI, confidence interval; CMH, Cochran–Mantel–Haenszel; EQ-5D-5L, European Quality of Life-5 Dimensions 5 Levels; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; MWPC, clinically meaningful within-patient change; QD, once daily; SF-36, Short Form 36; UC-SQ, Ulcerative Colitis Symptoms Questionnaire; WPAI, Work Productivity and Activity Impairment.

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Tricia Finney-Hayward (Writing – review & editing: Equal; Data interpretation: Equal)

Wen Zhou (Conceptualization: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)

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Yuri Sanchez Gonzalez (Methodology: Supporting; Writing – review & editing: Supporting; Data interpretation: Lead)

Lei Shu (Statistical analysis: Lead)

Xuan Yao (Validation: Equal; Statistical analysis: Equal)

Qing Zhou (Validation: Equal; Statistical analysis: Equal)

Severine Vermeire (Data acquisition: Equal)

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                    ┌─────────────────────────┐
                    │       Randomized        │
                    │   U-ACHIEVE (N=474)     │
                    │                         │
                    │   U-ACCOMPLISH (N=522)  │
                    └─────────────────────────┘
                                 │
                 ┌───────────────┴────────────────┐
                 ▼                                ▼
         ┌───────────────┐              ┌─────────────────────┐
         │    Placebo    │              │ Upadacitinib 45 mg QD│
         │    (N=332)    │              │       (N=664)       │
         └───────────────┘              └─────────────────────┘
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Supplementary Figure 1. Patient disposition for U-ACHIEVE Induction and U-ACCOMPLISH studies. U-ACHIEVE Induction: all patients did not meet the inclusion/exclusion criteria. *One patient in the placebo group was excluded from efficacy analysis from a significant non-compliant site. The patient was included in the safety analysis. U-ACCOMPLISH: ‡All randomized patients, except one randomized to the upadacitinib 45 mg QD group, received at least 1 dose of treatment. Three patients in placebo group were excluded from efficacy analysis from a significant non-compliant site. These patients were included in the safety analysis. AE, adverse event; QD, once daily. Adapted from Danese S, et al. Lancet 2022;399:2113–2128.
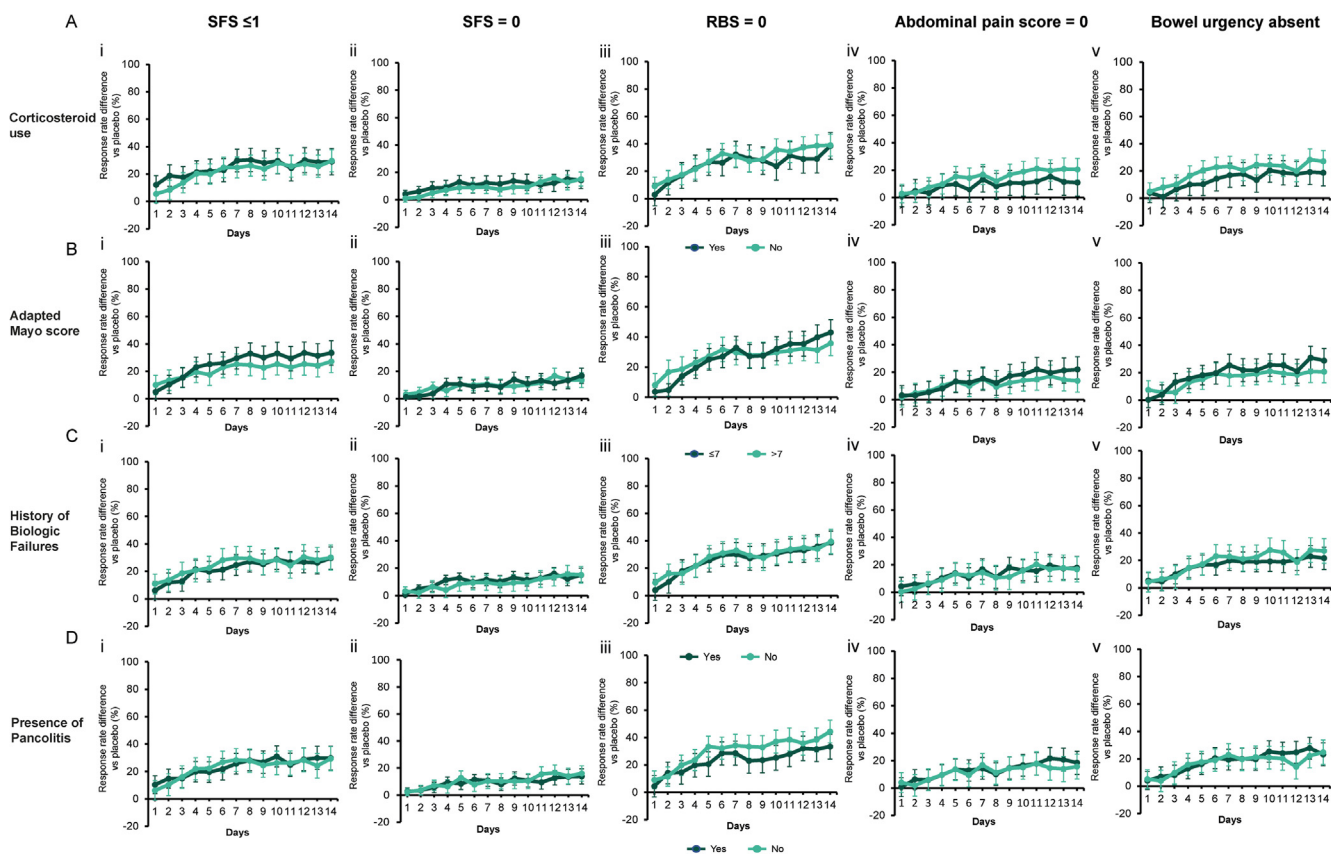
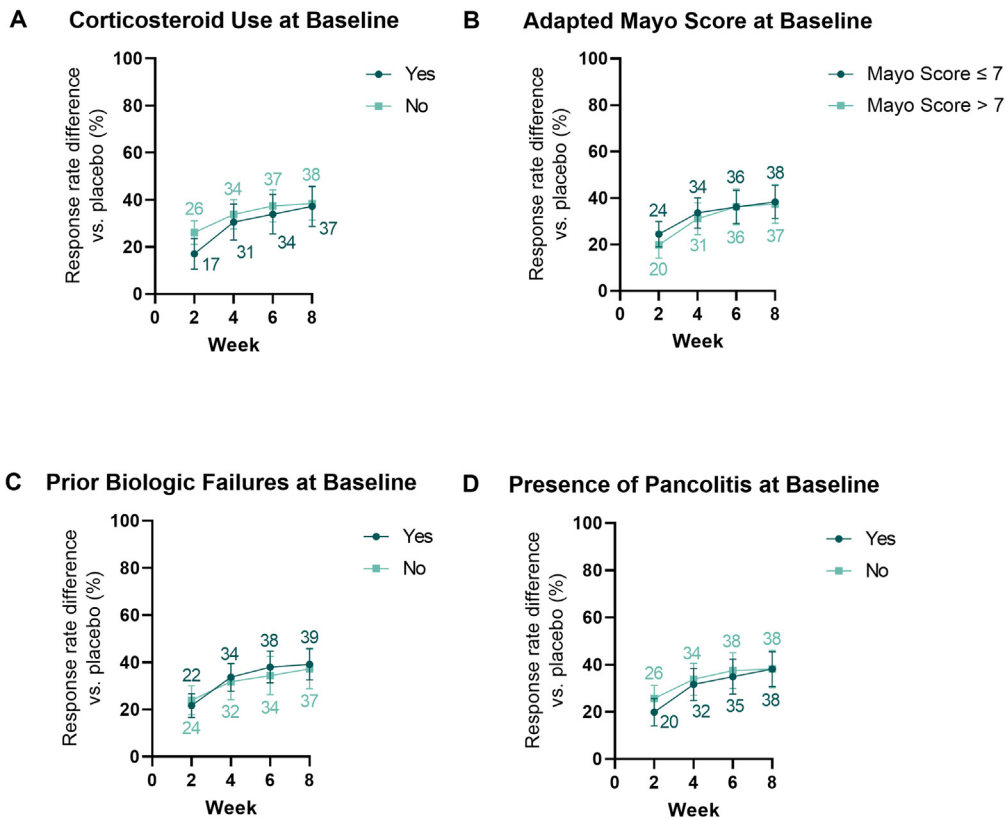| Placebo	Upadacitinib 45 mg QD
Included in efficacy analysis* (N=328)	Included in efficacy analysis‡ (N=660)
Discontinued treatment (n=32; 9.8%) Primary reason: AEs n=12 Withdrew consent n=6 Lack of efficacy n=13 Other n=1	Discontinued treatment (n=23; 3.5%) Primary reason: AEs n=12 Withdrew consent n=7 Lack of efficacy n=2 Lost to follow up n=1 Other n=1
Completed (N=296; 89.2%)	Completed (N=637; 96.5%)

Supplementary Figure 2. Upadacitinib 45 mg QD improves daily abdominal symptoms early during induction phase irrespective of baseline clinical characteristics. Response rate differences for upadacitinib 45 mg QD versus placebo for daily symptoms including in (*A*) i, SFS ≤1; ii, SFS = 0; iii, RBS = 0; iv, abdominal pain score = 0; v, bowel urgency absent for first 14 days of treatment by baseline corticosteroid use (yes or no); (*B*) i, SFS ≤1; ii, SFS = 0; iii, RBS = 0; iv, abdominal pain score = 0; v, bowel urgency absent for first 14 days of treatment by Adapted Mayo score (≤7 or >7) at baseline; (*C*) i, SFS ≤1; ii, SFS = 0; iii, RBS = 0; iv, abdominal pain score = 0; v, bowel urgency absent for first 14 days of treatment by biologic-IR status (biologic-IR or non-biologic-IR) at baseline; and (*D*) i, SFS ≤1; ii, SFS = 0; iii, RBS = 0; iv, abdominal pain score = 0; v, bowel urgency absent for first 14 days of treatment by presence of pancolitis at baseline (yes or no). Day 0 represents first day of randomization and first day of treatment. Patient numbers for all parameters were n = 117–190 placebo and n = 224–401 upadacitinib 45 mg QD. Error bars are ± 95% CI. 95% CI for adjusted difference and *P* values were calculated according to CMH test adjusted for strata. Biologic-IR, inadequate response to biologic treatment; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; QD, once daily; RBS, rectal bleeding score; SFS, stool frequency score.
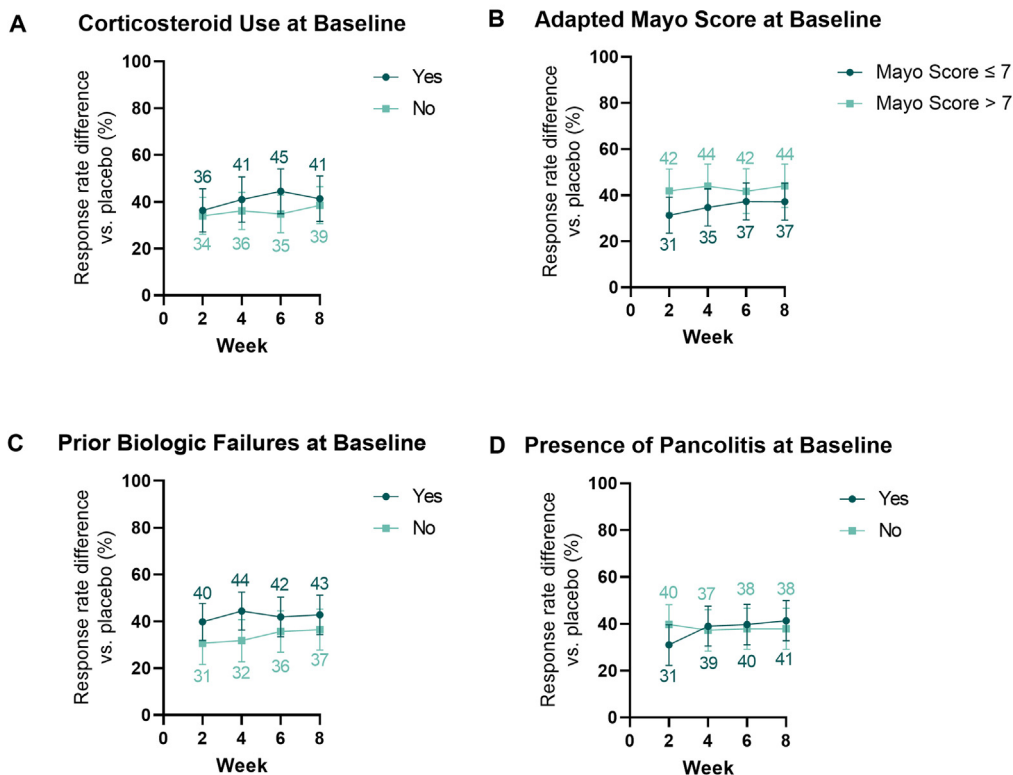
Subgroup Analysis for Clinical Remission PRO2

Supplementary Figure 3. Stratified analysis for clinical remission PRO2 score at week 2 through week 8 of induction phase. Shown are response rate differences for upadacitinib 45 mg QD versus placebo for analyses stratified by (A) baseline corticosteroid use (yes or no), (B) Adapted Mayo score (≤7 or >7), (C) prior biologic failure status (yes or no), and (D) presence of pancolitis (yes or no) for clinical remission. 95% CI for response rate difference was calculated on basis of normal approximation to binomial distribution. Calculations were based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation if there are no missing data due to COVID-19.


A   Corticosteroid Use at Baseline

B   Adapted Mayo Score at Baseline

C   Prior Biologic Failures at Baseline

D   Presence of Pancolitis at Baseline

Subgroup Analysis for Clinical Response per Partial Adapted Mayo score

A   Corticosteroid Use at Baseline

B   Adapted Mayo Score at Baseline

C   Prior Biologic Failures at Baseline

D   Presence of Pancolitis at Baseline

Supplementary Figure 4. Stratified analysis for clinical response per Partial Adapted Mayo score at weeks 2 through week 8 of induction phase. Shown are response rate differences for upadacitinib 45 mg QD versus placebo for analyses stratified by (A) baseline corticosteroid use (yes or no), (B) Adapted Mayo score (≤7 or >7), (C) prior biologic failure status (yes or no), and (D) presence of pancolitis (yes or no). 95% CI for response rate difference was calculated on basis of normal approximation to binomial distribution. Calculations were based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 or non-responder imputation if there are no missing data due to COVID-19.
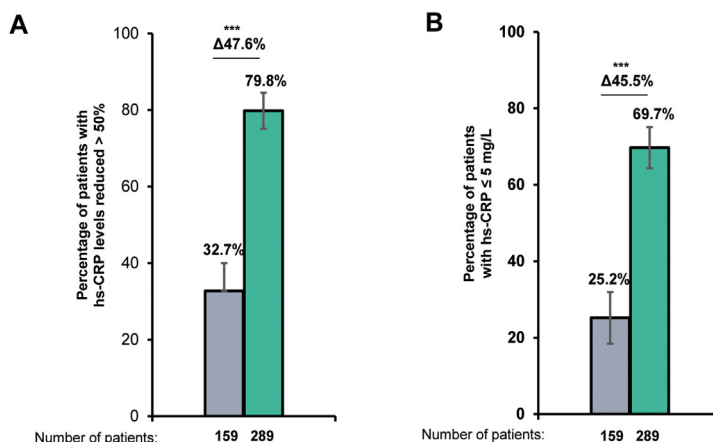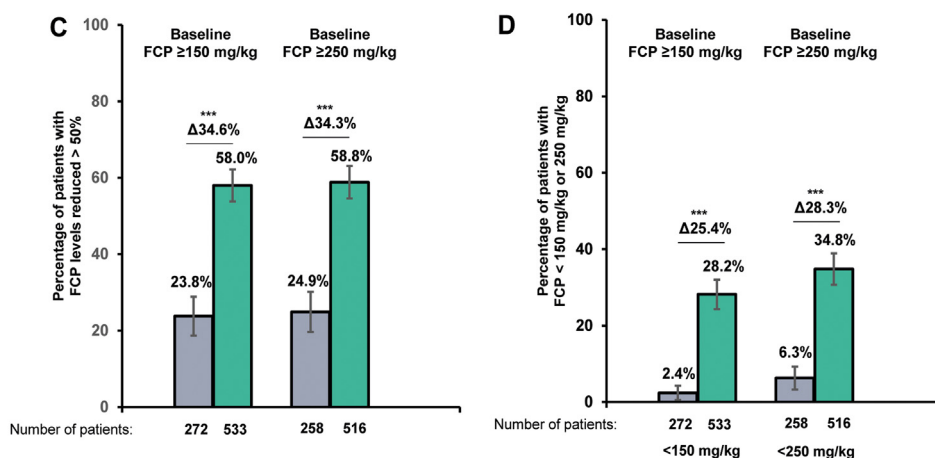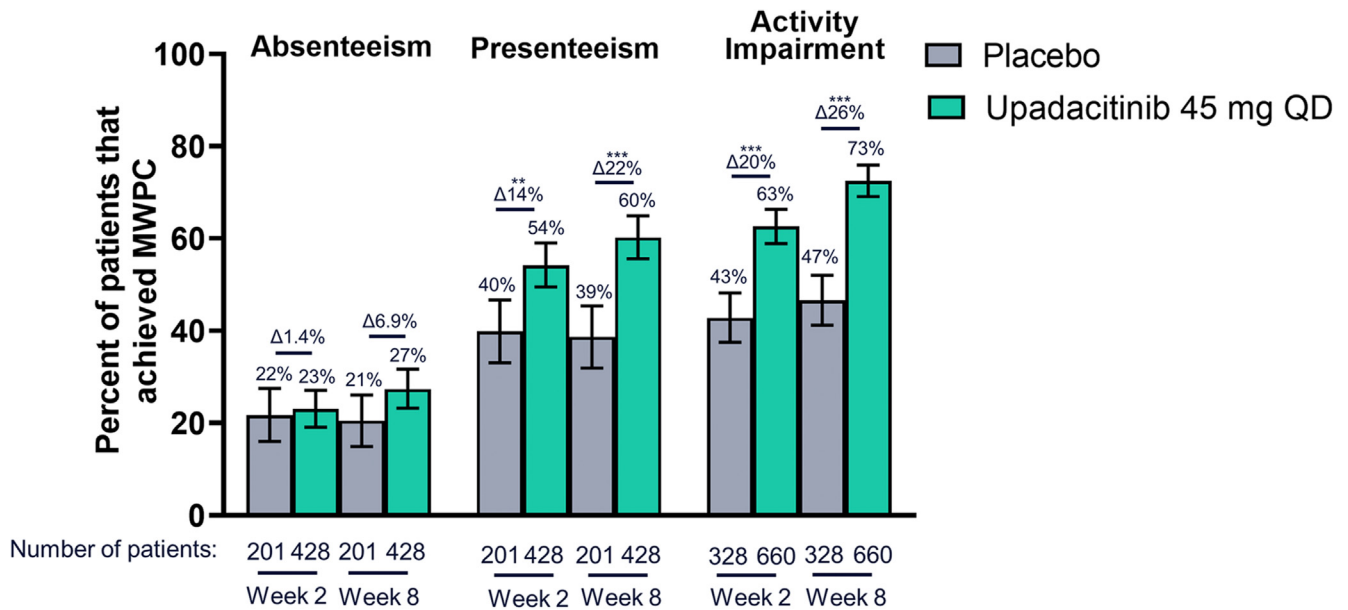
Supplementary Figure 5. Upadacitinib 45 mg QD promotes reduction in systemic and intestinal inflammatory markers, hs-CRP, and FCP at week 2 in patients with elevated values at baseline. Shown are percentages of patients with (*A*) hs-CRP reduced >50% among those with baseline hs-CRP ≥5 mg/L; (*B*) hs-CRP ≤5 mg/L among those with baseline hs-CRP ≥5 mg/L; (*C*) FCP reduced >50% among those with baseline FCP ≥150 mg/kg and ≥250 mg/kg; and (*D*) FCP levels <150 mg/kg among those with baseline FCP ≥150 mg/kg and FCP levels <250 mg/kg among those with baseline FCP ≥250 mg/kg. FCP was expressed in mg/kg of fecal matter. 95% CI for response rate is the synthetic result based on Student *t* distribution from the PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on normal approximation to binomial distribution if there are no missing data due to COVID-19. Error bars are ± 95% CI. ***P < .001 vs placebo. CI, confidence interval; FCP, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; QD, once daily.

Supplementary Figure 6. Upadacitinib 45 mg QD improves quality of life at weeks 2 and 8. Shown are percentages of patients who achieved MWPC for absenteeism, presenteeism, and activity impairment. 95% CI for response rate is the synthetic result based on Student t distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on normal approximation to binomial distribution if there are no missing data due to COVID-19. Error bars are $\pm$ 95% CI. **$P \leq$ .01; ***$P <$ .001. CI, confidence interval; MWPC, clinically meaningful within-patient change.

Supplementary Table 1. Components of Adapted Mayo, Partial Mayo, and Partial Adapted Mayo Subscores

Mayo subscore	Endoscopic subscore	Stool frequency subscore	Rectal bleeding subscore	Physician's global assessment subscore
Adapted Mayo score	✓	✓	✓	
Partial Mayo score		✓	✓	✓
Partial Adapted Mayo score		✓	✓	

Supplementary Table 2. Prediction Coefficients for Clinical Remission at Week 8

Variable	Coefficient estimate ± SE	P value
Day 3 SFS ≤1	0.16 ± 0.12	.190
Day 7 SFS ≤1	0.48 ± 0.12	<.001***
Day 7 RBS = 0	0.11 ± 0.10	.258
Day 3 No bowel urgency	–0.15 ± 0.13	.237
Day 7 No bowel urgency	0.43 ± 0.12	<.001***
Week 4 hs-CRP drop of 50%	0.16 ± 0.11	.138
Week 2 FCP <150 mg/kg	0.36 ± 0.11	.001**
Week 2 FCP 150 to 250 mg/kg	0.26 ± 0.17	.119
Week 2 FCP drop of 50%	0.23 ± 0.10	.027*

FCP, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; RBS, rectal bleeding score; SE, standard error; SFS, stool frequency score.
*P ≤ .05.
**P ≤ .01.
***P ≤ .001.

Supplementary Table 3. Prediction Coefficients for Clinical Response at Week 8

Variable	Coefficient estimate ± SE	P value
Day 3 SFS ≤1	0.14 ± 0.13	.288
Day 7 SFS ≤1	0.45 ± 0.12	<.001***
Day 7 RBS = 0	0.13 ± 0.09	.142
Day 3 No bowel urgency	–0.14 ± 0.13	.283
Day 7 No bowel urgency	0.20 ± 0.12	.104
Week 2 < hs-CRP <5 mg/L	0.19 ± 0.09	.044*
Week 2 hs-CRP drop of 50%	0.25 ± 0.10	.015*
Week 4 hs-CRP drop of 50%	0.31 ±0.09	.001*
Week 2 FCP <150 mg/kg	0.30 ±0.12	.013*
Week 2 FCP drop of 50%	0.21 ± 0.09	.016*

FCP, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; RBS, rectal bleeding score; SE, standard error; SFS, stool frequency score.
*P ≤ .05.
***P ≤ .001.