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Efficacy and Safety of Upadacitinib in a Randomized Trial of Patients With Crohn's Disease

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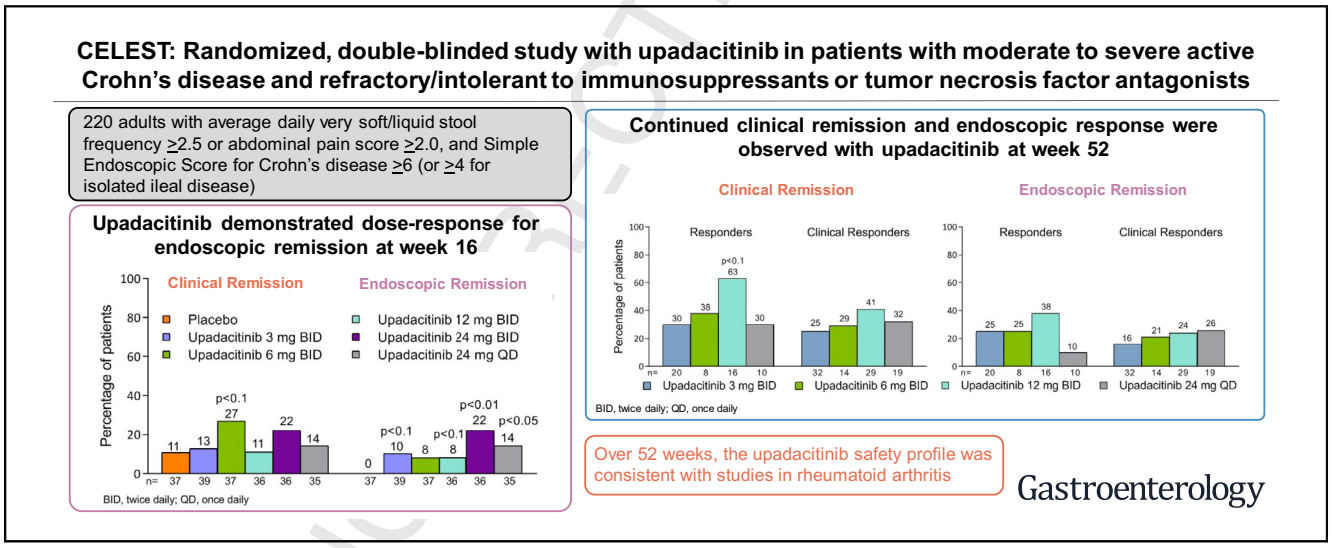

BACKGROUND & AIMS: We evaluated the efficacy and safety of upadacitinib, an oral selective Janus kinase 1 inhibitor, in a randomized trial of patients with Crohn's disease (CD). **METHODS:** We performed a double-blind, phase 2 trial in adults with moderate to severe CD and inadequate response or intolerance to immunosuppressants or tumor necrosis factor antagonists. Patients were randomly assigned (1:1:1:1:1:1) to groups given placebo; or 3 mg, 6 mg, 12 mg, or 24 mg upadacitinib twice daily; or 24 mg upadacitinib once daily and were evaluated by ileocolonoscopy at weeks 12 or 16 of the induction period. Patients who completed week 16 were re-randomized to a 36-week period of maintenance therapy with upadacitinib. The primary endpoints were clinical remission at week 16 and endoscopic remission at week 12 or 16 using the multiple comparison procedure and modeling and the Cochran-Mantel-Haenszel test, with a 2-sided level of 10%. **RESULTS:** Among the 220 patients in the study, clinical remission was achieved by 13% of patients receiving 3 mg upadacitinib, 27% of patients receiving 6 mg upadacitinib ($P < .1$ vs placebo), 11% of patients receiving 12 mg upadacitinib, and 22% of patients receiving 24 mg upadacitinib twice daily, and by 14% of patients receiving 24 mg upadacitinib once daily, vs 11% of patients receiving placebo. Endoscopic remission was achieved by 10% ($P < .1$ vs placebo), 8%, 8% ($P < .1$ vs placebo), 22% ($P < .01$ vs placebo), and 14% ($P < .05$ vs placebo) of patients receiving upadacitinib, respectively, vs none of the patients receiving placebo. Endoscopic but not clinical

remission increased with dose during the induction period. Efficacy was maintained for most endpoints through week 52. During the induction period, patients in the upadacitinib groups had higher incidences of infections and serious infections vs placebo. Patients in the twice daily 12 mg and 24 mg upadacitinib groups had significant increases in total, high-density lipoprotein, and low-density lipoprotein cholesterol levels, compared with patients in the placebo group. **CONCLUSIONS:** In a phase 2 trial of patients with CD, upadacitinib induced endoscopic remission in a significant proportion of patients compared with placebo. Upadacitinib's benefit/risk profile supports further development for treatment of CD. (Clinicaltrials.gov, Number: NCT02365649)

Keywords: CELEST Trial; CDAI; JAK Inhibitor; IBD.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

This study evaluated the efficacy and safety of upadacitinib, an oral selective inhibitor of Janus kinase 1, in a phase 2, randomized trial of patients with moderate to severe Crohn's disease.

NEW FINDINGS

Upadacitinib led to endoscopic remission in a significant proportion of patients during induction therapy, compared with placebo.

LIMITATIONS

This was a phase 2 study that included only 220 patients. No multiplicity-adjustment for the secondary endpoints was conducted.

IMPACT

Upadacitinib's benefit–risk profile supports further studies in patients with Crohn's disease.

Crohn's disease (CD) is a chronic, progressive, inflammatory disease of the gastrointestinal tract. Current goals of therapy are to induce and maintain clinical and endoscopic remission, prevent relapse, and slow or halt disease progression.[1–3] Currently approved therapies, including corticosteroids, immunosuppressants, and biologic agents, are not effective in some patients and may be associated with adverse effects that limit their use.[4,5] There remains an unmet need for additional targeted therapies for CD that provide short- and long-term benefits as measured by both patients' symptoms and endoscopic outcomes.

The 4 members of the Janus kinase (JAK) family (JAK1, JAK2, JAK3, and tyrosine kinase [TYK] 2) are part of transmembrane cytokine receptor complexes that are activated upon binding of a ligand, leading to recruitment, phosphorylation, and activation of signal transducers and activators of transcription.[6,7] Signal transducers and activators of transcription control many functions of innate and adaptive immunity, hematopoiesis, and cellular complex processes, such as cell growth, survival, differentiation, and migration.[7] Several JAK inhibitors with different selectivity have been studied for the treatment of CD.[8–10] Upadacitinib (ABT-494) is an oral JAK1 inhibitor with increased selectivity for JAK1 compared with JAK2, JAK3, and TYK2.[11] Upadacitinib down-regulates multiple proinflammatory cytokines, including interleukin (IL) 2, IL-4, IL-6, IL-7, IL-9, IL-15, IL-21, and interferon gamma, that are relevant to the pathogenesis of CD.[12,13]

The main objectives of the phase 2 CELEST study were to evaluate the efficacy, safety, and pharmacokinetics of multiple doses of upadacitinib vs placebo as induction therapy and upadacitinib as maintenance therapy in adult patients with moderately to severely active CD, who had refractory symptoms or were intolerant to immunosuppressive treatment or tumor necrosis factor (TNF) antagonists, by using a model-based dose-response testing and estimation statistical method.

Methods

Study Design

CELEST was a 52-week, multicenter, randomized, double-blind, dose-ranging, phase 2 study that consisted of a 16-week placebo-controlled induction period, followed by a 36-week double-blind maintenance period (Supplementary Figure 1). CELEST was conducted at 93 sites in 19 countries in the United States, Europe, Israel, Australia, and New Zealand.

The study protocol was approved by the relevant ethics committees or institutional review boards. The protocol was executed in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulations. All patients provided written informed consent before participating in any study-related procedures. Protocol deviations were monitored at study entry and throughout the study duration.

Participants

The study enrolled adult patients (aged 18–75 years) with confirmed ileal, ileocolonic, or colonic CD for ≥3 months; active disease with a CD Activity Index (CDAI) of 220–450; average daily liquid/very soft stool frequency (SF) ≥2.5; or daily abdominal pain (AP) score ≥2.0, as well as evidence of mucosal inflammation defined as Simplified Endoscopic Score for CD (SES-CD) ≥6 (or ≥4 for those with isolated ileal disease). The original protocol was designed to enroll patients with inadequate response/intolerance to at least 1 of the TNF antagonists approved for CD (adalimumab, infliximab, or certolizumab pegol). The protocol was subsequently amended to include

Abbreviations used in this paper: **AE, adverse event; AP, abdominal pain; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CPK, creatinine phosphokinase; CR-70, decrease in Crohn's Disease Activity Index from baseline by ≥70 points; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; IL, interleukin; JAK, Janus kinase; MCP-Mod, multiple comparison procedure and modeling; MI, myocardial infarction; mITT, modified intent-to-treat; PBO, placebo; PRO, patient-reported outcome; RA, rheumatoid arthritis; SES-CD, Simplified Endoscopic Score for Crohn's Disease; SF, stool frequency; TNF, tumor necrosis factor.**

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patients with inadequate response/intolerance to azathioprine, mercaptopurine, or methotrexate. (Full inclusion/exclusion criteria are in Supplementary Table 1.) Patients could enter the study while receiving stable doses of aminosalicylates, oral corticosteroids (equivalent prednisone dose of ≤30 mg/d or budesonide of ≤9 mg/d), methotrexate, and/or CD-related antibiotics but had to discontinue azathioprine or mercaptopurine ≥10 days before baseline. Starting at week 2, patients receiving oral corticosteroids initiated a mandatory corticosteroid tapering following a protocol-specified schedule until discontinuation (Supplementary Table 2).

Randomization and Masking

At baseline, patients were randomized (1:1:1:1:1:1) to receive double-blind, 16-week induction treatment with placebo or the immediate-release formulation of upadacitinib 3-mg, 6-mg, 12-mg, or 24-mg twice daily or 24-mg once daily oral doses. The randomization was stratified by endoscopic disease severity (SES-CD <15 and ≥15), prior TNF antagonist use (yes or no), and participation in the substudy of gene expression in intestinal biopsy specimens (yes or no). Patients were equally randomized for the follow-up ileocolonoscopy at either week 12 or 16 for evaluation of the optimal timing of endoscopic assessment for future studies. Patients were centrally randomized using interactive response technology. The patients, investigators, site coordinators, and sponsor were blinded to treatment assignment.

All patients who completed the 16-week induction period were re-randomized 1:1:1 to receive double-blind maintenance therapy with the immediate-release formulation of upadacitinib at 3 mg twice daily, 12 mg twice daily, or 24 mg once daily for 36 weeks.

With the availability of results from phase 1 studies assessing the 24-mg once daily dose compared with the 12-mg twice daily dose and from rheumatoid arthritis (RA) phase 2 studies showing the efficacy of the 6-mg twice daily dose, the 24 mg once daily arm in the maintenance period was stopped, and a 6 mg twice daily arm was initiated in a protocol amendment. Patients who were already assigned to 24 mg once daily continued to receive this dosage to the end of the study. After the protocol amendment, all subsequent patients entering the maintenance period were re-randomized 1:1:1 to receive upadacitinib 3 mg, 6 mg, or 12 mg twice daily. The re-randomization was stratified by dose received during the first 16 weeks and clinical response (clinical responder vs nonresponder) at week 16. Clinical response was defined as a ≥30% reduction from baseline in SF and/or AP score, with neither parameter worse than patients' baseline score.

Procedures

Eligible patients were assessed at baseline and weeks 2, 4, 8, 12, 16, 20, 28, 36, 44, and 52 for vital signs, physical examination, patient-reported outcome (PRO) measures, CDAI, adverse events (AEs), and blood laboratory test results. Stool samples were collected for fecal calprotectin measurements at baseline and weeks 4, 16, 28, and 52. SF, AP score, and general well-being were collected daily using electronic patient diaries for the CDAI calculation, and SF and AP score were also calculated as an average from 7 days before the study visit for the PRO-related clinical endpoints. The Inflammatory Bowel Disease Questionnaire (IBDQ) was completed at baseline and weeks 8, 16, and 52. One plasma sample for the determination of upadacitinib concentration was collected at each postbaseline study visit. Ileocolonoscopies performed during screening, week 12 or 16, and week 52 for the SES-CD were centrally read for eligibility and for the efficacy assessments by readers who were blinded to patient data and timepoints. The SES-CD data at weeks 12 and 16 were pooled for the induction period assessments.

Outcomes

The coprimary endpoints of this study were clinical remission at week 16 (hereafter called *clinical remission 1.5/1.0* and defined as average daily SF of ≤1.5 and AP score of ≤1.0, with neither worse than the baseline value) and endoscopic remission at week 12/16 (defined as SES-CD od ≤4 and a ≥2-point reduction from baseline, with no subscore >1).[14]

Key prespecified secondary endpoints assessed during the induction and maintenance periods at various timepoints included clinical remission 1.5/1.0; endoscopic remission; endoscopic response 25% (defined as ≥25% reduction in SES-CD from baseline); clinical response; CDAI <150 and decrease in CDAI from baseline ≥70 points (CR-70); combined clinical remission 1.5/1.0 and endoscopic remission (referred to as *Remission*) and combined clinical response and endoscopic response 25% (referred as *Response*); corticosteroid-free and CDAI <150, corticosteroid-free clinical remission 1.5/1.0, endoscopic remission and Remission; and change from baseline in fecal calprotectin, serum high-sensitivity C-reactive protein (hs-CRP), and IBDQ response (increase in IBDQ ≥16 points from baseline) and IBDQ remission (IBDQ ≥170). Clinical remission 1.5/1.0 was also assessed in patients with SF ≥2.5 and AP score ≥2.0 at baseline and in those with isolated ileal disease.

Two exploratory secondary endpoints of clinical remission 2.8/1.0 (defined as SF ≤2.8 and AP score ≤1.0, neither worse than baseline, among patients with baseline SF ≥4.0 or AP score ≥2.0) and endoscopic response 50% (defined as >50% reduction in SES-CD or endoscopic remission) were incorporated into the statistical analysis plan before the database lock. Clinical remission 2.8/1.0 emerged while the trial was ongoing as a more suitable clinical outcome measure for patients with moderate to severe CD, and endoscopic response 50% was chosen as a reliable predictor of the 1-year outcomes with the potential to adequately demonstrate the endoscopic improvement in a clinical trial setting.[15,16]

Treatment-emergent AEs were monitored in all patients who received at least 1 dose of study medication from the time of first administration to 30 days after discontinuation of the study drug. Serious AEs were collected from the date of signed informed consent. AEs were tabulated by system organ class and preferred term using the Medical Dictionary for Regulatory Activities, version 20.0. Changes from baseline in laboratory parameters were categorized according to Common Toxicity Criteria, version 4.03 or version 3.0 (for hemoglobin only).

Statistical Analysis

The sample size was calculated based on the multiple comparison procedure and modeling (MCP-Mod) approach, which is a data analysis methodology that combines multiple

Table 1. Baseline Patient Demographics and Disease Characteristics

Characteristics	Placebo n = 37	Upadacitinib 3 mg BID n = 39	Upadacitinib 6 mg BID n = 37	Upadacitinib 12 mg BID n = 36	Upadacitinib 24 mg BID n = 36	Upadacitinib 24 mg QD n = 35
Female, n (%)	24 (64.9)	19 (48.7)	21 (56.8)	17 (47.2)	25 (69.4)	19 (54.3)
Age, *y*, median (range)	40 (20–68)	37 (19–66)	39 (22–76)	41 (19–70)	44 (20–65)	41 (21–64)
CD duration, *y*, median (range)	8.7 (1.2–41.6)	10.7 (0.1–44.7)	8.8 (2.2–46.4)	9.1 (1.2–38.3)	14.1 (1.1–35.5)	10.8 (0.7–36.3)
Disease location, n (%)						
Ileal only	9 (24.3)	10 (25.6)	6 (16.2)	5 (13.9)	6 (16.7)	10 (28.6)
Colonic only	6 (16.2)	9 (23.1)	13 (35.1)	11 (30.6)	11 (30.6)	10 (28.6)
Ileocolonic	22 (59.5)	20 (51.3)	18 (48.6)	20 (55.6)	19 (52.8)	15 (42.9)
CDAI, median (range)	276.0 (188–447)	288.0 (180–445)	296.0 (230–599)	280.0 (224–446)	277.5 (162–556)	305.0 (231–421)
Daily very soft/liquid SF, median (range)	5.7 (1.9–12.4)	5.1 (0.3–15.7)	6.8 (2.6–22.1)	5.7 (2.0–14.7)	4.9 (0.1–19.7)	6.4 (2.6–12.6)
Daily AP score, median (range)	1.7 (0.9–3.0)	1.9 (0.8–3.0)	1.9 (1.0–3.0)	2.0 (0.4–3.0)	1.7 (0.3–2.9)	2.0 (0.9–3.0)
SES-CD, median (range)	15.0 (4–37)	12.0 (4–32)	14.0 (4–35)	12.5 (4–38)	12.0 (5–29)	12.0 (4–31)
hs-CRP, *mg/L*, median (range)	7.0 (0–179)	6.0 (1–308)	11.7 (0–72)	16.6 (1–117)	5.9 (1–135)	7.4 (0–98)
Fecal calprotectin, *μg/g*, median (range)	896.0 (126–9600)	916.0 (11–9600)	1602.5 (81–9600)	1622.0 (71–9600)	1377.0 (39–8087)	814.0 (76–9600)
Baseline corticosteroid use, n (%)	15 (40.5)	21 (53.8)	18 (48.6)	17 (47.2)	15 (41.7)	10 (28.6)
Baseline daily corticosteroid dose,[a] *mg*, median (range)	20.0 (5–45)	20.0 (5–45)	22.5 (10–45)	20.0 (5–45)	20.0 (10–45)	30.0 (10–45)
Prior immunosuppressants, n (%)	16 (43.2)	12 (30.8)	12 (32.4)	12 (33.3)	13 (36.1)	16 (45.7)
Prior TNF antagonist, n (%)						
0	2 (5.4)	2 (5.1)	1 (2.7)	2 (5.6)	0	2 (5.7)
1	15 (40.5)	17 (43.6)	12 (32.4)	6 (16.7)	10 (27.8)	10 (28.6)
2	15 (40.51)	16 (41.0)	20 (54.1)	24 (66.7)	15 (41.7)	16 (45.7)
≥3	5 (13.5)	4 (10.3)	4 (10.8)	4 (11.1)	9 (25.0)	7 (20.0)
Prior non-TNF antagonist biologics, n (%)	14 (37.8)	15 (38.5)	19 (51.4)	15 (41.7)	16 (44.4)	14 (40.0)

BID, twice daily; QD, once daily.
[a]Prednisone equivalent.

comparison and modeling techniques to evaluate a dose-response signal and estimate target effective doses in phase 2 studies.[17] Five prespecified potential candidate models were considered: linear, E_{max}, exponential, logistic, and sigmoid E_{max}. Assuming clinical remission and endoscopic remission rates of 12% in the placebo arm and a maximum of 35% in at least 1 of the upadacitinib twice daily treatment arms compared with placebo at week 12/16, 35 patients per treatment arm had at least 80% power to detect a 1-sided 5% level of significance (or 2-sided 10% level) for the presence of a dose-response curve. The prespecified models did not include the 24-mg once daily arm in the dose-ranging evaluations.

During the induction period, efficacy endpoints were analyzed for the modified intention-to-treat population, defined as all randomized patients who received at least 1 dose of the study drug. For selected endpoints (clinical remission 1.5/1.0 and clinical remission 2.8/1.0 at week 16, endoscopic remission and endoscopic response 50% at week 12/16), the overall dose-response relationships between multiple upadacitinib doses and placebo were tested by MCP-Mod (Supplementary Table 3).

Coprimary endpoints and categorical secondary endpoints between each of the upadacitinib dose groups and placebo were also compared using the Cochran-Mantel-Haenszel (CMH) test, stratified by baseline SES-CD (SES-CD <15 and ≥15). No prespecified primary contrast or prespecified dose-placebo testing sequences were performed. The CMH-based 2-sided 95% confidence intervals (CIs) for the difference in proportions between arms were calculated. Comparisons of mean change from baseline in IBDQ between each upadacitinib dose and placebo were analyzed using a mixed model for repeated measures with treatment, baseline SES-CD (SES-CD <15 and

Table 2. MCP-Mod Dose-Response Modeling

Outcome	Rate, %	Models, 2-sided *P* value
Clinical remission 1.5/1.0	Placebo: 11	Exponential: .6856
	3 mg BID: 13	Linear: .6312
	6 mg BID: 27	E_{max}: .4152
	12 mg BID: 11	$SigE_{max}$: .5012
	24 mg BID: 22	Logistic: .6464
		Quadratic: .5540
Endoscopic remission	Placebo: 0	Exponential: .0406
	3 mg BID: 10	Linear: .0439
	6 mg BID: 8	E_{max}: .0570
	12 mg BID: 8	$SigE_{max}$: .0912
	24 mg BID: 22	Logistic: .1815
		Quadratic: .1279
Clinical remission 2.8/1.0	Placebo: 12	Exponential: .1567
	3 mg BID: 16	Linear: .0678
	6 mg BID: 30	E_{max}: .0344
	12 mg BID: 27	$SigE_{max}$: .0380
	24 mg BID: 37	Logistic: .0560
		Quadratic: .0484
Endoscopic response 50%	Placebo: 3	Exponential: .1605
	3 mg BID: 13	Linear: .0369
	6 mg BID: 21	E_{max}: .0069
	12 mg BID: 29	$SigE_{max}$: .0099
	24 mg BID: 33	Logistic: .0150
		Quadratic: .0084

Q33 NOTE. MCP-Mod was used to test a predefined group of candidates' dose-response curves against a flat dose-response curve to best characterize the dose-response relationship. The 6 prespecified candidate models were linear, E_{max}, exponential, logistic, $sigE_{max}$, and quadratic. The MCP-Mod method was implemented to identify the significant models among the prespecified models while controlling the overall type 1 error in the strong sense at a 2-sided significance level of .10.

Q34 ADDPLAN software, version 3.1.8, was used to evaluate different dose-response models and to make dose recommendations.

Models were applied to characterize the dose-response for upadacitinib for the 2 coprimary endpoints of clinical 1.5/1.0 and endoscopic remission and 2 exploratory endpoints of clinical remission 2.8/1.0 and endoscopic response 50%. All statistical significances were tested at the 2-sided 10% level. BID, twice daily. E_{max}, maximum effect; $SigE_{max}$, sigmoid E_{max}.

≥15), week, baseline, and interaction of treatment and week as covariates.

During the maintenance period, the efficacy analyses included patients who received upadacitinib during the induction period in 2 modified intent-to-treat (mITT) subpopulations: clinical responders (patients who achieved clinical response at week 16) and responders (patients who achieved both clinical response at week 16 and endoscopic response 25% at week 12/16).

Comparisons between the 6- and 12-mg twice daily and 24-mg once daily doses of upadacitinib with the 3-mg twice daily dose were performed using the chi-squared test (or Fisher's exact test if ≥20% of the cells had expected cell count of <5) for categorical efficacy endpoints and analysis of covariance with treatment as a factor and value at induction baseline as a covariate for mean change from baseline in hs-CRP and fecal calprotectin, using last observation carried forward. Missing values and data for patients who prematurely discontinued or who initiated or received corticosteroids at a dose higher than at baseline were imputed as nonresponders. Nonresponder imputation was also applied to patients with inadequate response and who received open-label rescue treatment during the maintenance period.

All tests of statistical significance were at the 2-sided 10% level of significance ($P \leq .1$), which is frequently used in phase 2b trials, where the focus of the study is to facilitate the dose selection for future phase 3 trials.[18] No multiplicity adjustments were applied for this dose-ranging study on key secondary endpoints. Upadacitinib pharmacokinetic parameters were estimated using a nonlinear mixed-effects population modeling approach.

Safety analyses included all randomized patients who received at least 1 dose of upadacitinib and were summarized by study arm and study period and presented as proportions of patients. All analyses were performed with SAS software, version 9.4 (SAS Institute Inc, Cary, NC). This trial was registered with ClinicalTrials.gov, number NCT02365649.

All authors had access to study data, reviewed and approved the final report, and take full responsibility for the accuracy of the data and statistical analysis. The first and corresponding authors had final responsibility for the decision to submit for publication.

Results

The study was conducted between March 17, 2015, and August 3, 2017. Of the 370 patients who were screened, 150 were excluded (41%); the most common reason for screening failure was not meeting inclusion criteria (n = 123/150; 82%), namely, the SES-CD criterion, baseline CDAI below 220, and abnormal laboratory values at screening. The remaining 220 patients were randomized to receive placebo (n = 37), or upadacitinib 3 mg (n = 39), 6 mg (n = 37), 12 mg (n = 36), or 24 mg twice daily (n = 36), or 24 mg once daily (n = 35) (Supplementary Figure 2). Overall, 180 patients (82%) completed the induction period and were re-randomized for the maintenance period to receive upadacitinib 3 mg (n = 61), 6 mg (n = 23), or 12 mg twice daily (n = 59) or 24 mg once daily (n = 37) (Supplementary Figure 2). Of these, 153 patients received upadacitinib in the induction period, ; 94 were mITT clinical responders and 54 were mITT responders at week 16. The most common primary reasons for discontinuations were AEs (upadacitinib, 14/183 [8%]; placebo, 3/37 [8%]) and lack of efficacy (upadacitinib, 6/183 [3%]; placebo, 3/37 [8%]) during the induction period and lack of efficacy (27/180 [15%]) and AEs (14/180 [8%]) during the maintenance period (Supplementary Figure 2).

At baseline, the median disease duration was 9.6 years, and 96% (211/220) of patients had an inadequate response or intolerance to ≥1 TNF antagonist; 64% of patients (141/220) had been exposed to ≥2 TNF antagonists and 42% (93/220) to non-TNF antagonist biologics (Table 1).

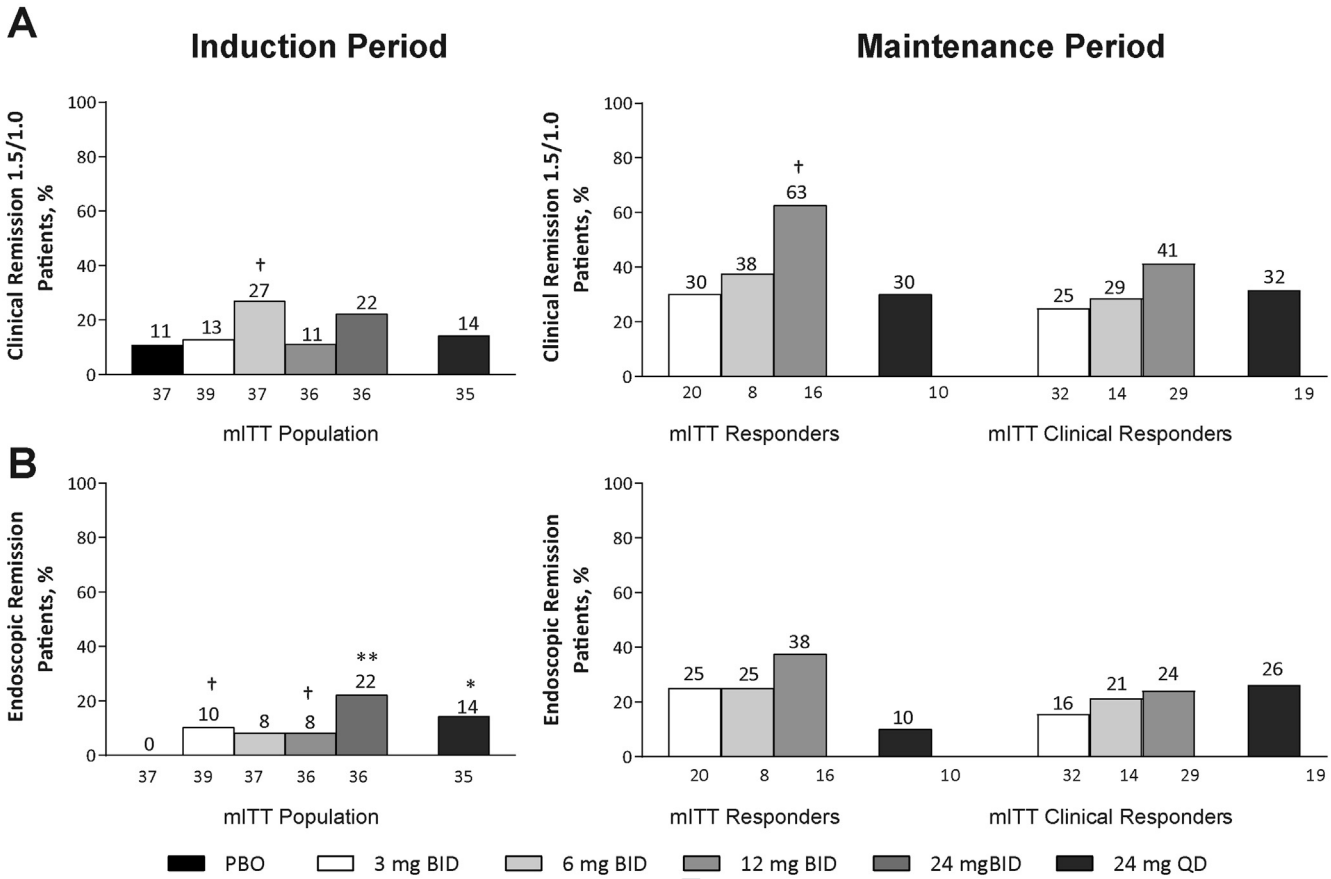

Figure 1. Coprimary endpoints of (*A*) clinical remission 1.5/1.0 and (*B*) endoscopic remission at induction period week 12/16 in all patients and maintenance period week 52 in responders and clinical responders. Nonresponder imputation. Statistical significance: $^{\dagger}P < .1$, $^{*}P < .05$, $^{**}P < .01$ vs placebo during the induction period and vs 3 mg twice daily during the maintenance period. Clinical responders were defined as patients who achieved clinical response at week 16, and responders were defined as patients who achieved both clinical response and endoscopic response 25% at week 16. BID, twice daily; PBO, placebo; QD, once daily.

Coprimary Endpoints

For the coprimary endpoint of clinical remission 1.5/1.0, the overall dose-response relationship between upadacitinib and placebo was not significant by MCP-Mod in any of the prespecified candidate models (Table 2). At week 16, clinical remission 1.5/1.0 occurred in 13% (5/39), 27% (10/37; $P < .1$), 11% (4/36), 22% (8/36), and 14% (5/35) of patients receiving upadacitinib 3, 6, 12, and 24 mg twice daily and 24 mg once daily, respectively, compared with 11% (4/37) of patients receiving placebo (Figure 1*A*). CMH-adjusted risk differences (95% CIs) for clinical remission were 2.5 (−12.3 to 17.3) for the 3 mg twice daily, 16.2 (−2.0 to 34.3) for the 6 mg twice daily, 0.5 (−14.1 to 15.0) for the 12 mg twice daily, 11.2 (−6.1 to 28.5) for the 24 mg twice daily, and 4.1 (−11.5 to 19.6) for the 24 mg once daily arms.

For endoscopic remission, the overall dose-response relationship between upadacitinib and placebo was detected by MCP-Mod in 4 of the 6 prespecified candidate models (exponential [$P = .04$], linear [$P = .04$], E_{max} [$P = .06$] and sigmoid E_{max} [$P = .09$]) (Table 2). At week 12/16, endoscopic remission occurred in 10% (4/39; $P < .1$), 8% (3/37), 8% (3/36; $P < .1$), 22% (8/36; $P < .01$), and 14% (5/35; $P < .05$) of patients receiving upadacitinib 3 mg, 6 mg, 12 mg, and 24 mg twice daily and 24 mg once daily, respectively, compared with 0% (0/37) of patients receiving placebo (Figure 1*B*). CMH-adjusted risk differences (95% CI) were 9.9 (−0.3 to 20.1) for the 3 mg twice daily, 7.4 (−1.6 to 16.4) for the 6 mg twice daily, 7.7 (−1.5 to 16.8) for the 12 mg twice daily, 21.0 (6.8 to 35.2) for the 24 mg twice daily, and 13.6 (1.8 to 25.5) for the 24 mg once daily arms.

Secondary and Exploratory Efficacy Endpoints

Induction Period. Using the exploratory endpoints, dose-response relationships with upadacitinib twice daily doses were observed for clinical remission 2.8/1.0 and endoscopic response 50% per MCP-Mod in 5 of the 6 prespecified candidate models (all except the exponential model) (Table 2). More patients achieved clinical remission 2.8/1.0 at week 16 with 6 mg twice daily (30% [10/33]; $P < .1$) and 24 mg twice daily (37% [11/30]; $P < .05$) compared with placebo (12% [4/33]) (Figure 2*A*).

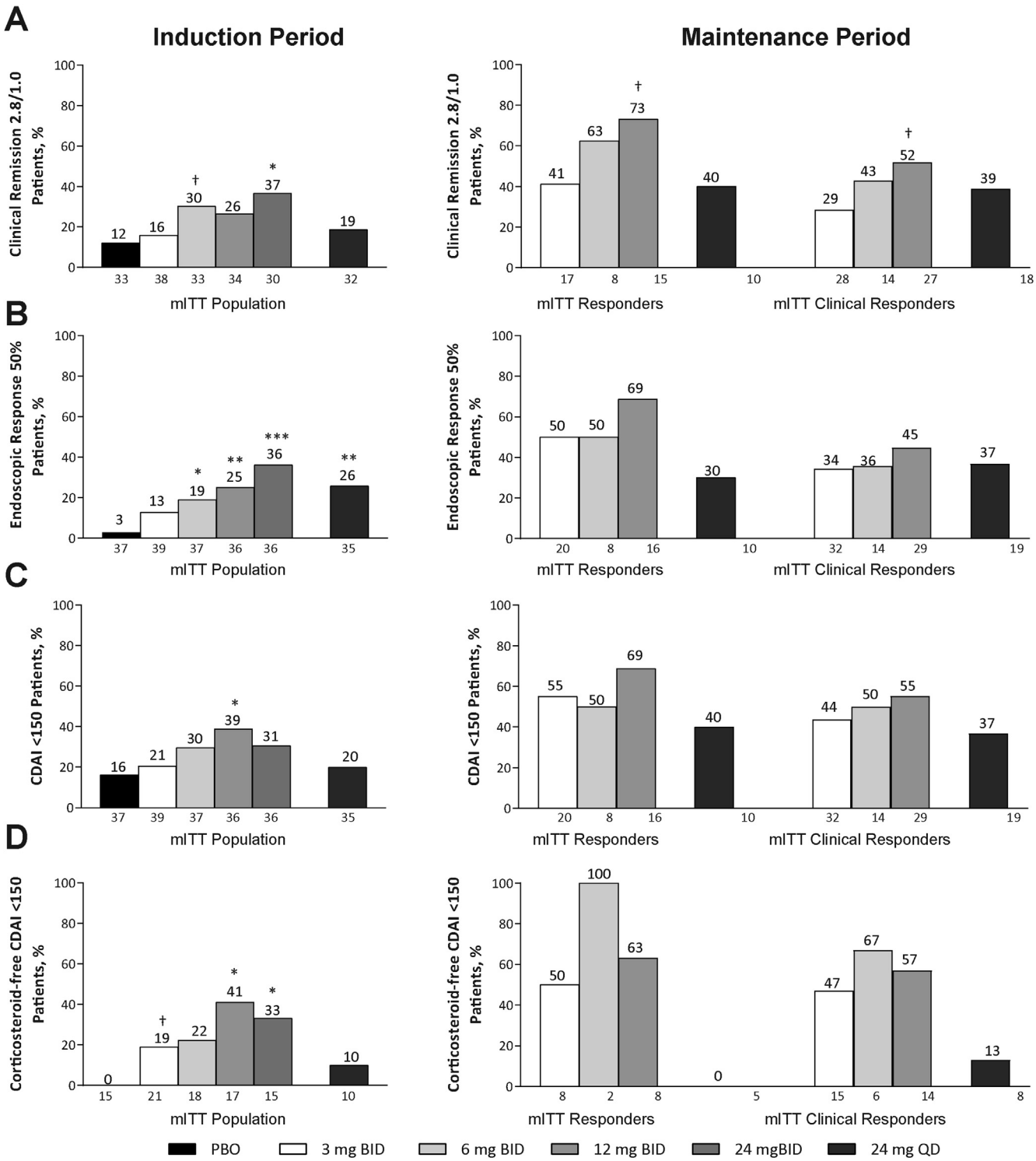

Figure 2. Secondary endpoints of (*A*) clinical remission 2.8/1.0, (*B*) endoscopic response 50%, (*C*) CDAI <150, and (*D*) corticosteroid-free CDAI <150 at induction period week 12/16 in all patients and maintenance period week 52 in responders and clinical responders. Nonresponder imputation. Statistical significance: $^{\dagger}P < .1$, $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$ vs placebo during the induction period and vs 3 mg twice daily during the maintenance period. Clinical responders were defined as patients who achieved clinical response at week 16, and responders were defined as patients who achieved both clinical response and endoscopic response 25% at week 16. BID, twice daily; PBO, placebo; QD, once daily.

Table 3. Summary of Additional Key Secondary Endpoints During the Induction Period

Endpoints	Placebo n = 37	Upadacitinib 3 mg BID n = 39	Upadacitinib 6 mg BID n = 37	Upadacitinib 12 mg BID n = 36	Upadacitinib 24 mg BID n = 36	Upadacitinib 24 mg QD n = 35
Secondary endpoint						
Clinical remission 1.5/1.0 at week 12, n (%)	4 (10.8)	4 (10.3)	11 (29.7)[a]	5 (13.9)	9 (25.0)	3 (8.6)
Clinical remission 2.8/1.0 at week 12, n (%)	3 (9.1) (n = 33)	6 (15.8) (n = 38)	9 (27.3)[a] (n = 33)	10 (29.4)[b] (n = 34)	10 (33.3)[b] (n = 30)	4 (12.5) (n = 32)
Clinical response at week 16, n (%)	12 (32.4)	17 (43.6)	21 (56.8)[a]	17 (47.2)	22 (61.1)[b]	17 (48.6)
CR-70 at week 16, n (%)	13 (35.1)	18 (46.2)	20 (54.1)	16 (44.4)	22 (61.1)[b]	17 (48.6)
Endoscopic response 25% at week 12/16, n (%)	5 (13.5)	9 (23.1)	16 (43.2)[c]	13 (36.1)[a]	18 (50.0)[d]	17 (48.6)[d]
Remission at week 16, n (%)	0	1 (2.6)	2 (5.4)	1 (2.8)	3 (8.3)[a]	2 (5.7)
Response at week 16, n (%)	1 (2.7)	6 (15.4)[b]	12 (32.4)[c]	10 (27.8)[c]	14 (38.9)[d]	12 (34.3)[d]
Clinical remission 1.5/1.0 in patients with SF ≥2.5 and AP ≥2.0 at baseline, n (%)	1 (7.1) n = 14	3 (17.6) n = 17	3 (18.8) n = 16	3 (16.7) n = 18	3 (25.0) n = 12	2 (11.1) n = 18
Clinical remission 1.5/1.0 in patients with isolated ileal disease, n (%)	0 n = 9	2 (20.0) n = 10	1 (16.7) n = 6	1 (20.0) n = 5	0 n = 6	2 (20.0) n = 10
Endoscopic remission among patients with no missing individual variables, n (%)	0 n = 15	4 (14.3) n = 28	2 (8.7) n = 23	3 (13.0) n = 23	8 (30.8)[b] n = 26	5 (22.7)[a] n = 22
Change from baseline in hs-CRP at week 16, mean ± SD (median)	–0.1 ± 12.0 (0.0)	–3.0 ± 19.6 (0.0)	–3.9 ± 19.5 (–4.6)	–6.1 ± 27.0 (–0.3)	–14.8 ± 26.4[b] (–3.2)	–2.7 ± 13.7 (–0.2)
Change from baseline in fecal calprotectin at week 16, mean ± SD (median)	–128.9 ± 373.5 (0.0)	–534.5 ± 3279.2 (91.0)	–429.4 ± 2505.2 (–233.0)	–475.1 ± 2668.9 (–134.0)	–828.7 ± 986.1 (–671.5)	–698.4 ± 2228.9 (0.0)
Change in IBDQ from baseline at week 16, mean ± SD (median)	14.5 ± 29.2 (2.0)	24.6 ± 43.0 (17.0)	41.8 ± 47.0[c] (38.0)	32.1 ± 38.6[a] (22.0)	44.4 ± 40.1[c] (37.0)	22.5 ± 27.8 (18.5)

	Placebo n = 15	Upadacitinib 3 mg BID n = 21	Upadacitinib 6 mg BID n = 18	Upadacitinib 12 mg BID n = 17	Upadacitinib 24 mg BID n = 15	Upadacitinib 24 mg QD n = 10
Secondary endpoints in patients with corticosteroid-use at baseline, n (%)						
Corticosteroid-free clinical remission 1.5/1.0 at week 16	0	3 (14.3)	4 (22.2)	2 (11.8)	5 (33.3)[b]	1 (10.0)
Corticosteroid-free endoscopic remission at week 16	0	0	2 (11.1)	1 (5.9)	3 (20.0)	1 (10.0)
Corticosteroid-free remission at week 16	0	0	1 (5.6)	1 (5.9)	2 (13.3)	0

NOTE. Clinical remission 1.5/1.0 was defined as average daily very soft/liquid SF ≤1.5 and average daily AP score ≤1, without worsening from baseline. Clinical remission 2.8/1.0 was defined as average daily very soft/liquid SF ≤2.8 and average daily AP score ≤1, neither worse than baseline, among patients with baseline average daily very soft/liquid SF ≥4.0 or average daily AP score ≥2.0. Clinical response was defined as ≥30% reduction from baseline in average daily very soft/liquid SR and/or average daily AP score, neither worse than baseline. CR-70 was defined as decrease in CDAI ≥70 points from baseline. Remission was defined as combined clinical remission 1.5/1.0 and endoscopic remission, and response was defined as combined clinical response and endoscopic response 25%.
BID, twice daily; QD, once daily.
[a]Significance vs placebo at $P < .1$.
[b]Significance vs placebo at $P < .05$.
[c]Significance vs placebo at $P < .01$.
[d]Significance vs placebo at $P < .001$.

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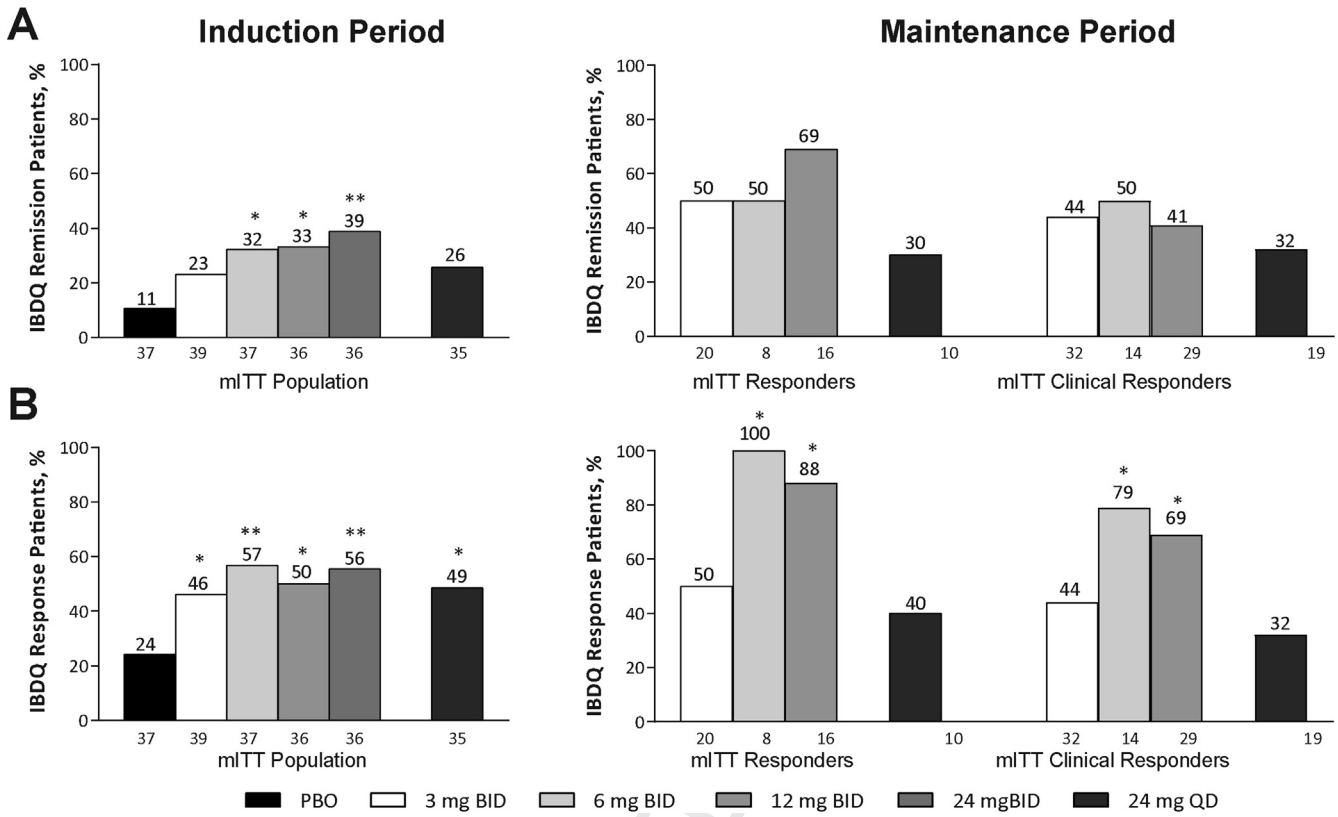

Figure 3. (*A*) IBDQ remission and (*B*) IBDQ response at induction period week 12/16 in all patients and maintenance period week 52 in responders and clinical responders. IBDQ remission was defined as IBDQ ≥170. IBDQ response was defined as increase in IBDQ ≥16 points from baseline. Nonresponder imputation. Statistical significance: $^{\dagger}P < .1$, $^{*}P < .05$, $^{**}P < .01$ vs placebo during the induction period and vs 3 mg twice daily during the maintenance period. Clinical responders were defined as patients who achieved clinical response at week 16, and responders were defined as patients who achieved both clinical response and endoscopic response 25% at week 16. BID, twice daily; PBO, placebo; QD, once daily.

Endoscopic response 50% at week 12/16 occurred in a higher proportion of patients receiving 6 mg (19% [7/37]; $P < .05$), 12 mg (25% [9/36]; $P < .01$) and 24 mg twice daily (36% [13/36]; $P < .001$) and 24 mg once daily (26% [9/35]; $P < .01$) compared with placebo (3% [1/37]) (Figure 2*B*).

At week 16, 20%–39% of patients receiving upadacitinib achieved CDAI <150 vs 16% receiving placebo (Figure 2*C*); a similar trend was observed for other secondary endpoints at week 16 (Table 3). Efficacy was observed as early as week 2 and maintained to week 16 with upadacitinib (Supplementary Figure 3). Endoscopic remission was nonsignificantly higher in the 24 mg twice daily group compared with the placebo group at week 12 (data not shown).

Among the subgroup of patients receiving corticosteroids at baseline, significantly more patients were able to discontinue their corticosteroid and achieve a CDAI <150 at week 16 with upadacitinib 12 mg (41% [7/17]) and 24 mg twice daily (33% [5/15]) compared with placebo (0% [0/15]; both $P < .05$) (Figure 2*D*). The proportion of patients with corticosteroid-free clinical remission 1.5/1.0 was significantly higher with upadacitinib 24 mg twice daily (33%) vs placebo (0%; $P < .05$) at week 16 (Table 3).

The mean change (reduction) from baseline to week 16 in hs-CRP was significant for the 24 mg twice daily arm (−14.8) vs placebo (−0.1; $P < .05$); changes in fecal calprotectin did not reach significance vs placebo (Table 3).

Maintenance Period. At week 52, among mITT responders and clinical responders, the percentage of patients with clinical remission 1.5/1.0 (63% and 41%) and endoscopic remission (38% and 24%) (Figure 1*A* and *B*) and clinical remission 2.8/1.0 (73% and 52%), endoscopic response 50% (69% and 45%), and CDAI <150 (69% and 55%) (Figure 2*A*–*C*), respectively, was highest among patients receiving 12 mg twice daily compared with the other dose groups, but these differences were not significant.

Other secondary endpoints showed similar trends (Supplementary Table 3). At week 52, the percentage of patients who achieved corticosteroid-free efficacy endpoints increased with increasing twice daily doses (Figure 2*D* and Supplementary Table 3).

Quality of Life. A significantly greater proportion of patients achieved IBDQ remission with upadacitinib 6 mg, 12 mg, and 24 mg twice daily doses and IBDQ response with upadacitinib 3 mg, 6 mg, 12 mg, and 24 mg twice daily and 24 mg once daily doses at week 16 compared with placebo (all $P < .05$) (Figure 3). Mean improvements from baseline

Table 4. Treatment-Emergent AEs During the Induction and Maintenance Periods, n (%)

	Induction Period						Maintenance Period			
		Upadacitinib					Upadacitinib			
AE	Placebo n = 37	3 mg BID n = 39	6 mg BID n = 37	12 mg BID n = 36	24 mg BID n = 36	24 mg QD n = 35	3 mg BID n = 60[a]	6 mg BID n = 23	12 mg BID n = 59	24 mg QD n = 36[a]
Any AE	27 (73.0)	34 (87.2)	29 (78.4)	29 (80.6)	30 (83.3)	29 (82.9)	45 (75.0)	14 (60.9)	43 (72.9)	23 (63.9)
Any serious AE	2 (5.4)	5 (12.8)	2 (5.4)	10 (27.8)	3 (8.3)	7 (20.0)	15 (25.0)	2 (8.7)	5 (8.5)	4 (11.1)
Any AE leading to discontinuation	5 (13.5)	4 (10.3)	1 (2.7)	9 (25.0)	3 (8.3)	4 (11.4)	6 (10.0)	0	5 (8.5)	3 (8.3)
Infections[b]	12 (32.4)	16 (41.0)	19 (51.4)	16 (44.4)	20 (55.6)	12 (34.3)	22 (36.7)	6 (26.1)	22 (37.3)	10 (27.8)
Serious infections	0	3 (7.7)	0	3 (8.3)	1 (2.8)	2 (5.7)	5 (8.3)	0	1 (1.7)	0
Herpes zoster[c]	0	0	0	0	1 (2.8)	0	0	0	1 (1.7)	1 (2.8)
Tuberculosis	0	0	0	0	0	0	0	0	0	0
Opportunistic infection[d]	0	0	0	0	0	1 (2.9)	1 (1.7)	0	0	0
Intestinal perforations	0	0	0	0	1 (2.8)	1 (2.9)	0	0	0	0
Malignancy, excluding nonmelanoma skin cancer	0	0	0	0	0	0	0	0	2 (3.4)	0
Nonmelanoma skin cancer	0	0	0	0	1 (2.8)	0	0	0	0	0
Adjudicated cardiovascular events	0	0	0	1 (2.8)	0	0	1 (1.7)	0	0	0
Deaths	0	0	0	0	0	0	0	0	0	0

BID, twice daily; QD, once daily.

[a]Two patients did not receive upadacitinib during the maintenance period and were not included in the safety analysis set.

[b]Serious infections during the induction period included 4 patients with sepsis (1 patient each receiving 3, 12, and 24 mg BID and 24 mg QD), 2 patients with urinary tract infection (1 patient each receiving 12 mg BID and 24 mg QD), and 1 patient each with *Escherichia coli* bacteremia associated with mesenteric vein thrombophlebitis (3 mg BID), subcutaneous (gluteal) abscess (3 mg BID), and rectal abscess (12 mg BID); of these, 3 events (sepsis, rectal abscess, and subcutaneous abscess) led to discontinuation, and 3 events (urinary tract infection, thrombophlebitis, and sepsis) were among patients with baseline corticosteroid use. During the maintenance period, there were 1 event each of abdominal abscess, anal abscess, cellulitis, influenza, and sepsis in the 3 mg BID group and 1 event of abdominal abscess in the 12 mg BID group; of these, 2 events (abdominal abscess and influenza) led to discontinuation, and 1 event (abdominal abscess) was in a patient with baseline corticosteroid use. Three patients with serious infections during the study were receiving concomitant mesalazine.

[c]During the induction period, the event was of moderate severity in 2 contiguous dermatomes; during the maintenance period, 1 event was of moderate severity in 1 Q37 dermatome with the 12-mg BID dose and 1 was of mild severity in 2 contiguous dermatomes with the 24-mg QD dose.

[d]One patient receiving 24 mg QD had a nonserious opportunistic infection of esophageal candidiasis of moderate severity during the induction period; 1 patient in the 3 mg BID group had a nonserious oral candidiasis event during the maintenance period.

to week 16 in IBDQ were significantly greater in patients receiving upadacitinib 6 mg and 24 mg twice daily compared with those receiving placebo (both $P < .01$) (Table 3). During the maintenance period, a significantly greater proportion of responders and clinical responders receiving upadacitinib 6 mg twice daily and 12 mg twice daily vs 3 mg twice daily achieved IBDQ response at week 52 (all $P < .05$) (Figure 3). The improvement from baseline to week 52 in IBDQ was highest with the 12-mg twice daily dose among responders and clinical responders, but these improvements were not significant vs 3 mg twice daily (Supplementary Table 3).

Pharmacokinetics

Upadacitinib average plasma concentration during a dosing interval increased proportionally with increasing dose (Supplementary Figure 4). As expected, the upadacitinib minimum concentration with the 24-mg once daily dose was significantly lower than with the 12-mg twice daily dose and was comparable to the 3-mg twice daily dose (Supplementary Figure 4). During the maintenance period, the observed upadacitinib plasma concentrations were consistent with upadacitinib concentrations during the induction period for the respective doses.

Safety

During the induction period, higher incidences of some AEs were observed at higher upadacitinib doses (>12 mg twice daily) (Table 4). The majority of the AEs were assessed by the investigator as mild or moderate in severity. The incidence of serious AEs varied from 2 (5%) to 10 (28%) across arms, with the highest incidence in the 12-mg twice daily arm. The most frequently reported AEs occurring in ≥5% of patients receiving upadacitinib were headache, worsening of CD, AP, fatigue, upper respiratory tract infection, urinary tract infection, nausea, vomiting, and acne. During the induction period, 9 patients receiving upadacitinib developed serious infections (Table 4). During the maintenance period, 6 serious infections were observed, of which 5 were in patients receiving upadacitinib 3 mg twice daily and 1 in patient receiving 12 mg twice daily (Table 4). During the induction period, 1 patient receiving upadacitinib 24 mg twice daily had a nonserious herpes zoster event, and 2 patients experienced herpes zoster events during the maintenance period. Each event resolved with antiviral treatment (Table 4). All other infections resolved, and none of the events led to discontinuation. No deaths occurred during the study.

During the induction period, 1 nonserious event of nonmelanoma skin cancer was reported in a patient who received upadacitinib 24 mg twice daily and had prior exposure to azathioprine. During the maintenance period, 2 malignancies were reported (Table 4). Hodgkin's disease was reported in a 29-year-old male patient who received 6 mg twice daily induction treatment for 16 weeks followed by12 mg twice daily for 36 weeks; this patient had a family history of non-Hodgkin's lymphoma (mother) and prior exposure to 6-mercaptopurine, adalimumab, infliximab, vedolizumab, and natalizumab. A malignant neoplasm of the thymus was reported in a 62-year-old male patient who received 24 mg once daily induction treatment for 16 weeks, followed by 12 mg twice daily for 13 weeks; this patient had no family history of malignancy or prior exposure to 6-mercaptopurine, azathioprine, methotrexate, infliximab, and vedolizumab.

A 67-year-old male receiving 12 mg twice daily with a history of diabetes mellitus, smoking, and family history of myocardial infarction (MI) had an acute MI during the induction period. This event was assessed as severe and led to discontinuation of the study drug. During the maintenance period, a 55-year-old male with history of obesity, hypertension, diabetes mellitus, gout, and gastroesophageal reflux disease receiving 3 mg twice daily had a pneumonia aspiration adjudicated as an MI.

During the induction period, 2 acute, serious intestinal perforations with associated serious infections that required surgical intervention were reported, and both occurred in areas of active intestinal inflammation of CD in patients with worsening of disease being treated with upadacitinib and corticosteroids at baseline (24 mg once daily, event on day 36; 24 mg twice daily, event on day 41; no colonoscopy was performed near these events). No intestinal perforations occurred during the maintenance period. One patient receiving 3 mg twice daily developed a mesenteric vein thrombophlebitis during the induction period. No events of deep vein thrombosis or pulmonary embolism were observed.

No clinically meaningful changes from baseline in mean hemoglobin, leukocytes, neutrophils, transaminases, and creatinine concentrations were observed across all treatment arms by week 16 (Supplementary Table 4) or week 52 (Supplementary Table 5). Decreases in platelet counts were observed at week 16 in the upadacitinib 24 mg once daily group compared with placebo ($P < .1$). One patient in the 24 mg twice daily group had a transient grade 4 decrease (63 g/L) in hemoglobin after a total proctocolectomy. Two patients receiving 24 mg once daily discontinued the study because of nonserious anemia (each of mild and moderate severity). Four nonserious events of lymphocyte count decrease were reported, 1 each in the upadacitinib 12 (grade 1) and 24 mg twice daily (grade 3) arms during the induction period and 1 each in the 3 (grade 4) and 6 mg twice daily (grade 3) arms during the maintenance period; none of these led to discontinuation of the study drug. Significant elevations in total, low-density, and high-density cholesterol and creatinine phosphokinase (CPK) levels and decreases in triglyceride levels were observed in the upadacitinib 24 mg twice daily arm compared with the placebo group at week 16; total and low-density cholesterol levels were also significantly elevated in the 12 mg twice daily group vs placebo (Supplementary Table 4). Nonsignificant differences in laboratory values were observed between dose groups at week 52 (Supplementary Table 5). During the study, 15 AEs of CPK elevation were reported, all of which were of mild to moderate severity and were asymptomatic. One patient in the 12 mg twice daily arm had a >10-fold elevation in CPK levels from the upper limit of

normal with a concurrent acute event of bronchitis. No patients had rhabdomyolysis or discontinued the study drug because of increased CPK.

Discussion

CELEST was the first study to evaluate the efficacy, safety, pharmacokinetics, and dose-response of upadacitinib immediate-release formulation in patients with moderate to severe CD and refractory to TNF antagonist therapy using PRO-based clinical and endoscopic endpoints. The results of the induction period showed that the 3-mg, 12-mg, and 24-mg twice daily and 24-mg once daily upadacitinib doses were superior to placebo for endoscopic remission with significant dose-response relationships and, separately, that the 6-mg twice daily dose was superior to placebo for clinical remission 1.5/1.0 at the $P < .10$ level. Furthermore, maintenance treatment over 36 weeks was associated with continued clinical and endoscopic responses as well as decreases in markers of inflammation in patients who responded to the 16-week induction regimen.

During the induction period, the 24-mg twice daily dose exhibited the most consistent association with meaningful improvements for multiple clinical and endoscopic endpoints at weeks 12 or 16 (including endoscopic remission, endoscopic response 25%, clinical response, CR-70, combined clinical and endoscopic remission and response, corticosteroid-free clinical remission, and corticosteroid-free CDAI <150). Decreases in serum hs-CRP concentrations were observed, indicating a systemic anti-inflammatory effect that was consistent with the clinical and endoscopic findings. Furthermore, upadacitinib was also associated with improvements in quality of life, based on IBDQ, observed as early as week 8, further improved by week 16, and accompanied by achievement of IBDQ remission at the end of the induction period.

During the maintenance period, patients receiving the 12-mg twice daily dose had the highest, although nonsignificant, responses compared with the other upadacitinib doses. More than 63% of responders receiving 12 mg twice daily upadacitinib achieved most clinical, endoscopic, and quality of life endpoints at week 52. Among clinical responders, ≥41% of patients achieved the same endpoints at week 52. Furthermore, serum hs-CRP concentrations continued to decrease from baseline, indicating that the anti-inflammatory effect was maintained. Overall, these results suggest that in patients with active CD who for whom previous treatments have failed, continued use of JAK inhibitor therapy may induce and preserve remission over extended periods of time.

The identification of specific PRO endpoints that are relevant for patients with CD is of high interest to better evaluate individual patients with different levels of disease severity. We assessed 2 exploratory clinical and endoscopic endpoints in this study (clinical remission 2.8/1.0 and endoscopic response 50%) and observed a significant dose-response relationship in 5 of the 6 models used. These additional endpoints were determined from a post hoc analysis of a large data set of patients with moderately to severely active CD receiving adalimumab[15] and tested here with the intention of choosing clinically relevant PROs for use in future clinical trials. The more stringent clinical remission 1.5/1.0 definition, which was initially chosen as the coprimary endpoint for CELEST, was proposed by Khanna et al[14] and developed in patients with mild to moderate CD without exposure to TNF antagonists. Our results are consistent with the adalimumab analysis[15] and suggest that the clinical remission 1.5/1.0 endpoint is infrequently achieved in patients with moderate to severe, long-standing CD that was already refractory to drugs with known efficacy such as TNF antagonists, vedolizumab, and ustekinumab. The most statistically efficient measurement of endoscopic healing has not been established. In this study, both endoscopic remission and response 50% were more common in the patients receiving upadacitinib, but there was a more linear dose-response relationship evident with the endoscopic response 50%. These results indicate that different thresholds for the coprimary endpoints are useful in assessing efficacy in this patient population, especially because clearer dose-responses were observed with upadacitinib, whereas placebo rates essentially remained unchanged.

Nearly half of the patients enrolled in CELEST (44% [96/220]) were taking oral corticosteroids at baseline and underwent a mandatory taper starting at week 2. The intent was to determine if induction treatment with upadacitinib could facilitate earlier corticosteroid taper. Our results showed that a greater proportion of patients receiving upadacitinib were able to discontinue corticosteroids and achieve clinical remission 1.5/1.0 and CDAI <150 compared with placebo during the induction period. Although this could be considered an aggressive approach in this population with treatment-refractory disease, it further differentiated active treatment with upadacitinib from placebo. To our knowledge, this is the first time a JAK inhibitor or any therapy other than methotrexate has been shown to be effective in achieving corticosteroid-free clinical remission in an induction trial of CD.[19]

Upadacitinib plasma exposures with the twice daily doses of upadacitinib in patients with CD were consistent with the previously characterized upadacitinib pharmacokinetics in healthy participants and in patients with RA.[20–22] Furthermore, there were no time-dependent changes in upadacitinib plasma exposures during the study, consistent with the well-characterized pharmacokinetic profile of upadacitinib. In 2 dose-ranging studies of patients with RA, upadacitinib 6 and 12 mg twice daily appeared to maximize efficacy.[23,24] In contrast, in CELEST, the 24-mg twice daily induction dose was generally more effective, particularly for the endoscopic endpoints, hs-CRP, and quality of life measures in patients with moderately to severely active CD. The 24-mg once daily dose resulted in comparable average plasma concentrations to the 12-mg twice daily dose but significantly lower upadacitinib trough plasma concentrations than the 12-mg twice daily dose, which may explain the suboptimal efficacy noted for 24 mg once daily in numerous clinical

endpoints. This suggests the importance of maintaining exposure during the entire dosing interval. For this reason, an extended-release once daily formulation of upadacitinib has been developed to enhance patients' convenience and is currently being evaluated in multiple trials for various treatment indications.[25]

The AEs reported in this study were consistent with those previously observed in clinical trials with JAK inhibitors in patients with moderately to severely active inflammatory bowel disease[8,9,26] and RA.[23,24,27–31] No fatal AEs were observed during the study. Overall, the incidence of serious AEs and serious infections was highest with the 12 mg twice daily and 3 mg twice daily upadacitinib dose during the induction and maintenance periods, respectively. Infections and viral reactivation have been reported with JAK inhibitors previously,[27,28] and an increased risk of herpes zoster was reported with tofacitinib 10 mg twice daily.[32] An estimation of the risk and incidence of infections with upadacitinib exposure warrants additional evaluation in larger and long-term studies.

Two intestinal perforations were observed during the induction period and none during maintenance period of the CELEST study. Intestinal perforations were initially reported with tocilizumab[33] and tofacitinib[29] and may be related to an effect on IL-6, which plays an important function in the intestinal barrier. Additional identified risk factors for intestinal perforations include age, current and cumulative use of corticosteroids and nonsteroidal anti-inflammatory drugs, and complicated diverticular disease.[29,34] In CELEST, the 2 intestinal perforation events occurred in areas of active intestinal inflammation of CD in patients treated with upadacitinib and corticosteroids.

Two patients with cardiovascular risk factors had MI events, and 1 patient had a mesenteric vein thrombophlebitis, a rare complication of IBD. No events of deep vein thrombosis or pulmonary embolism were observed; however, this phase 2 study was limited in its ability to detect these rare events. Dose-dependent, meaningful increases in lipids and CPK were also observed. Similar effects were reported with drugs of the same class in prior trials of patients with CD,[9] ulcerative colitis,[21] and RA[35]; the mechanisms are currently unknown.

This phase 2 study provided long-term, double-blind data for safety and efficacy for the JAK inhibitor class in patients with CD. Although the sample size was sufficient to assess dose-response relationships for efficacy endpoints in the induction period, it was inadequate to fully evaluate some efficacy parameters, particularly more stringent measures, between individual upadacitinib doses and placebo or to characterize the safety of upadacitinib, which are typically addressed in a larger phase 3 program. The lack of placebo control during the maintenance period and small sample size, particularly for the 6-mg twice daily dose group, were limitations of this study. The threshold for statistical significance was set a priori at 0.1 for the purpose of this dose-finding study, with no multiplicity adjustment for the secondary endpoints; therefore, the potential for false positive findings was greater. Also, the stringency of the novel protocol-specified coprimary endpoints may have affected the evaluation of upadacitinib therapy. This study evaluated several other novel clinical and endoscopic endpoints based on recent regulatory guidance and post hoc analyses of existing data from other trials.[14,15] Further evaluation is needed to determine if these endpoints are optimal to differentiate between effective doses and placebo.

In conclusion, upadacitinib was superior to placebo primarily in inducing endoscopic improvements in patients with moderately to severely active long-standing CD and largely refractory to biologics. Furthermore, after achievement of response during a 16-week induction period, maintenance therapy with upadacitinib led to sustained clinical, endoscopic, and patient-reported benefits. Upadacitinib safety and efficacy in moderately to severely active CD will be further characterized in the phase 3 program.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.01.047.

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AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided after review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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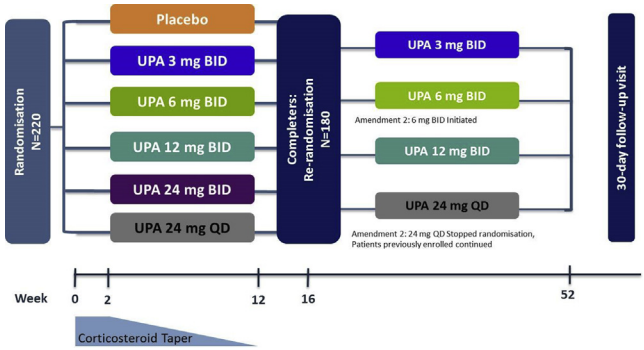
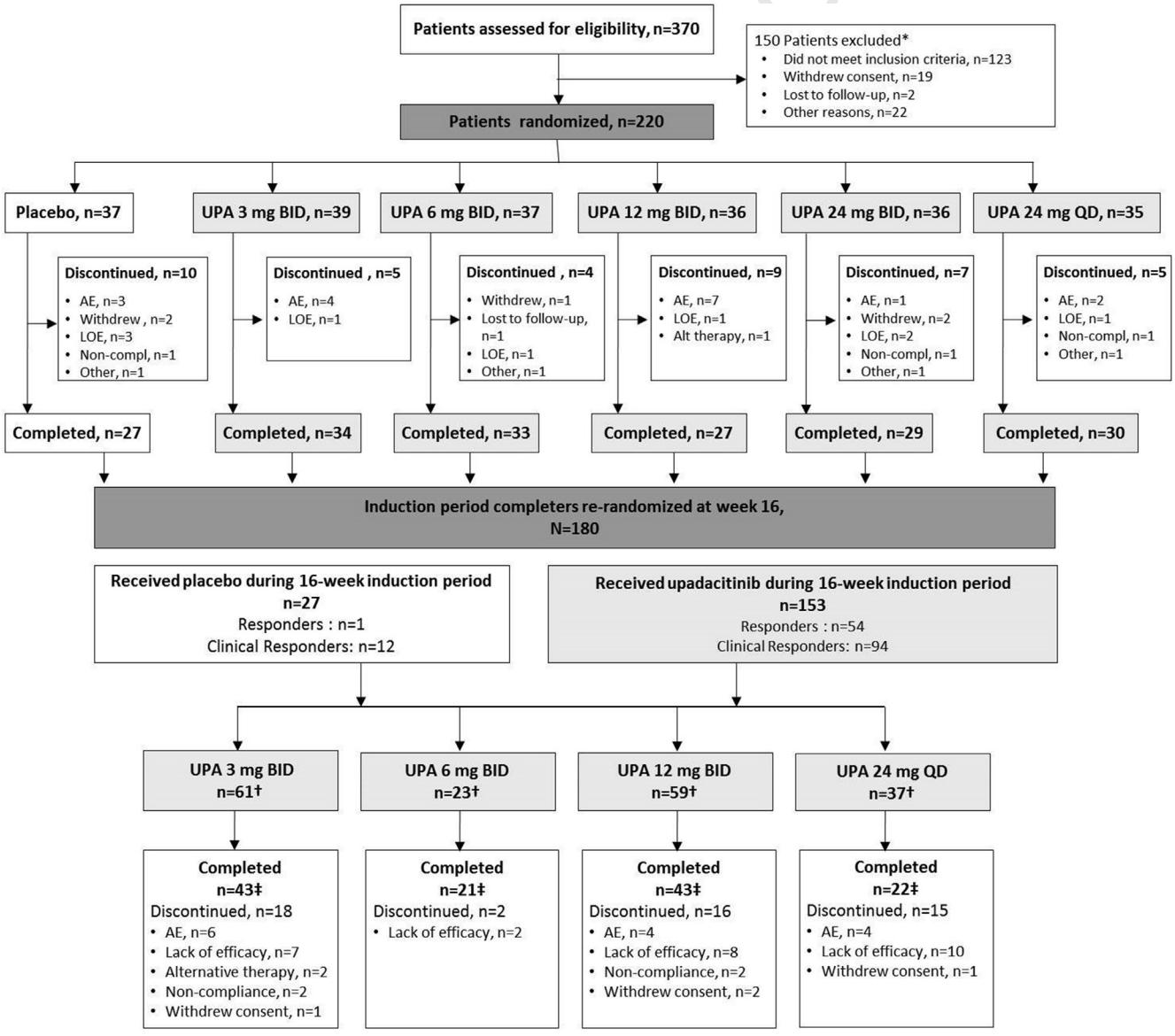
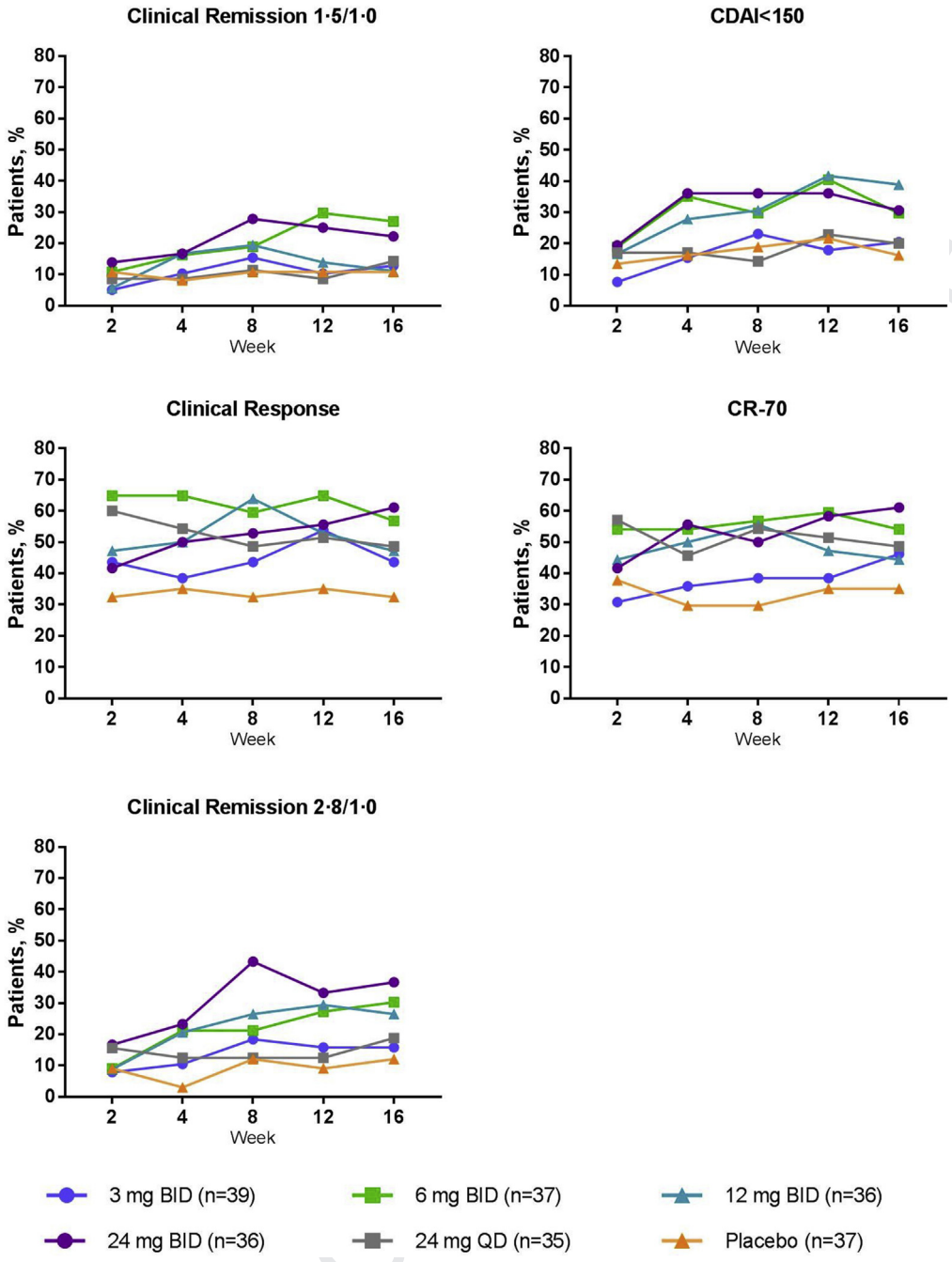


Supplementary Figure 1. CELEST study design. BID, twice daily; QD, once daily; UPA, upadacitinib.



Supplementary Figure 2. Patient disposition. *Some patients were excluded due to multiple reasons. †Received UPA during the induction period: 3 mg BID, n = 52 (responders: n = 20; clinical responders, n = 32); 6 mg BID, n = 18 (responders: n = 8; clinical responders, n = 14); 12 mg BID, n = 50 (responders: n = 16; clinical responders, n = 29); 24 mg QD, n = 33 (responders: n = 10; clinical responders, n = 19). ‡Completers among those who received UPA during induction period: 3 mg BID, n = 37; 6 mg BID, n = 16; 12 mg BID, n = 37; 24 mg QD, n = 18. Alt therapy, alternative therapy; BID, twice daily; LOE, lack of efficacy; Non-compl, noncompliance; QD, once daily; UPA, upadacitinib.



Supplementary Figure 3. Efficacy endpoints over time in the upadacitinib and placebo groups. Nonresponder imputation analysis. BID, twice daily; QD, once daily.

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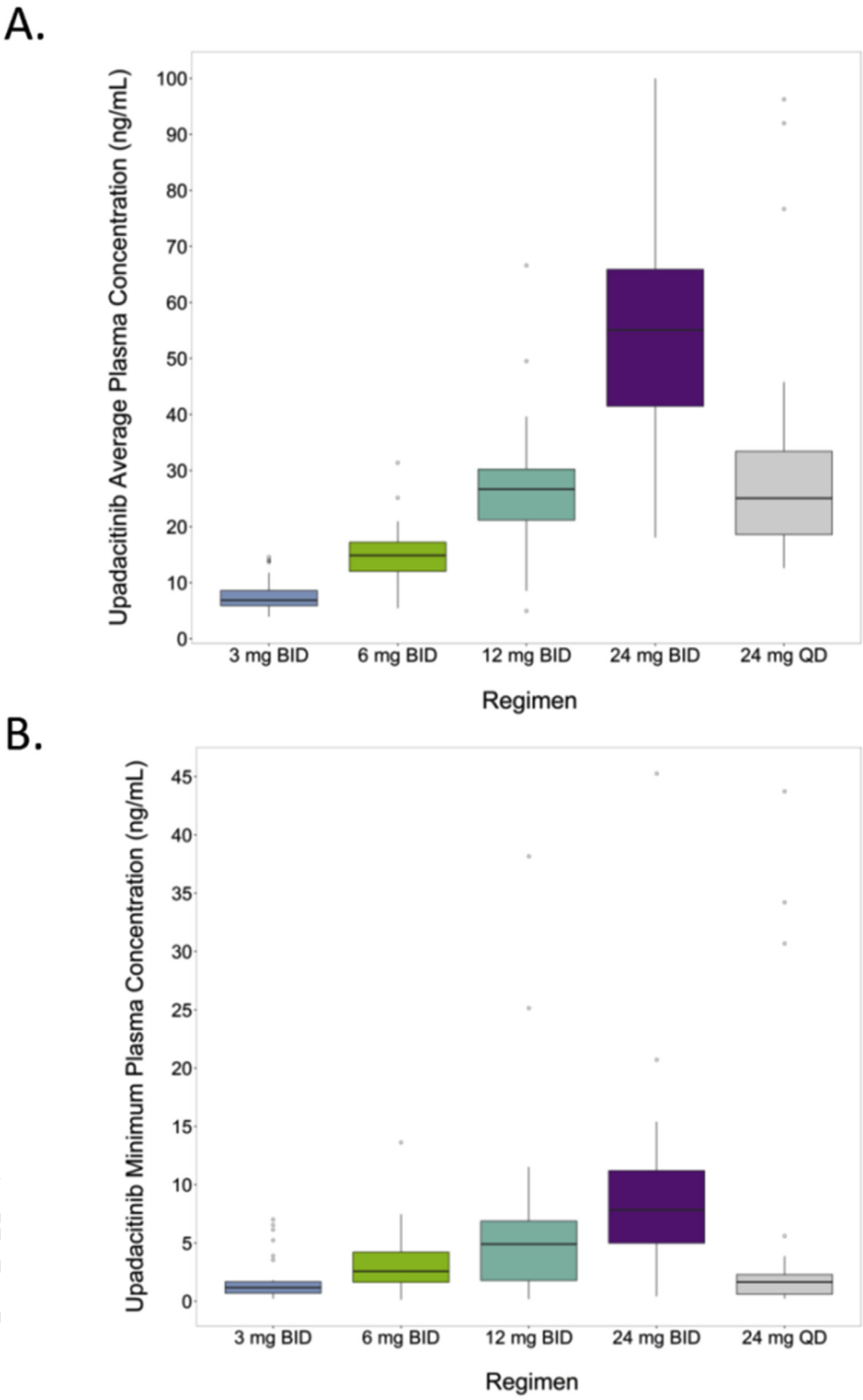

Supplementary Figure 4. Upadacitinib model-estimated plasma exposures for patients with CD in the CELEST Study. (*A*) Upadacitinib average plasma concentration over a dosing interval by dose and (*B*) upadacitinib minimum plasma concentration during a dosing interval by dose. BID, twice daily; QD, once daily.

Supplementary Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
1. Male or female ≥18 and ≤75 years of age at baseline
2. Diagnosis of ileal, colonic, or ileocolonic CD for ≥3 months before baseline confirmed by endoscopy during the screening period or endoscopy performed within 15 days of the screening visit. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the investigator, must be available
3. Average daily liquid/very soft SF score ≥2.5 daily or average daily AP score ≥2.0
4. CDAI score ≥220 and ≤450
5. SES-CD ≥6 (or ≥4 for patients with disease limited to the ileum), confirmed by a central reader. A video-recorded ileocolonoscopy performed within 15 days before screening can be used for the local and central reader assessment
6. Patient has inadequately responded to or experienced intolerance to previous treatment with immunomodulators (eg, azathioprine, 6-MP, MTX) and/or an anti-TNF agent (eg, infliximab, adalimumab, certolizumab pegol). The clinical measures that defined inadequate response should be based on the physician/investigator clinical assessment. Criteria for inadequate response to or experienced intolerance to previous treatment with an immunomodulator or anti-TNF agent defined as: • Signs and symptoms of persistently active disease despite a history of induction regimen with 1 of the following agents: o At least a consecutive 42-day course of azathioprine, 6-MP, or injectable MTX before baseline, with a stable dose for at least 28 days before baseline of azathioprine ≥1.5 mg/kg/d or 6-MP ≥1 mg/kg/d (rounded to the nearest available tablet or half-tablet formulation or a documented 6-TGN level of at least 230 pmol/8 × 10^8 RBC or higher on the current dosing regimen) or MTX ≥15 mg/week (SC/IM), or a dose that is the highest tolerated by the patient (eg, due to leukopenia, elevated liver enzymes, nausea) during that time o At least 1 6-week induction with infliximab: 5 mg/kg IV, 2 doses at least 2 weeks apart o At least 1 4-week induction with adalimumab: one 160-mg SC dose (or 80-mg SC dose in approved countries) followed by one 80-mg SC dose (or 40-mg SC dose in approved countries) followed by one 40-mg dose at least 2 weeks apart o At least one 4-week induction with certolizumab pegol: 400 mg SC, 2 doses at least 2 weeks apart OR o Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify) OR o History of intolerance of at least one TNF antagonist (including, but not limited to, infusion-related reaction, demyelination, congestive heart failure, and infection)
7. Patient has a negative TB screening assessment result. If the patient has evidence of a latent TB infection, the patient must initiate and complete a minimum of 2 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis or have documented completion of a full course of anti-TB prophylaxis, before baseline Q38
8. A negative serum pregnancy test result for all female patients at the screening visit and a negative urine pregnancy test result for all female patients of childbearing potential at baseline before the first dose of study drug Q39
9. If female, patient must be either postmenopausal OR permanently surgically sterile OR, for women of childbearing potential, practicing at least 1 protocol-specified method of birth control that is effective from study day 1 through at least 180 days after the last dose of study drug
10. Male patients who are sexually active with female partner(s) of childbearing potential must agree from study day 1 through 90 days after the last dose of study drug to practice the protocol-specified contraception
11. Patient must be able and willing to give written informed consent and to comply with the requirements of this study protocol
12. Patient is judged to be in otherwise good health as determined by the principal investigator based on the results of medical history, laboratory profile, physical examination, and a 12-lead ECG performed during screening
Exclusion criteria
1. Patient with a current diagnosis of UC, collagenous colitis, or indeterminate colitis
2. Patient with previous exposure to JAK inhibitor (eg, tofacitinib, baricitinib)
3. Patients who discontinued biologic therapy such as infliximab (Remicade), certolizumab (Cimzia), adalimumab (Humira), vedolizumab (Entyvio), or natalizumab (Tysabri) <8 weeks before baseline. Patients who discontinued ustekinumab (Stelara) <12 weeks before baseline Q40
4. Patient received azathioprine or 6-MP within 10 days of baseline
5. Patient who previously or currently uses oral aminosalicylates or MTX and meets 1 of the following criteria: • Has not been on stable doses for at least 14 days before baseline; or • Has discontinued use of aminosalicylates or MTX within 14 days of baseline
6. Patient who previously or currently uses oral corticosteroid and meets 1 of the following criteria: • Is receiving prednisone or prednisone equivalent >30 mg/day within 7 days of baseline; • Is receiving budesonide >9 mg/day within 7 days of baseline; • Has discontinued use of corticosteroid within 7 days of baseline; • Has not been on stable doses of corticosteroid for at least 7 days before baseline; or • Has been taking both oral budesonide and oral prednisone (or equivalent) simultaneously
7. Received IV corticosteroids within 14 days before screening or during the screening period
8. Patient on probiotics who has not been on stable dose for at least 14 days before baseline
9. Patient who previously or currently uses CD-related antibiotics and meets 1 of the following criteria: • Has not been on stable doses for at least 14 days before baseline; • Has discontinued CD-related antibiotics within 14 days of baseline
10. Patient received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days before baseline
11. Patient has received therapeutic enema or suppository, other than required for endoscopy, within 7 days before screening and/or during the screening period

Supplementary Table 1. Continued

Exclusion criteria
12. Patient who has had surgical bowel resections within the past 6 months or is planning any resection while enrolled in the study
13. Patient with an ostomy, ileoanal pouch, or symptomatic bowel stricture
14. Patient with an abdominal or perianal abscess
15. Patient who has short bowel syndrome
16. Patient who previously received stem cell transplantation in the past 3 months or patient who previously received fecal microbial transplantation in the past 1 month
17. Patient who received NSAIDs (except topical NSAIDs and the use of low-dose aspirin for cardiovascular protection) within 14 days before screening and during the screening visit
18. Infection(s) requiring treatment with IV anti-infectives within 30 days before the baseline visit or oral anti-infectives within 14 days before the baseline visit
19. Patient currently receiving TPN or plans to receive TPN at any time during the course of the study
20. Patient with positive *Clostridium difficile* toxin stool assay result during the screening period
21. Screening laboratory tests and other analyses show any of the following abnormal results:
• Serum AST or ALT >2.5 × the ULN
• Estimated glomerular filtration rate by simplified 4-variable MDRD formula <40 mL/min/1.73 m2
• Total WBC count <3000/μL
• ANC <1200/μL
• Platelet count <100,000/μL
• Absolute lymphocytes count <750/μL
• Hemoglobin <9 gm/dL
22. Any active or recurrent viral infection that, based on the investigator's clinical assessment, makes the patient an unsuitable candidate for the study, including recurrent/disseminated herpes zoster or known history of HIV
23. Hepatitis B (HBs antigen positive [+] or detected sensitivity on the HBV DNA PCR qualitative test for HBc antibody–positive patients) or hepatitis C virus (HCV RNA detectable in any patient with anti-HCV antibodies)
24. Patient with active or chronic recurring infections or untreated latent TB
25. History of moderate to severe congestive heart failure (NYHA class III or IV), cerebrovascular accident, and any other condition within 6 months that, in the opinion of the investigator, would put the patient at risk by participation in the study
26. Use of known strong CYP3A inhibitors (eg, clarithromycin, conivaptan, itraconazole, ketoconazole, posaconazole, telithromycin, voriconazole, grapefruit juice) or strong CYP3A inducers (eg, rifampin, carbamazepine, phenytoin, St. John's Wort) from screening through the end of the study
27. Receipt of any live vaccine within 1 month before the screening visit or will require live vaccination during study participation, including up to 1 month after the last dose of study drug
28. Evidence of current colonic dysplasia, history of high-grade colonic dysplasia, or history of malignancy (including of the gastrointestinal tract) other than a successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix
29. Has had any uncontrolled and/or clinically significant (per investigator's judgment) illness or has had any surgical procedure within 30 days before screening
30. Positive pregnancy test result at screening (serum) or baseline (urine)
31. Female patients who are breastfeeding or considering becoming pregnant during the study
32. Patient is considered by the investigator, for any reason, to be an unsuitable candidate for the study
33. Patient who received any investigational agent or procedure within 30 days or 5 half-lives before baseline, whichever is longer
34. History of clinically significant drug or alcohol abuse in the last 12 months

6-MP, 6-mercaptopurine; 6-TGN, 6-thioguanine nucleotide; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CYP3A, cytochrome P45a 3A; ECG, electrocardiogram; HBV, hepatitis B virus; HCV, hepatitis C virus; IM, intramuscular; IV, intravenous; MDRD, modification of diet in renal disease; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; NYHA, New York Heart Association; PCR, polymerase chain reaction; RBC, red blood cell; SC, subcutaneous; TB, tuberculosis; TPN, total parenteral nutrition; UC, ulcerative colitis; ULN, upper limit of normal; WBC, white blood cell.

Supplementary Table 2. Mandatory Corticosteroid Taper Starting on Week 2

Prednisone (or equivalent)	The taper consisted of a weekly decrease of prednisone (or equivalent) by 5 mg/d for doses >10 mg/d until 10 mg/d was reached, then a weekly decrease by 2.5 mg/day until discontinuation.
Budesonide	Budesonide was decreased by 3 mg every week.

NOTE. If patients experienced an inadequate response during corticosteroid taper, the dose could be increased according to the investigator's discretion; however, if the dose was higher than the baseline dose, patients would be censored for efficacy.

Supplementary Table 3. Clinical and Endoscopic Endpoints at Week 52 Among Responders or Clinical Responders in Patients Randomized to Upadacitinib During the Induction Period

	Responders (n = 54)				Clinical Responders (n = 94)			
Endpoints	3 mg BID n = 20	6 mg BID n = 8	12 mg BID n = 16	24 mg QD n = 10	3 mg BID n = 32	6 mg BID n = 14	12 mg BID n = 29	24 mg QD n = 19
Endpoint at week 52								
Clinical response, n (%)	11 (55)	7 (88)	11 (69)	5 (50.0)	16 (50)	10 (71)	18 (62)	8 (42)
CR-70, n (%)	11 (55)	6 (75)	12 (75)	4 (40)	15 (47)	10 (71)	18 (62)	7 (37)
Endoscopic response 25%, n (%)	12 (60)	6 (75)	12 (75)	4 (40)	13 (41)	8 (57)	16 (55)	8 (42)
Remission, n (%)	4 (20)	1 (13)	4 (25)	0	4 (13)	1 (7)	4 (14)	3 (16)
Response, n (%)	10 (50)	5 (63)	11 (69)	10 (40)	11 (34)	6 (43)	15 (52)	7 (37)
Clinical remission 1.5/1.0 in patients with SF ≥2.5 and AP ≥2.0 at baseline, n (%)	3 (33) n = 9	2 (33) n = 6	4 (50) n = 8	1 (20) n = 5	4 (24) n = 17	3 (30) n = 10	6 (40) n = 15	3 (33) n = 9
Clinical remission 2.8/1.0 in patients with isolated ileal disease, n (%)	2 (67) n = 3	NA n = 0	0 n = 1	NA n = 0	2 (33) n = 6	1 (50) n = 2	0 n = 3	0 n = 1
hs-CRP, change from baseline to week 52, LOCF data, mean ± SD (median)	−4.3 ± 22.7 (−0.4) n = 19	−7.0 ± 12.7 (−1.1)	−20.4 ± 18.8 (−17.2)	6.2 ± 35.8 (−3.1) n = 9	−2.8 ± 18.9 (−0.2) n = 30	−2.1 ± 18.4 (−1.1)	−13.9 ± 37.1 (−8.0) n = 28	10.2 ± 55.7 (0.0) n = 17
Fecal calprotectin, change from baseline to week 52, LOCF data, mean ± SD (median)	−51.9 ± 2651.0 (−422.0) n = 16	−524.1 ± 521.3 (−235.0) n = 7	−3047.5 ± 2509.3 (−2305.5) n = 10	−2371.8 ± 3787.0 (−748.0) n = 4	1.0 ± 2457.2 (−100.5) n = 26	−239.3 ± 1443.1 (−188.5) n = 12	−2617.4 ± 3232.0 (−1879.0) n = 18	−1510.3 ± 2773.9 (−120.5) n = 10
IBDQ, change from baseline to week 52, observed data, mean ± SD (median)	43.9 ± 38.1 (40.0) n = 14	56.4 ± 14.5 (51.5)	82.3 ± 35.6 (83.5) n = 14	45.3 ± 49.9 (37.0) n = 7	42.8 ± 44.1 (33.0) n = 22	46.6 ± 27.8 (48.0) n = 13	70.7 ± 47.0 (80.0) n = 23	26.6 ± 53.1 (9.5) n = 14
Endpoints in patients with corticosteroid use at baseline	3 mg BID n = 8	6 mg BID n = 2	12 mg BID n = 8	24 mg QD n = 5	3 mg BID n = 15	6 mg BID n = 6	12 mg BID n = 14	24 mg QD n = 8
Corticosteroid-free clinical remission 1.5/1.0, n (%)	2 (25)	2 (100)	5 (63)	0	4 (27)	3 (50)	6 (43)	1 (13)
Corticosteroid-free endoscopic remission	2 (25)	0	4 (50)	0	2 (13)	1 (17)	5 (36)	1 (13)
Corticosteroid-free remission at week, n (%)	2 (25)	0	3 (38)	0	2 (13)	0	3 (21)	1 (13)

NOTE. Data are n (%) using nonresponder imputation unless indicated otherwise. Clinical responders were defined as patients who achieved clinical response at week 16, and responders were defined as patients who achieved both clinical response and endoscopic response 25% at week 16. Clinical remission 1.5/1.0 was defined as average daily very soft/liquid SF ≤1.5 and average daily AP score ≤1, without worsening from baseline. Clinical remission 2.8/1.0 was defined as average daily very soft/liquid SF ≤2.8 and average daily SP score ≤1, neither worse than baseline, among patients with baseline average daily very soft/liquid SF ≥4.0 or average daily AP score ≥2.0. Clinical response was defined as ≥30% reduction from baseline in average daily very soft/liquid SF and/or average daily AP score, neither worse than baseline. Remission was defined as combined clinical remission 1.5/1.0 and endoscopic remission, and response was defined as combined clinical response and endoscopic response 25%.

BID, twice daily; LOCF, last observation carried forward; NA, not applicable; QD, once daily; SD, standard deviation.

[a]Risk difference: upadacitinib higher dose vs upadacitinib 3 mg BID.

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Supplementary Table 4. Changes From Baseline in Laboratory Values at Week 16

Laboratory parameter	Placebo n = 37	Upadacitinib 3 mg BID n = 39	Upadacitinib 6 mg BID n = 37	Upadacitinib 12 mg BID n = 36	Upadacitinib 24 mg BID n = 36	Upadacitinib 24 mg QD n = 35
Hemoglobin, *g/L*						
Mean ± SD	2.3 ± 9.6	0.9 ± 10.5	−1.3 ± 10.6	1.0 ± 14.5	−1.4 ± 9.9	−1.4 ± 11.4
Median	0.5	1.0	−2.0	1.0	−2.0	−2.0
Lymphocytes, cells $\times 10^9$/L						
Mean ± SD	−0.03 ± 0.72	−0.08 ± 0.66	−0.03 ± 0.99	−0.40 ± 1.04	−0.24 ± 1.01	−0.27 ± 0.84
Median	0.00	−0.01	−0.18	−0.07	−0.12	−0.19
Neutrophils, cells $\times 10^9$/L						
Mean ± SD	−0.61 ± 3.15	−0.61 ± 2.91	−1.22 ± 2.99	−1.16 ± 3.95	−1.26 ± 2.81	−1.05 ± 2.81
Median	−0.35	−0.16	−0.74	−1.51	−1.38	−0.62
Platelets count, $\times 10^9$/L						
Mean ± SD	25.9 ± 71.2	2.4 ± 65.3	−3.9 ± 97.1	11.6 ± 116.9	24.4 ± 52.5	−12.4 ± 85.5[a]
Median	13.0	13.0	1.0	26.0	17.0	−6.0
ALT, *U/L*						
Mean ± SD	2.1 ± 31.1	3.3 ± 20.5	−1.3 ± 22.5	7.4 ± 13.9	4.1 ± 12.1	5.4 ± 17.5
Median	0.0	−2.0	2.0	2.0	4.0	3.0
AST, *U/L*						
Mean ± SD	4.5 ± 20.6	6.4 ± 23.9	4.9 ± 14.2	6.0 ± 9.4	9.0 ± 9.0	5.6 ± 11.0
Median	1.0	1.5	6.0	6.0	8.0	1.1
Creatinine, *μmol/L*						
Mean ± SD	3.7 ± 7.7	0.3 ± 9.6	4.6 ± 14.3	7.5 ± 25.6	1.7 ± 6.8	3.8 ± 9.8
Median	5.2	0.1	1.0	1.2	2.4	3.1
CPK, *U/L*						
Mean ± SD	−9.1 ± 49.7[a]	164.1 ± 822.8	82.1 ± 84.5	106.0 ± 115.4	228.0 ± 434.5[b]	78.8 ± 229.7
Median	1.0	17.0	54.0	82.0	113.0	31.0
Total cholesterol, *mmol/L*						
Mean ± SD	−0.10 ± 0.68	0.19 ± 0.81	0.17 ± 0.77	0.44 ± 0.94[b]	0.70 ± 0.68[c]	0.29 ± 0.78
Median	0.08	0.15	0.25	0.54	0.75	0.21
HDL cholesterol, *mmol/L*						
Mean ± SD	−0.02 ± 0.34	0.13 ± 0.48	0.05 ± 0.35	0.15 ± 0.28[a]	0.48 ± 0.47[c]	0.01 ± 0.26
Median	−0.06	−0.04	0.07	0.18	0.49	0.03
LDL cholesterol, mmol/L						
Mean ± SD	−0.01 ± 0.47	0.05 ± 0.51	0.15 ± 0.57	0.43 ± 0.69[d]	0.42 ± 0.48[d]	0.20 ± 0.62
Median	0.00	0.08	0.21	0.37	0.44	0.27
Triglyceride, *mmol/L*						
Mean ± SD	0.09 ± 0.68	0.09 ± 0.61	−0.08 ± 0.63	−0.28 ± 0.86[a]	−0.43 ± 0.67[b]	0.40 ± 1.18
Median	0.17	−0.03	−0.13	−0.30	−0.26	0.25

ALT, alanine aminotransferase; AST, aspartate aminotransferase. BID, twice daily; HDL, high-density lipoprotein; LDL, low-density lipoprotein; QD, once daily; SD, standard deviation.

[a]Significant differences with placebo at $P < .1$.

[b]Significant differences with placebo at $P < .05$.

[c]Significant differences with placebo at $P < .001$.

[d]Significant differences with placebo at $P < .01$.

Supplementary Table 5. Changes From Baseline in Laboratory Values at Week 52

Laboratory parameter	3 mg BID n = 42	6 mg BID n = 21	12 mg BID n = 43	24 mg QD n = 24
Hemoglobin, *g/L*				
Mean ± SD	0.7 ± 11.7	−2.5 ± 12.5	1.9 ± 13.8	1.8 ± 14.6
Median	0.0	−5.0 n = 17	4.0	5.0
Lymphocytes, cells $\times 10^9$/L				
Mean ± SD	−0.4 ± 0.7	−0.4 ± 0.7	−0.5 ± 0.9	−0.1 ± 0.9
Median	−0.3	−0.2 n = 17	−0.4	0.0
Neutrophils, cells $\times 10^9$/L				
Mean ± SD	−1.6 ± 3.2	−0.2 ± 2.7	−1.2 ± 3.4	−1.6 ± 3.8
Median	−1.6	0.0 n = 17	−1.1	−1.6
Platelets count, $\times 10^9$/L				
Mean ± SD	−15.0 ± 112.3	−0.3 ± 73.9	−14.9 ± 115.7	−11.3 ± 136.0
Median	8.0	−12.0 n = 17	−7.0	−24.0
ALT, *U/L*				
Mean ± SD	4.9 ± 33.8	3.8 ± 18.6	9.8 ± 23.8	5.5 ± 17.5
Median	3.0	0.0 n=19	5.0	7.0
AST, *U/L*				
Mean ± SD	5.7 ± 18.7	4.3 ± 9.5	11.8 ± 14.6	9.8 ± 18.6
Median	4.0	3.0 n = 20	10.0	11.0 n = 23
Creatinine, *μmol/L*				
Mean ± SD	4.6 ± 9.5	4.2 ± 10.2	3.9 ± 11.2	1.7 ± 8.9
Median	3.2	5.1	3.5	3.8
CPK, *U/L*				
Mean ± SD	122.9 ± 205.6	165.0 ± 543.6	99.8 ± 118.1	171.9 ± 333.6
Median	72.0	36.0	90.0	85.5
Total cholesterol, *mmol/L*				
Mean ± SD	0.22 ± 1.05	0.38 ± 1.08	0.67 ± 0.85	0.42 ± 0.83
Median	0.23	0.28	0.75	0.48
HDL cholesterol, *mmol/L*				
Mean ± SD	0.08 ± 0.31	0.13 ± 0.42	0.21 ± 0.31	0.10 ± 0.32
Median	0.10	0.19	0.18	0.10
LDL cholesterol, *mmol/L*				
Mean ± SD	0.15 ± 0.89	0.33 ± 0.90	0.49 ± 0.64	0.29 ± 0.60
Median	0.12 n = 40	0.24	0.57	0.27
Triglyceride, *mmol/L*				
Mean ± SD	0.21 ± 1.75	−0.31 ± 0.97	−0.08 ± 0.66	0.09 ± 0.64
Median	0.04	−0.09	0.03	0.12

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; HDL, high-density lipoprotein; LDL, low-density lipoprotein; QD, once daily; SD, standard deviation.