ORIGINAL ARTICLE

Upadacitinib Induction and Maintenance Therapy for Crohn's Disease

E.V. Loftus, Jr., J. Panés, A.P. Lacerda, L. Peyrin-Biroulet, G. D'Haens, R. Panaccione, W. Reinisch, E. Louis, M. Chen, H. Nakase, J. Begun, B.S. Boland, C. Phillips, M.-E.F. Mohamed, J. Liu, Z. Geng, T. Feng, E. Dubcenco, and J.-F. Colombel

ABSTRACT

BACKGROUND

Upadacitinib, an oral selective Janus kinase (JAK) inhibitor, is under investigation for the treatment of Crohn's disease.

METHODS

In two phase 3 induction trials (U-EXCEL and U-EXCEED), we randomly assigned patients with moderate-to-severe Crohn's disease to receive 45 mg of upadacitinib or placebo (2:1 ratio) once daily for 12 weeks. Patients who had a clinical response to upadacitinib induction therapy were randomly assigned in the U-ENDURE maintenance trial to receive 15 mg of upadacitinib, 30 mg of upadacitinib, or placebo (1:1:1 ratio) once daily for 52 weeks. The primary end points for induction (week 12) and maintenance (week 52) were clinical remission (defined as a Crohn's Disease Activity Index score of <150 [range, 0 to 600, with higher scores indicating more severe disease activity]) and endoscopic response (defined as a decrease in the Simple Endoscopic Score for Crohn's Disease [SES-CD; range, 0 to 56, with higher scores indicating more severe disease] of >50% from baseline of the induction trial [or for patients with an SES-CD of 4 at baseline, a decrease of ≥2 points from baseline]).

RESULTS

A total of 526 patients underwent randomization in U-EXCEL, 495 in U-EXCEED, and 502 in U-ENDURE. A significantly higher percentage of patients who received 45-mg upadacitinib than those who received placebo had clinical remission (in U-EXCEL, 49.5% vs. 29.1%; in U-EXCEED, 38.9% vs. 21.1%) and an endoscopic response (in U-EXCEL, 45.5% vs. 13.1%; in U-EXCEED, 34.6% vs. 3.5%) (P<0.001 for all comparisons). At week 52 in U-ENDURE, a higher percentage of patients had clinical remission with 15-mg upadacitinib (37.3%) or 30-mg upadacitinib (47.6%) than with placebo (15.1%), and a higher percentage had an endoscopic response with 15-mg upadacitinib (27.6%) or 30-mg upadacitinib (40.1%) than with placebo (7.3%) (P<0.001 for all comparisons). Herpes zoster infections occurred more frequently in the 45-mg and 30-mg upadacitinib groups than in the respective placebo groups, and hepatic disorders and neutropenia were more frequent in the 30-mg upadacitinib group than in the other maintenance groups. Gastrointestinal perforations developed in 4 patients who received 45-mg upadacitinib and in 1 patient each who received 30-mg or 15-mg upadacitinib.

CONCLUSIONS

Upadacitinib induction and maintenance treatment was superior to placebo in patients with moderate-to-severe Crohn's disease. (Funded by AbbVie; U-EXCEL, U-EXCEED, and U-ENDURE ClinicalTrials.gov numbers, NCT03345849, NCT03345836, and NCT03345823.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Colombel can be reached at jean-frederic.colombel@mssm.edu or at the Henry D. Janowitz Division of Gastroenterology, Department of Medicine, Icahn School of Medicine at Mount Sinai, 1470 Madison Ave., New York, NY 10029.

A list of the trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Loftus and Panés contributed equally to this article.

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Crohn's disease is a chronic and relapsing inflammatory bowel disease characterized by transmural inflammation within the gastrointestinal tract.[1] New treatment options with novel mechanisms of action that provide adequate symptomatic and endoscopic control for patients with moderate-to-severe disease are needed.[2]

Activation of signal transducers and activators of transcription (STATs) that are mediated by Janus kinases (JAKs) in T cells play an important pathogenic role in Crohn's disease.[3,4] Upadacitinib, an oral, reversible JAK inhibitor, has been approved for the treatment of ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, and ankylosing spondylitis.[5-11] In a phase 2, double-blind, randomized trial involving patients with Crohn's disease, the proportion of patients with clinical remission was higher with 6 mg of immediate-release upadacitinib twice daily than with placebo after 16 weeks of induction treatment, and the proportion with endoscopic remission was higher with 24 mg of immediate-release upadacitinib twice daily than with placebo, without apparent benefit of the other doses tested.[12] These doses provide plasma exposures to upadacitinib similar to those with 15 mg and 30 mg of extended-release upadacitinib once daily, respectively.[13] Here, we report the phase 3 results regarding the efficacy and safety of upadacitinib in patients with moderate-to-severe Crohn's disease.

Methods

Trial Design and Oversight

A phase 3 clinical program consisting of two induction trials, U-EXCEL (December 2017 through January 2022) and U-EXCEED (November 2017 through August 2021), and one maintenance trial, U-ENDURE (started March 2018), was conducted in 43 countries at 277 sites. U-EXCEL and U-EXCEED consisted of a 12-week double-blind, placebo-controlled induction treatment period (Fig. S1A in the Supplementary Appendix, available with the full text of this article at NEJM.org) and a 12-week extended treatment period for patients who did not have a clinical response at week 12 (Fig. S1B). A clinical response was defined as a decrease of at least 30% in the average daily frequency of very soft or liquid stools or in the abdominal pain score (range, 0 [no pain] to 3 [severe pain]), with neither worse than baseline. U-EXCEED had an additional 12-week open-label, active single-group induction period to allow the accrual of a sufficient number of patients who had a clinical response while receiving upadacitinib for entry into U-ENDURE. U-ENDURE was a 52-week double-blind, placebo-controlled maintenance trial for patients who had a clinical response to 12 weeks of upadacitinib induction treatment in U-EXCEL or U-EXCEED.

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These trials were conducted in accordance with the International Council for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. An independent ethics committee or institutional review board at each trial site approved the protocol, which is available at NEJM.org. All the patients provided written informed consent. The sponsor (AbbVie) designed the trials, and the investigators and sponsor jointly gathered data. The sponsor analyzed the data and provided medical writing support; the sponsor and authors interpreted the data. All the authors reviewed and approved the manuscript, had access to the data, and made the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trials to the protocol. The sponsor, investigators, and participating institutions agreed to maintain confidentiality of the data.

Patients

At baseline, eligible patients were 18 to 75 years of age and had had moderate-to-severe Crohn's disease for at least 3 months. Moderate-to-severe Crohn's disease was defined as an average of four or more instances of very soft or liquid stools daily or an abdominal pain score of 2 or more, plus a Simple Endoscopic Score for Crohn's Disease (SES-CD) of 6 or more (≥4 for patients with isolated ileal disease), excluding the component of the scale regarding the presence of narrowing.[14] Patients reported their daily frequency of very soft or liquid stools with the use of the Bristol Stool Chart; higher 7-day averages indicate more severe diarrhea. The SES-CD evaluates four components in five intestinal segments (each scored on a scale of 0 to 3); total scores range from 0 to 56, with higher scores indicating more severe disease.[14] Patients who were enrolled in U-EXCEL had a history of failure of one or more conventional or biologic therapies, whereas patients in U-EXCEED had a history of failure of one or more biologic thera-

pies. Failure of therapy was defined as an inadequate response to or unacceptable side effects from therapy. (Full eligibility criteria are listed in the Supplementary Appendix.)

Concomitant use of biologic therapies and immunosuppressants other than methotrexate or glucocorticoids was prohibited; a full list of prohibited medications and required washout criteria are provided in the Supplementary Appendix. At week 4, patients who were enrolled while receiving glucocorticoids began a protocol-specified taper (see the Supplementary Appendix); in U-ENDURE, patients receiving glucocorticoids who did not complete the glucocorticoid taper continued the taper according to the protocol.

RANDOMIZATION

For the induction trials, patients were randomly assigned through Web-based interactive response technology to receive upadacitinib at a dose of 45 mg or placebo (2:1 ratio) once daily for 12 weeks. Randomization was stratified according to baseline glucocorticoid use (yes or no), severity of endoscopic disease (SES-CD of <15 or ≥15), and the number of failed biologic therapies (0, 1, or >1 for U-EXCEL and 1 or >1 for U-EXCEED).

For U-ENDURE, patients were randomly assigned through interactive response technology to 15 mg of upadacitinib, 30 mg of upadacitinib, or placebo (1:1:1 ratio) once daily for 52 weeks. Randomization was stratified according to status with respect to previous failure of biologic therapy (yes or no), status with respect to clinical remission in terms of stool frequency and abdominal pain score (yes or no), and status with respect to an endoscopic response (yes or no) at the end of the induction treatment (see below for definitions of end points). Upadacitinib was administered in all the trials as extended-release tablets.

EFFICACY AND SAFETY EVALUATIONS

Clinical outcomes were assessed with the use of patient-reported measures (through an electronic diary), investigator assessments, and laboratory data, whereas central readers determined the SES-CD for endoscopic outcomes (see the Supplementary Appendix). The primary end points of clinical remission and endoscopic response were evaluated at week 12 of induction and week 52 of maintenance. Clinical remission was defined as a Crohn's Disease Activity Index (CDAI) score of less than 150 (CDAI clinical remission) in the analysis plan for the Food and Drug Administration, and an endoscopic response was defined as a decrease in the SES-CD of more than 50% from baseline (or for patients with a baseline SES-CD of 4, a decrease of ≥2 points from baseline). The CDAI consists of eight factors, and scores range from 0 to approximately 600, with higher scores indicating more severe disease activity.[15]

Key secondary end points for the induction or maintenance trials were clinical response in terms of the CDAI score (decrease of ≥100 points from baseline), clinical remission in terms of stool frequency or abdominal pain score (average daily frequency of very soft or liquid stools of ≤2.8 and average daily abdominal pain score of ≤1.0, with both not greater than baseline), glucocorticoid-free CDAI clinical remission (discontinuation of glucocorticoids for Crohn's disease and CDAI clinical remission at week 12 in patients receiving glucocorticoids at baseline), endoscopic remission (an SES-CD of ≤4, a decrease of ≥2 points from baseline, and no subscore >1 in any individual variable), change from baseline in quality of life (as assessed with the Inflammatory Bowel Disease Questionnaire [IBDQ] score), change from baseline in fatigue (as assessed with the Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-F] score), the occurrence of Crohn's disease–related hospitalization, and resolution of extraintestinal manifestations. Additional key secondary end points in U-ENDURE were deep remission (both CDAI clinical remission and endoscopic remission) and maintenance of CDAI clinical remission. The primary end points and key secondary end points according to European Medicines Agency (EMA) guidance are described in Section 3 in the Supplementary Appendix.

Safety was assessed according to adverse events reported through 12 weeks of induction and 52 weeks of maintenance among all the patients who underwent randomization and received at least one dose of upadacitinib or placebo. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 24.0. The severity of adverse events and laboratory abnormalities was graded with the use of the Common Terminology Criteria for Adverse Events, version 4.03. Cardiovascular, thromboembolic, and gastrointestinal events

were evaluated by independent adjudication committees.

STATISTICAL ANALYSIS

For U-EXCEL and U-EXCEED, the primary efficacy analyses were performed in the modified intention-to-treat population (denoted as ITT in the protocol and statistical analysis plan), including all the patients who underwent randomization and received at least one dose of upadacitinib or placebo, after all patients had completed all the scheduled trial activities. Primary efficacy analyses for U-ENDURE were performed after the first 502 randomly assigned patients who had received at least one dose of upadacitinib or placebo (modified intention-to-treat population) completed the week 52 visit. The sample-size and power calculations for each trial are provided in Section 4 in the Supplementary Appendix.

Categorical variables were analyzed with the use of the Cochran–Mantel–Haenszel model, with adjustment for randomization stratification factors except in the analysis of the occurrence of Crohn's disease–related hospitalization, for which we used normal approximation to binomial distribution in U-EXCEL and U-EXCEED and to Poisson distribution in U-ENDURE. Continuous end points were analyzed with the use of a mixed-effects repeated-measures model. The initial nonresponse imputation was revised in response to the coronavirus disease 2019 pandemic, with incorporation of multiple imputation to handle missing data owing to the pandemic. The overall type I error rate of the primary end points and all key secondary end points was multiplicity-controlled at the 0.05 level with the use of a hierarchical testing procedure and a Holm procedure in U-EXCEL and U-EXCEED and a graphical approach that included a prespecified α transfer path in U-ENDURE. Safety data were summarized descriptively; missing data were not imputed. All analyses were performed with the use of SAS software (version 9.4 or newer).

RESULTS

PATIENT CHARACTERISTICS

In U-EXCEL, 526 patients were randomly assigned to receive 45-mg upadacitinib (350 patients) or placebo (176 patients); in U-EXCEED, 495 patients underwent randomization (324 to 45-mg upadacitinib and 171 to placebo). In U-EXCEL, 54.6% of the patients had a history of failure of conventional therapy only and 45.4% had previous failure of biologic therapy. In U-ENDURE, 502 patients were randomly assigned to receive 15-mg upadacitinib (169 patients), 30-mg upadacitinib (168 patients), or placebo (165 patients). Of these patients, 75.1% had previous failure of biologic therapy.

The demographic and clinical characteristics of the patients at baseline were well-balanced across trial groups in all the trials (Table 1 and Table S1) and representative of the overall global population with moderate-to-severe Crohn's disease (Table S2). Details on screening, randomization, and follow-up for each trial are provided in Figure S2.

INDUCTION EFFICACY OUTCOMES

In U-EXCEL, a significantly higher percentage of patients who received 45-mg upadacitinib than those who received placebo met the primary end points at week 12 of CDAI clinical remission (49.5% vs. 29.1%, P<0.001) and endoscopic response (45.5% vs. 13.1%, P<0.001) (Table 2). In U-EXCEED, a significantly higher percentage of patients who received 45-mg upadacitinib than those who received placebo met the primary end points at week 12 of CDAI clinical remission (38.9% vs. 21.1%, P<0.001) and endoscopic response (34.6% vs. 3.5%, P<0.001).

The 45-mg dose of upadacitinib was also superior to placebo for 8 of the 10 multiplicity-controlled secondary end points in the hierarchical statistical testing for each trial. Upadacitinib provided rapid symptom relief, with significant differences in clinical response in terms of the CDAI score at week 2 and CDAI clinical remission at week 4 in both induction trials (P<0.001). A significantly higher percentage of patients who received 45-mg upadacitinib than those who received placebo discontinued glucocorticoids early and subsequently had CDAI clinical remission at 12 weeks (P<0.001). At week 12, patients who received upadacitinib were more likely to have endoscopic remission, in addition to significant improvements in fatigue (FACIT-F) and quality-of-life (IBDQ) assessments. Results were not significant for the occurrence of Crohn's disease–related hospitalization during the induction period and resolution of extraintestinal manifestations at week 12.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	U-EXCEL Induction Trial (12 wk)		U-EXCEED Induction Trial (12 wk)		U-ENDURE Maintenance Trial (52 wk)		
	Placebo (N = 176)	Upadacitinib, 45 mg (N = 350)	Placebo (N = 171)	Upadacitinib, 45 mg (N = 324)	Placebo (N = 165)	Upadacitinib, 15 mg (N = 169)	Upadacitinib, 30 mg (N = 168)
Male sex — no. (%)	94 (53.4)	189 (54.0)	96 (56.1)	169 (52.2)	88 (53.3)	102 (60.4)	93 (55.4)
Age — yr	39.3±13.6	39.7±13.7	37.5±12.1	38.4±13.7	38.1±13.0	38.1±13.5	37.0±13.3
Body-mass index†	25.6±7.0	24.5±6.0	23.9±6.2	24.2±6.0	24.6±6.6	24.1±6.0	24.2±6.6
Median duration of disease (range) — yr	5.7 (0.3–46.3)	6.7 (0.1–52.1)	9.8 (0.6–46.1)	9.3 (0.5–55.2)	7.6 (0.3–48.7)	7.9 (0.3–40.1)	7.2 (0.3–44.9)
Location of disease — no. (%)							
Ileal only	27 (15.3)	58 (16.6)	23 (13.5)	48 (14.8)	24 (14.5)	22 (13.0)	20 (11.9)
Colonic only	57 (32.4)	121 (34.6)	68 (39.8)	112 (34.6)	67 (40.6)	62 (36.7)	70 (41.7)
Ileal–colonic	92 (52.3)	171 (48.9)	80 (46.8)	164 (50.6)	74 (44.8)	85 (50.3)	78 (46.4)
CDAI score‡							
No. of patients evaluated	176	349	171	322	164	168	168
Mean score	293.9±85.4	292.4±81.3	308.1±84.3	306.6±89.4	308.4±82.3	300.8±90.8	312.1±75.4
Daily abdominal pain score§							
No. of patients evaluated	176	350	171	323	165	168	168
Mean score	1.9±0.7	1.9±0.7	1.8±0.7	1.9±0.7	1.9±0.7	1.8±0.7	1.9±0.6
Average daily frequency of very soft or liquid stools¶							
No. of patients evaluated	176	350	171	323	165	168	168
Mean frequency	5.1±2.8	5.2±2.6	6.1±3.3	5.7±3.4	5.6±2.8	5.4±3.3	5.5±2.8
SES-CD‖	13.6±7.0	13.7±7.3	14.9±7.8	15.2±7.8	14.8±7.7	15.8±7.6	15.5±8.1
High-sensitivity C-reactive protein**							
No. of patients evaluated	176	341	163	319	162	164	164
Median (range) — mg/liter	7.0 (0.2–113.0)	8.2 (0.2–120.0)	9.5 (0.4–126.0)	10.5 (0.2–144.0)	8.9 (0.2–96.7)	10.7 (0.2–110.0)	9.3 (0.2–124.0)

Fecal calprotectin††							
No. of patients evaluated	161	319	159	298	156	151	148
Median (range) — μg/g	949.0 (30–24,234)	904.0 (30–28,800)	1115.0 (30–19,104)	1041.0 (30–28,800)	1102.5 (30–17,033)	1658.0 (30–28,800)	1221.0 (30–28,800)
Concomitant Crohn's disease medications — no. (%)							
Immunosuppressants	3 (1.7)	13 (3.7)	13 (7.6)	24 (7.4)	11 (6.7)	5 (3.0)	9 (5.4)
Aminosalicylates	50 (28.4)	81 (23.1)	29 (17.0)	47 (14.5)	33 (20.0)	36 (21.3)	26 (15.5)
Glucocorticoids	64 (36.4)	126 (36.0)	60 (35.1)	108 (33.3)	61 (37.0)	63 (37.3)	63 (37.5)
Previous failure of biologic therapy — no. (%)‡‡							
Yes	78 (44.3)	161 (46.0)	—	—	126 (76.4)	124 (73.4)	127 (75.6)
No	98 (55.7)	189 (54.0)	—	—	39 (23.6)	45 (26.6)	41 (24.4)
No. of previous failures of biologic therapy — no./total no. (%)‡‡							
1	28/78 (35.9)	58/161 (36.0)	68/171 (39.8)	126/324 (38.9)	52/126 (41.3)	52/124 (41.9)	43/127 (33.9)
2	24/78 (30.8)	52/161 (32.3)	55/171 (32.2)	92/324 (28.4)	32/126 (25.4)	31/124 (25.0)	35/127 (27.6)
≥3	26/78 (33.3)	51/161 (31.7)	48/171 (28.1)	106/324 (32.7)	42/126 (33.3)	41/124 (33.1)	49/127 (38.6)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The Crohn's Disease Activity Index (CDAI) consists of eight factors, with each factor adjusted with a weighting factor. CDAI scores range from 0 to approximately 600, with higher scores indicating more severe disease activity.[15]
§ Patients reported their abdominal pain level on a scale from 0 (no pain) to 3 (severe pain); an average score was calculated on the basis of the scores from the 7 days before baseline.
¶ Shown is the average number of daily events of Type 6 (very soft) or Type 7 (liquid) stools according to the Bristol Stool Chart over the 7 days before baseline; a higher stool frequency reflects more severe diarrhea.
‖ For the Simple Endoscopic Score for Crohn's Disease (SES-CD), five intestinal segments (terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum) were evaluated for four endoscopic variables (presence of ulcers, ulcerated surface, affected surface, and presence of narrowing), each scored on a scale of 0 to 3; total scores range from 0 to 56, with higher scores indicating more severe disease.
** The normal range for high-sensitivity C-reactive protein is 0 to 10 mg per liter.
†† The normal value for fecal calprotectin is less than 50 μg per gram.
‡‡ Failure of therapy was defined as an inadequate response to or unacceptable side effects from therapy.

Table 2. Primary and Key Secondary End Points under Multiplicity Control for Upadacitinib as Induction Therapy, According to FDA Requirements.*

End Point	U-EXCEL Induction Trial (12 wk)			U-EXCEED Induction Trial (12 wk)		
	Placebo (N=176)	Upadacitinib, 45 mg (N=350)	Adjusted Difference; P Value†‡	Placebo (N=171)	Upadacitinib, 45 mg (N=324)	Adjusted Difference; P Value†‡
Primary end points — % (95% CI)						
CDAI clinical remission‡	29.1 (22.4 to 35.8)	49.5 (44.2 to 54.8)	20.8 (12.7 to 28.8); P<0.001	21.1 (14.9 to 27.2)	38.9 (33.6 to 44.2)	17.9 (10.0 to 25.8); P<0.001
Endoscopic response§	13.1 (8.1 to 18.0)	45.5 (40.3 to 50.8)	33.0 (26.2 to 39.9); P<0.001	3.5 (0.8 to 6.3)	34.6 (29.4 to 39.8)	31.2 (25.5 to 37.0); P<0.001
Ranked secondary end points						
SF–APS clinical remission at wk 12 — % (95% CI)¶	22.2 (16.0 to 28.3)	50.7 (45.5 to 56.0)	28.7 (20.9 to 36.4); P<0.001	14.0 (8.8 to 19.2)	39.8 (34.5 to 45.1)	25.9 (18.7 to 33.1); P<0.001
Endoscopic remission at wk 12 — % (95% CI)‖	7.4 (3.5 to 11.3)	28.9 (24.2 to 33.7)	21.8 (15.8 to 27.8); P<0.001	2.3 (0.1 to 4.6)	19.1 (14.9 to 23.4)	16.8 (12.0 to 21.6); P<0.001
Glucocorticoid-free CDAI clinical remission at wk 12**						
No. of patients evaluated	64	126	—	60	108	—
Percent (95% CI)	15.7 (6.8 to 24.7)	42.9 (34.2 to 51.5)	27.7 (15.7 to 39.8); P<0.001	11.7 (3.5 to 19.8)	34.3 (25.3 to 43.2)	22.5 (11.1 to 34.0); P<0.001
Change from baseline to wk 12 in FACIT-F score††						
No. of patients evaluated	133	304	—	129	278	—
Least-squares mean change (95% CI)	5.0 (3.2 to 6.8)	11.3 (10.0 to 12.5)	6.3 (4.2 to 8.3); P<0.001	3.9 (2.0 to 5.8)	11.4 (10.1 to 12.8)	7.5 (5.2 to 9.8); P<0.001
Change from baseline to wk 12 in IBDQ total score‡‡						
No. of patients evaluated	134	304	—	130	280	—
Least-squares mean change (95% CI)	24.4 (19.0 to 29.8)	46.3 (42.5 to 50.0)	21.8 (15.6 to 28.1); P<0.001	21.6 (15.7 to 27.6)	46.0 (41.7 to 50.2)	24.3 (17.2 to 31.5); P<0.001
Clinical response — % (95% CI)§§						
At wk 2	20.4 (14.4 to 26.5)	32.2 (27.3 to 37.1)	11.7 (4.2 to 19.2); P=0.002	12.4 (7.4 to 17.4)	33.2 (28.0 to 38.3)	20.7 (13.7 to 27.8); P<0.001
At wk 12	37.3 (30.1 to 44.5)	56.6 (51.4 to 61.8)	19.8 (11.3 to 28.4); P<0.001	27.5 (20.8 to 34.2)	50.5 (45.1 to 56.0)	22.8 (14.4 to 31.2); P<0.001
CDAI clinical remission at wk 4 — % (95% CI)‡	26.7 (20.2 to 33.3)	37.1 (32.1 to 42.2)	10.8 (2.9 to 18.6); P=0.007	17.7 (11.9 to 23.4)	29.6 (24.7 to 34.6)	12.1 (4.7 to 19.5); P=0.001

Occurrence of hospitalization due to Crohn's disease — % (95% CI)¶¶	5.1 (1.9 to 8.4)	3.7 (1.7 to 5.7)	−1.4 (−5.2 to 2.4); NS	8.8 (4.5 to 13.0)	6.2 (3.6 to 8.8)	−2.6 (−7.6 to 2.4); NS
Resolution of EIMs at wk 12						
No. of patients evaluated	78	151	—	60	131	—
Percent (95% CI)	20.9 (11.8 to 30.1)	28.5 (21.3 to 35.7)	9.0 (−1.9 to 19.9); NS	21.7 (11.2 to 32.1)	32.8 (24.8 to 40.9)	11.5 (−1.5 to 24.4); NS

* Results for categorical end points (except the occurrence of hospitalization due to Crohn's disease) are based on nonresponse imputation incorporating multiple imputation to handle missing data owing to the coronavirus disease 2019 (Covid-19) pandemic. Results for continuous end points are based on a mixed-effects repeated-measures model. CI denotes confidence interval, EIMs extraintestinal manifestations, FDA Food and Drug Administration, and NS not significant.

† Point estimates and 95% confidence intervals for between-group differences (45-mg upadacitinib group minus placebo group) are based on the Cochran–Mantel–Haenszel model for categorical end points and a mixed-effect repeated-measures model for continuous end points. Differences in categorical end points are shown in percentage points.

‡ CDAI clinical remission was defined as a CDAI score of less than 150.

§ An endoscopic response was defined as a decrease in the SES-CD of more than 50% from baseline of the induction trial (or for patients with an SES-CD of 4 at baseline, a decrease of ≥2 points from baseline).

¶ Clinical remission in terms of stool frequency and abdominal pain score (SF–APS clinical remission) was defined as an average daily frequency of very soft or liquid stools of 2.8 or less and an average daily abdominal pain score of 1.0 or less, with both not greater than baseline.

‖ Endoscopic remission was defined as an SES-CD of 4 or less, a decrease of at least 2 points from baseline, and no subscore of more than 1 in any individual variable.

** Glucocorticoid-free CDAI clinical remission was defined as discontinuation of glucocorticoids for Crohn's disease and CDAI clinical remission at week 12 in patients receiving glucocorticoids at baseline.

†† The responses to the 13 items on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire are each measured on a 4-point scale. Total scores range from 0 to 52, with higher scores indicating less fatigue.

‡‡ The Inflammatory Bowel Disease Questionnaire (IBDQ) scale contains four component subscales: bowel symptoms, systemic symptoms, emotional function, and social function. Total scores range from 32 to 224, with higher scores indicating better health-related quality of life.

§§ A clinical response was defined as a decrease of at least 100 points in the CDAI score from baseline.

¶¶ For the occurrence of Crohn's disease–related hospitalization, normal approximation to binomial distribution was used.

MAINTENANCE EFFICACY OUTCOMES

In U-ENDURE, with respect to CDAI clinical remission at week 52, maintenance treatment with 15-mg upadacitinib (37.3%) or 30-mg upadacitinib (47.6%) was superior to placebo (15.1%) (P<0.001 for both comparisons) (Table 3). An endoscopic response at week 52 was significantly more likely among patients who received 15-mg upadacitinib (27.6%) or 30-mg upadacitinib (40.1%) than among those who received placebo (7.3%) (P<0.001 for both comparisons).

The 15-mg dose of upadacitinib was superior to placebo for 8 of the 11 multiplicity-controlled secondary end points, and the 30-mg dose was superior to placebo for 10 of the 11 secondary end points. A significantly higher percentage of patients who received 15-mg or 30-mg upadacitinib than those who received placebo maintained CDAI clinical remission at week 0 through week 52. A significantly higher percentage of patients who received 15-mg or 30-mg upadacitinib than those who received placebo had glucocorticoid-free CDAI clinical remission at week 52, both among all the patients and among those receiving glucocorticoids at baseline. The 15-mg and 30-mg doses of upadacitinib were superior to placebo with respect to endoscopic remission and deep remission at week 52. Quality of life (IBDQ) at week 52 was higher with both maintenance upadacitinib doses than with placebo. Patients who received 30-mg upadacitinib (but not those who received 15-mg upadacitinib) had less fatigue (FACIT-F) and were more likely to have resolution of extraintestinal manifestations at week 52 than those who received placebo. The occurrence of Crohn's disease–related hospitalization during U-ENDURE did not differ significantly between either upadacitinib dose and placebo.

OTHER EFFICACY OUTCOMES

In U-EXCEL, U-EXCEED, and U-ENDURE, differences between the upadacitinib doses and placebo were significant for the EMA-defined primary end points and most multiplicity-controlled end points (Tables S3 and S4) and were generally consistent across all subgroups analyzed (Fig. S3). Incidences of clinical response and remission were higher with upadacitinib than with placebo through week 12 in both induction trials (Figs. S4 through S7). Among patients with endoscopic ulcers at baseline, the percentage

Table 3. Primary and Secondary End Points under Multiplicity Control for Upadacitinib as Maintenance Therapy, According to FDA Requirements.*

End Point, Wk 52	Placebo (N=165)	Upadacitinib, 15 mg (N=169)	Adjusted Difference vs. Placebo; P Value†‡	Upadacitinib, 30 mg (N=168)	Adjusted Difference vs. Placebo; P Value†‡
Primary end points — % (95% CI)					
CDAI clinical remission‡	15.1 (9.6 to 20.6)	37.3 (30.0 to 44.6)	23.7 (15.2 to 32.1); P<0.001	47.6 (40.1 to 55.2)	32.8 (23.9 to 41.6); P<0.001
Endoscopic response§	7.3 (3.3 to 11.2)	27.6 (20.8 to 34.4)	21.0 (13.6 to 28.4); P<0.001	40.1 (32.7 to 47.6)	33.7 (26.0 to 41.3); P<0.001
Ranked secondary end points¶					
SF–APS clinical remission — % (95% CI)‖	14.4 (9.0 to 19.8)	35.5 (28.3 to 42.7)	21.9 (13.7 to 30.0); P<0.001	46.4 (38.9 to 54.0)	31.8 (23.2 to 40.3); P<0.001
Clinical response — % (95% CI)**	15.2 (9.7 to 20.6)	41.4 (34.0 to 48.8)	27.1 (18.3 to 35.8); P<0.001	51.2 (43.6 to 58.7)	36.4 (27.5 to 45.2); P<0.001
Endoscopic remission — % (95% CI)††	5.5 (2.0 to 9.0)	19.1 (13.1 to 25.0)	14.4 (7.7 to 21.0); P<0.001	28.6 (21.8 to 35.5)	23.6 (16.1 to 31.0); P<0.001
Glucocorticoid-free CDAI clinical remission among all patients — % (95% CI)‡‡	14.5 (9.1 to 19.9)	36.7 (29.4 to 44.0)	23.8 (15.5 to 32.1); P<0.001	46.4 (38.9 to 54.0)	32.2 (23.4 to 40.9); P<0.001
Deep remission — % (95% CI)§§	3.7 (0.8 to 6.5)	14.8 (9.5 to 20.2)	12.2 (6.3 to 18.1); P<0.001	23.2 (16.8 to 29.6)	19.8 (13.0 to 26.6); P<0.001
Maintenance of CDAI clinical remission¶¶					
No. of patients evaluated	94	101	—	92	—
Percent (95% CI)	21.2 (12.9 to 29.5)	49.5 (39.8 to 59.3)	31.6 (19.6 to 43.6); P<0.001	65.2 (55.5 to 74.9)	43.4 (31.4 to 55.5); P<0.001
Glucocorticoid-free CDAI clinical remission among patients receiving glucocorticoids at baseline‖‖					
No. of patients evaluated	61	63	—	63	—
Percent (95% CI)	4.9 (0.0 to 10.3)	39.7 (27.6 to 51.8)	35.4 (23.3 to 47.5); P<0.001	39.7 (27.6 to 51.8)	32.3 (20.1 to 44.5); P<0.001
Change from induction baseline in IBDQ total score					
No. of patients evaluated	41	78	—	94	—
Least-squares mean change (95% CI)	46.4 (38.5 to 54.3)	59.3 (52.9 to 65.6)	12.9 (4.3 to 21.4); P=0.003	64.5 (58.3 to 70.7)	18.1 (9.8 to 26.4); P<0.001

Change from induction baseline in FACIT-F score					
No. of patients evaluated	40	78	—	94	—
Least-squares mean change (95% CI)	12.0 (9.4 to 14.7)	14.3 (12.2 to 16.4)	2.3 (–0.6 to 5.2); NS	16.1 (14.1 to 18.1)	4.1 (1.3 to 6.9); P=0.004
Occurrence of hospitalization due to Crohn's disease — % (95% CI)	12.0 (4.6 to 19.4)	11.2 (5.1 to 17.3)	–0.8 (–10.4 to 8.8); NS	7.8 (3.0 to 12.7)	–4.2 (–13.1 to 4.7); NS
Resolution of EIMs at wk 52 in patients with EIMs at baseline					
No. of patients evaluated	66	61	—	73	—
Percent (95% CI)	15.2 (6.5 to 23.8)	24.6 (13.8 to 35.4)	9.6 (–3.4 to 22.6); NS	35.6 (24.6 to 46.6)	22.0 (9.3 to 34.8); P<0.001

* Results for categorical end points (except the occurrence of hospitalization due to Crohn's disease) are based on nonresponse imputation incorporating multiple imputation to handle missing data owing to the Covid-19 pandemic. Results for continuous end points are based on a mixed-effects repeated-measures model.

† Point estimates and 95% confidence intervals for between-group difference (15-mg or 30-mg upadacitinib group minus placebo group) are based on the Cochran–Mantel–Haenszel model for categorical end points and a mixed-effects repeated-measures model for continuous end points. Differences in categorical end points are shown in percentage points.

‡ CDAI clinical remission was defined as a CDAI score of less than 150.

§ An endoscopic response was defined as a decrease in the SES-CD of more than 50% from baseline of the induction trial (or for patients with an SES-CD of 4 at baseline of the induction trial, a decrease of at least 2 points from baseline of the induction trial).

¶ Significance-ranked secondary end points were determined with the use of the hierarchical testing and Holm procedure outlined in the graphical plan provided in Section 4 in the Supplementary Appendix.

‖ SF–APS clinical remission was defined as an average daily frequency of very soft or liquid stools of 2.8 or less and an average daily abdominal pain score of 1.0 or less, with both not greater than baseline.

** A clinical response was defined as a decrease of at least 100 points in the CDAI score from baseline.

†† Endoscopic remission was defined as an SES-CD of 4 or less, a decrease of at least 2 points from baseline, and no subscore of more than 1 in any individual variable.

‡‡ This end point was defined as no glucocorticoid use for at least 90 days before the trial visit and CDAI clinical remission at week 52 among all the patients.

§§ Deep remission was defined as both CDAI clinical remission and endoscopic remission.

¶¶ This end point was defined as CDAI clinical remission at week 52 of maintenance in patients who were in CDAI clinical remission at week 0 of maintenance (also end of induction).

‖‖ This end point was defined as having CDAI clinical remission at week 52 and remaining glucocorticoid-free for at least 90 days, among patients receiving glucocorticoids at baseline.

Table 4. Overview of Adverse Events in the Induction Trials.*

Adverse Event	U-EXCEL Induction Trial (12 wk)		U-EXCEED Induction Trial (12 wk)	
	Placebo (N=176)	Upadacitinib, 45 mg (N=350)	Placebo (N=171)	Upadacitinib, 45 mg (N=324)
	number of patients (percent)			
Any adverse event	103 (58.5)	219 (62.6)	112 (65.5)	221 (68.2)
Severe adverse event	15 (8.5)	31 (8.9)	20 (11.7)	28 (8.6)
Serious adverse event	12 (6.8)	24 (6.9)	17 (9.9)	30 (9.3)
Adverse event possibly related to trial agent	38 (21.6)	109 (31.1)	39 (22.8)	112 (34.6)
Adverse event leading to discontinuation of trial agent	10 (5.7)	15 (4.3)	7 (4.1)	18 (5.6)
Adverse event related to Covid-19	1 (0.6)	3 (0.9)	0	2 (0.6)
Death from any cause†	0	0	0	1 (0.3)
Adverse events of special interest				
Serious infection	3 (1.7)	4 (1.1)	3 (1.8)	9 (2.8)
Opportunistic infection, excluding tuberculosis and herpes zoster infection‡	0	0	0	2 (0.6)
Herpes zoster infection	0	10 (2.9)	0	5 (1.5)
Tuberculosis	0	0	0	0
Anemia§	8 (4.5)	28 (8.0)	11 (6.4)	22 (6.8)
Lymphopenia	6 (3.4)	5 (1.4)	2 (1.2)	6 (1.9)
Neutropenia	1 (0.6)	9 (2.6)	0	4 (1.2)
Creatine kinase elevation	0	12 (3.4)	4 (2.3)	9 (2.8)
Hepatic disorder	4 (2.3)	10 (2.9)	6 (3.5)	8 (2.5)
Renal disorder	0	0	0	2 (0.6)
Adjudicated cardiovascular events¶	1 (0.6)	0	0	0
Adjudicated thrombotic events¶	0	0	0	0
Adjudicated gastrointestinal perforation¶‖	0	0	0	1 (0.3)
Cancer of any type	0	0	0	0

* The safety population included all the patients who received at least one dose of upadacitinib or placebo during the 12-week double-blind induction period.
† There was one death due to infectious shock (45-mg upadacitinib group in U-EXCEED) that occurred 159 days after premature discontinuation from the trial.
‡ Opportunistic infections (excluding tuberculosis and herpes zoster infection) during U-EXCEED included cytomegalovirus infection in one patient and *Pneumocystis jirovecii* pneumonia in one patient (both in the 45-mg upadacitinib group).
§ Anemia (as an adverse event of special interest) was based on customized *Medical Dictionary for Regulatory Activities* (MedDRA) queries, which included other preferred terms in addition to the preferred term "anaemia."
¶ Cardiovascular, thromboembolic, and gastrointestinal events were evaluated by independent adjudication committees.
‖ Gastrointestinal perforations developed in an additional three patients who received 45-mg upadacitinib during the extended treatment period of U-EXCEED, as described in Table S7.

who had an ulcer-free endoscopy at week 12 or week 52 appeared higher with upadacitinib than with placebo (Fig. S8). The results also suggested that 45-mg upadacitinib reduced levels of high-sensitivity C-reactive protein (CRP) and fecal calprotectin as early as weeks 2 and 4, respectively, and the between-group differences were maintained through week 12 of the induction trials and week 52 of the maintenance trial (Fig. S9).

SAFETY

Overall

The incidences of adverse events that emerged or worsened during the treatment period, serious adverse events, and severe adverse events were

Table 5. Overview of Exposure-Adjusted Adverse Events in the Maintenance Trial.*

Adverse Event	Placebo (N=223)	Upadacitinib, 15 mg (N=221)	Upadacitinib, 30 mg (N=229)
	no. of events (events per 100 person-yr)†		
Any adverse event	502 (469.2)	518 (349.5)	539 (323.7)
Severe adverse event	38 (35.5)	37 (25.0)	31 (18.6)
Serious adverse event	40 (37.4)	37 (25.0)	35 (21.0)
Adverse event possibly related to trial agent	135 (126.2)	135 (91.1)	139 (83.5)
Adverse event leading to discontinuation of trial agent	8 (7.5)	19 (12.8)	14 (8.4)
Adverse event related to Covid-19	11 (10.3)	12 (8.1)	18 (10.8)
Death from any cause	0	0	0
Adverse events of special interest			
Serious infection	9 (8.4)	9 (6.1)	13 (7.8)
Opportunistic infection, excluding tuberculosis and herpes zoster infection‡	0	1 (0.7)	1 (0.6)
Herpes zoster infection	5 (4.7)	6 (4.0)	12 (7.2)
Tuberculosis	0	0	0
Anemia§	13 (12.2)	15 (10.1)	11 (6.6)
Lymphopenia	10 (9.3)	4 (2.7)	10 (6.0)
Neutropenia	1 (0.9)	3 (2.0)	5 (3.0)
Creatine kinase elevation	3 (2.8)	5 (3.4)	8 (4.8)
Hepatic disorder	3 (2.8)	11 (7.4)	17 (10.2)
Renal disorder	2 (1.9)	0	0
Adjudicated cardiovascular events¶	0	0	0
Adjudicated thrombotic events¶	0	0	1 (0.6)
Adjudicated gastrointestinal perforation¶	1 (0.9)	1 (0.7)	1 (0.6)
Cancer of any type	0	1 (0.7)	2 (1.2)
Excluding NMSC	0	1 (0.7)	2 (1.2)

* The safety population includes all the patients who received at least one dose of upadacitinib or placebo during the maintenance period. NMSC denotes nonmelanoma skin cancer.
† Shown are exposure-adjusted event rates. The total number of person-years for each group was as follows: 107.0 for the placebo group, 148.2 for the 15-mg upadacitinib group, and 166.5 for the 30-mg upadacitinib group.
‡ Opportunistic infections (excluding tuberculosis and herpes zoster infection) during U-ENDURE were reported in one patient who received 15-mg upadacitinib (*P. jirovecii* pneumonia) and one patient who received 30-mg upadacitinib (esophageal candidiasis).
§ Anemia (as an adverse event of special interest) was based on customized MedDRA queries, which included other preferred terms in addition to the preferred term "anaemia."
¶ Cardiovascular, thromboembolic, and gastrointestinal events were evaluated by independent adjudication committees.

similar across trial groups at 12 weeks of induction (Table 4). Incidences were also similar after 52 weeks of maintenance (Table 5).

Induction

Among patients who received 45-mg upadacitinib, the most common adverse events (≥5% of patients) were acne (6.9%) and anemia (6.3%) in U-EXCEL and nasopharyngitis (7.1%), headache (6.2%), worsening of Crohn's disease (5.9%), and upper respiratory tract infections (5.2%) in U-EXCEED (Table S5). Serious infections occurred in 1.1% of the patients who received upadacitinib in U-EXCEL and 2.8% of those who received the drug in U-EXCEED, as compared with 1.7% and 1.8% of those who received pla-

cebo in the respective trials, and the most common serious infections across trial groups were gastrointestinal, such as anal abscess. Opportunistic infections were reported in 0.6% of the upadacitinib group in U-EXCEED (*Pneumocystis jirovecii* pneumonia and cytomegalovirus infection in one patient each); no opportunistic infections were reported in the other induction groups.

Herpes zoster infection was reported in the 45-mg upadacitinib groups only (2.9% in U-EXCEL and 1.5% in U-EXCEED). Of the 15 cases of herpes zoster infection, 8 (53%) involved one dermatome, 4 (27%) involved two dermatomes, and 3 (20%) involved three or more dermatomes; all were cutaneous and nonserious. An adjudicated gastrointestinal perforation was reported in 1 patient (0.3%) who received 45-mg upadacitinib in U-EXCEED. No active tuberculosis cases, cancers, adjudicated major cardiovascular or thromboembolic events, or Hy's law cases were reported in the 45-mg upadacitinib groups. Neutropenia and creatine kinase elevation were observed more frequently with 45-mg upadacitinib than with placebo.

In U-EXCEED, one death due to infectious shock occurred 159 days after premature discontinuation from the trial in a patient who had received 45-mg upadacitinib for 5 days. Safety results for the extended treatment periods (U-EXCEL and U-EXCEED) and open-label period (U-EXCEED) are provided in Table S7.

Maintenance

Exacerbation of Crohn's disease (29.7 events per 100 person-years for 15-mg upadacitinib, 12.0 events per 100 person-years for 30-mg upadacitinib, and 58.0 events per 100 person-years for placebo) was the most frequently reported adverse event during U-ENDURE (Table S8). Similar rates of serious infections were reported across trial groups (6.1 events per 100 person-years for 15-mg upadacitinib, 7.8 events per 100 person-years for 30-mg upadacitinib, and 8.4 per 100 person-years for placebo). One case of opportunistic infection was reported in the 15-mg upadacitinib group (*P. jirovecii* pneumonia), and one case was reported in the 30-mg group (esophageal candidiasis).

Rates of herpes zoster infection were higher in the 30-mg upadacitinib group (7.2 events per 100 person-years) than in the 15-mg group (4.0 events per 100 person-years). Herpes zoster infections were cutaneous and involved one or two dermatomes only. Gastrointestinal perforation was reported in one patient in each group (0.6 to 0.9 events per 100 person-years across groups). One case of hepatic vein thrombosis concurrent with exacerbation of Crohn's disease was reported in a patient receiving 30-mg upadacitinib. One case of metastatic ovarian cancer in the 15-mg upadacitinib group and two cases of cancer (colon cancer and invasive lobular breast cancer) in the 30-mg upadacitinib group were diagnosed on trial days 159, 8, and 183 after the first dose of maintenance treatment, respectively. No deaths, cases of active tuberculosis, adjudicated major cardiovascular events, or Hy's law cases were reported. Hepatic disorders, neutropenia, and creatine kinase elevations were reported more frequently in the 30-mg group than in the other maintenance groups. Further safety results are provided in Table S9.

DISCUSSION

In this phase 3 program involving patients with moderate-to-severe Crohn's disease, upadacitinib induction and maintenance therapy was superior to placebo with respect to the primary end points of clinical remission and endoscopic response as well as the majority of secondary end points, including clinical, endoscopic, and quality-of-life outcomes. Significant benefits were not observed for Crohn's disease–related hospitalizations across all trials or for resolution of extraintestinal manifestations in the induction trials.

U-EXCEL and U-EXCEED involved an early mandatory glucocorticoid taper, a critical design feature given the need to reduce long-term glucocorticoid use owing to the undesirable safety profile and inability to reduce the risk of disease relapse.[16,17] Indeed, these results showed that a higher percentage of patients had glucocorticoid-free remission with upadacitinib induction treatment than with placebo.

These phase 3 results with upadacitinib align with the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) clinical practice recommendations, which include short-term and intermediate-term treatment goals of early symptomatic response, remission, and normalization of high-sensitivity CRP and fecal

calprotectin levels, along with long-term goals of endoscopic healing and quality-of-life improvements.[18] Upadacitinib had a rapid onset of action, with a higher percentage of patients having a clinical response at week 2 and clinical remission at week 4 than with placebo. Maintenance of clinical remission at week 52 was more frequent in the upadacitinib groups than in the placebo group, and benefits with respect to endoscopic remission and quality of life were observed in both the induction and maintenance periods. Benefits were also observed for two important, frequent, and debilitating symptoms in patients with Crohn's disease: fatigue (with the 45-mg induction dose and 30-mg maintenance dose) and extraintestinal manifestations (with the 30-mg maintenance dose).[19,20] A dose–response relationship was suggested in U-ENDURE between the upadacitinib maintenance doses across most end points.

Adverse events that are associated with JAK inhibition, including serious infections, opportunistic infections, anemia, neutropenia, and creatine kinase elevation, were observed more frequently in patients who received upadacitinib than in those who received placebo. In U-ENDURE, a dose-dependent effect with upadacitinib therapy was observed for herpes zoster infection, hepatic disorder, neutropenia, and creatine kinase elevation. Four cases of gastrointestinal perforation were reported with 45-mg upadacitinib (one during the placebo-controlled period and three in patients who had received placebo during induction followed by 45-mg upadacitinib during the extended treatment period); one case was reported in each of the maintenance groups. On review, the perforations occurred when the patients had active Crohn's disease, either with flare, deep ulcers in the areas of perforation or with complications (stricture, obstruction, or fistula). It is unclear whether the gastrointestinal perforations observed in these trials reflect a safety risk with upadacitinib or the inherent high risk of disease progression and complications among patients with Crohn's disease, particularly in those with more severe conditions. Patients with Crohn's disease who receive immunosuppressive therapy have a modestly increased risk of cancer.[21] On the basis of the small number of cancers observed in U-ENDURE, limited exposure, timing of occurrence, and lack of pattern of the cancer types, an increased risk of cancer with upadacitinib cannot be concluded.

The main limitation of the trials is an inability to identify rare, low-incidence, or long-latency adverse events, including in high-risk subpopulations. The ongoing long-term extension trial of U-ENDURE is evaluating these patients for up to 5 years.

In these three trials, upadacitinib was effective in achieving and maintaining clinical remission and endoscopic response in patients with moderate-to-severe Crohn's disease, regardless of previous failure of biologic therapy.

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APPENDIX

The authors' full names and academic degrees are as follows: Edward V. Loftus, Jr., M.D., Julian Panés, M.D., Ana P. Lacerda, M.D., Laurent Peyrin-Biroulet, M.D., Ph.D., Geert D'Haens, M.D., Remo Panaccione, M.D., Walter Reinisch, M.D., Edouard Louis, M.D., Ph.D., Minhu Chen, M.D., Hiroshi Nakase, M.D., Jakob Begun, M.D., Brigid S. Boland, M.D., Charles Phillips, M.D., Mohamed-Eslam F. Mohamed, Ph.D., Jianzhong Liu, M.D., Ziqian Geng, Ph.D., Tian Feng, Ph.D., Elena Dubcenco, M.D., and Jean-Frederic Colombel, M.D.

The authors' affiliations are as follows: the Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, MN (E.V.L.); the Inflammatory Bowel Diseases Unit, Hospital Clinic Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Barcelona (J.P.); AbbVie, North Chicago, IL (A.P.L., C.P., M-E.F.M., J.L., Z.G., T.F., E.D.); the Department of Gastroenterology and INSERM Unité 1256, Nutrition–Genetics and Environmental Risk Exposure, Faculty of Medicine, University Hospital of Nancy, Lorraine University, Vandoeuvre, France (L.P.-B.); the Department of Gastroenterology, Amsterdam University Medical Centers, Amsterdam (G.D.); the Inflammatory Bowel Disease Unit, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, AB, Canada (R.P.); the Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna (W.R.); the Department of Hepato-Gastroenterology and Digestive Oncology, University Hospital Centre Hospitalier Universitaire of Liège, Liège, Belgium (E.L.); the Division of Gastroenterology, First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China (M.C.); the Department of Gastroenterology and Hepatology, Sapporo Medical University School of Medicine, Sapporo, Japan (H.N.); the Department of Gastroenterology, Mater Hospital Brisbane, Brisbane, QLD, Australia (J.B.); the Division of Gastroenterology, University of California, San Diego, La Jolla (B.B.); and the Henry D. Janowitz Division of Gastroenterology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York (J.-F.C.).

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