Upadacitinib Was Efficacious and Well-tolerated Over 30 Months in Patients With Crohn's Disease in the CELEST Extension Study

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BACKGROUND & AIMS: **The long-term efficacy and safety of upadacitinib was evaluated in an open-label extension (OLE) of a phase II, double-blind, randomized trial of patients with Crohn's disease.**

METHODS: **Patients who completed the 52-week study (CELEST) received upadacitinib in the CELEST OLE as follows: those who had received immediate-release upadacitinib 3, 6, or 12 mg twice daily or 24 mg once daily (QD) received extended-release upadacitinib 15 mg QD and those who had received immediate-release upadacitinib 12 or 24 mg twice daily as rescue therapy received extended-release upadacitinib 30 mg QD. If any patient initiating upadacitinib 15 mg QD in CELEST OLE lost response at or after week 4, the dose was escalated to upadacitinib 30 mg QD (dose-escalated group). Clinical, endoscopic, inflammatory and quality-of-life measures were assessed.**

RESULTS: **A total of 107 CELEST study completers entered CELEST OLE. The proportion of patients with clinical remission 2.8/1.0 was maintained between week 0 and month 30 in all groups (month 30: 15 mg, 61%; 30 mg, 54%; dose-escalation, 55%). Endoscopic response was maintained in all groups (month 24: 68%, 67%, and 40%, respectively). The rates of adverse events (AEs), serious AEs, AEs leading to discontinuation, infections, serious infections, herpes zoster, and creatine phosphokinase elevation were higher with upadacitinib 30 mg vs 15 mg.**

CONCLUSION: **Sustained long-term benefit at 30 months and further endoscopic improvements to month 24 were observed in patients with Crohn's disease receiving upadacitinib. Safety over 30 months was consistent with the known safety profile of upadacitinib. Clinicaltrials.gov ID no: NCT02782663.**

Keywords: ABT-494; CDAI; IBD; JAK inhibitor.

Crohn's disease (CD) is a chronic, progressive, inflammatory disease of the gastrointestinal tract, characterized by relapsing and remitting symptoms that, over time, may lead to complications, such as strictures, fistulas, abscesses, bowel damage, and disability.[1] Current treatment strategies aim to induce and maintain clinical and endoscopic remission, and prevent intestinal complications.[1–3] Endoscopic healing of the intestinal mucosa improves long-term clinical outcomes by reducing rates of relapse, the need for surgery, and progression of bowel damage.[1,4]

Currently available treatments for CD include corticosteroids, immunosuppressants, and biological therapies, such as tumor necrosis factor (TNF) and interleukin-12/23 inhibitors, and anti-integrin drugs.[1,3] Despite the diversity of available therapies, many patients fail to respond or lose their response because of

Abbreviations used in this paper: **AE, adverse event; AP, abdominal pain; BID, twice daily; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; E/100 PY, events per 100 patient-years; FCP, fecal calprotectin; hsCRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; JAK, Janus kinase; OLE, open-label extension; QD, once daily; QoL, quality of life; SES-CD, Simple Endoscopic Score for CD; SF, stool frequency; TNF, tumor necrosis factor.**

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the emergence of anti-drug antibodies or non-immune-mediated pharmacokinetic/pharmacodynamic mechanisms.[3] These treatments may be associated with adverse events (AEs) that limit their use.[5]

Upadacitinib (ABT-494) is an orally administered, selective, reversible inhibitor of Janus kinase (JAK) 1 that downregulates multiple proinflammatory cytokines involved in the pathogenesis of CD.[6,7] The specificity of upadacitinib for JAK 1 inhibition may result in a differential modulation of the inflammatory response and fewer immunosuppressive AEs compared with inhibitors with a broader range.[6]

CELEST was a 52-week, multicenter, randomized, double-blind, dose-ranging, phase II clinical trial (NCT02365649, EudraCT 2014-003240-12) in adults with active, moderate-to-severe CD who were refractory to immunosuppressants or TNF antagonists.[8] Significantly more patients receiving upadacitinib achieved endoscopic remission at week 16 vs those receiving placebo. Through week 52, efficacy was maintained for most study endpoints, and the safety profile of upadacitinib was comparable with that seen in clinical trials in rheumatoid arthritis.[8]

The ongoing CELEST open-label extension (CELEST OLE) study is a continuation of CELEST designed to evaluate the long-term (up to 96 months) efficacy and safety of upadacitinib. Efficacy and safety outcomes after 30 months of open-label treatment with upadacitinib are reported here.

What You Need to Know

Background

- Despite the availability of several therapies for Crohn's Disease (CD), many patients fail to respond or lose their response over time.
- Upadacitinib is an orally administered, selective, reversible inhibitor of Janus kinase 1 that demonstrated efficacy in CD over 52 weeks in the CELEST study.

Findings

- The results of CELEST open-label extension demonstrated that clinical and endoscopic remission and response were, in general, sustained with long-term upadacitinib therapy over 3.5 years of follow-up.
- Safety profile was similar as reported previously with upadacitinib in CD and other inflammatory conditions.

Implications for patient care

- Long-term treatment with upadacitinib leads to sustained clinical and endoscopic improvements, decreased inflammation, and increased patient-reported benefits, suggesting it is a potential treatment for patients with CD refractory to tumor necrosis factor therapy.

Methods

Study Design

CELEST OLE is an ongoing, 96-month, phase II, multicenter study (NCT02782663, EudraCT 2015-003759-23) that enrolled patients who had completed the 52-week CELEST study (Supplementary Figure 1).[8] Completers received open-label treatment with the once-daily extended-release formulation of upadacitinib starting at week 0 (week 52 of CELEST) according to the dose received during the CELEST study as follows: patients who received double-blind immediate-release upadacitinib at doses of 3, 6, or 12 mg twice daily (BID) or 24 mg once daily (QD) in CELEST received open-label extended-release upadacitinib 15 mg QD; patients who received open-label immediate-release upadacitinib 12 or 24 mg BID as rescue therapy in CELEST received open-label extended-release upadacitinib 30 mg QD. At or after week 4, patients who initiated with upadacitinib 15 mg QD and experienced an inadequate response without safety concerns could, at the discretion of the investigator, have their dose increased to 30 mg QD (ie, dose-escalated group). Patients who initiated with upadacitinib 30 mg QD and experienced an inadequate response could be withdrawn from the study at the investigator's discretion. Inadequate response was defined as an average daily liquid/soft stool frequency (SF) of >2.2 or an average daily abdominal pain (AP) score of >1.8 plus ≥ 1 of the following: an increase in the level of high-sensitivity C-reactive protein (hsCRP) of ≥ 1 mg/L from week 0 of the CELEST OLE study, hsCRP ≥ 5 mg/L, fecal calprotectin (FCP) >250 μg/g either at the current or previous visit, or a Simple Endoscopic Score for CD (SES-CD) ≥ 6 (excluding the narrowing component) or ≥ 4 for isolated ileal disease, as scored by the investigator (the latter criterion was added following a protocol amendment). Initiation or increase in the dose of CD-related medications, including corticosteroids, aminosalicylates, methotrexate, or CD-related antibiotics were allowed as rescue therapy at the investigator's discretion. Azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus, and biologics were not permitted as rescue treatment. Patients could be discontinued from the study if they continued to meet the criteria for inadequate response after adjustment of rescue therapy.

Patients in the dose-escalated group had the option of deescalating treatment to 15 mg QD after ≥ 3 months if they had normal hsCRP, FCP <150 μg/g at the current or last visit, and either an average daily SF ≤ 1.5 or an AP score ≤ 1.0 and neither worse than at baseline of the CELEST OLE study.

The study protocol was reviewed and approved by an independent ethics committee or independent review board. The study was conducted in accordance with the International Council for Harmonization guidelines and the ethical principles of the Declaration of Helsinki, Good Clinical Practice, and applicable local regulations. All patients provided written study-specific informed consent before any study-related procedures. All authors had access to the study data and reviewed and approved the final manuscript.

Participants

Patients entering CELEST OLE on stable doses of aminosalicylates and methotrexate were required to continue their medication with the option of decreasing or discontinuing at the investigator's discretion in the event of disease remission or adverse reactions. CD-related antibiotics and/or probiotics that were taken during CELEST could be discontinued at the investigator's discretion. Patients taking concomitant corticosteroids, who showed clinical response, could begin corticosteroid taper at week 12, and those who had started corticosteroid taper during the CELEST study could, at the discretion of the investigator, continue to taper after entering CELEST OLE.

Patients were ineligible for CELEST OLE if they had a current or previous malignancy other than successfully treated non-metastatic cutaneous squamous cell, basal cell, and/or localized carcinoma in situ of the cervix. Patients with colonoscopy results at week 12/16 or 52 of CELEST showing evidence of dysplasia or malignancy were excluded from CELEST OLE. Patients with poorly controlled conditions that would put the patient at risk, such as diabetes mellitus, unstable ischemic heart disease, moderate or severe congestive heart failure, or cerebrovascular events, were also excluded.

Outcomes

Study visits occurred at week 0, months 1 and 3, and every 3 months thereafter. Ileocolonoscopies were performed at week 0 and months 12 and 24. Prespecified endpoints for CELEST OLE included clinical remission 2.8/1.0 (defined as SF $\leq$2.8 and AP score $\leq$1.0, neither worse than at CELEST study baseline, among patients with SF $\geq$4 or AP score $\geq$2.0 at CELEST study baseline); enhanced clinical response (defined as $\geq$65% reduction in SF from CELEST study baseline, or $\geq$35% reduction in AP score from CELEST study baseline and neither worse than baseline); Crohn's Disease Activity Index (CDAI) remission (CDAI $<$150); endoscopic remission (defined as SES-CD $\leq$4 and $>$2-point reduction from CELEST study baseline, and no subscore $>$1); endoscopic response 50% (defined as $>$50% reduction in SES-CD from CELEST study baseline or endoscopic remission); mean change in SES-CD from CELEST study baseline; steroid-free CDAI remission (steroid-free for 90 days with CDAI $<$150); steroid-free clinical remission 2.8/1.0 (steroid-free for 90 days with SF $\leq$2.8 and AP score $\leq$1.0, neither worse than CELEST study baseline among patients with SF $\geq$4 or AP score $\geq$2.0 at baseline); Inflammatory Bowel Disease Questionnaire (IBDQ) remission (IBDQ $\geq$170); and median change in hsCRP and FCP from CELEST study baseline. A more stringent endpoint of remission (defined as clinical remission 2.8/1.0 and endoscopic remission) was also assessed.

Occurrence of AEs, vital signs, and laboratory values were recorded throughout the study. AEs in proportion of patients and events per 100 patient-years (E/100 PY) were reported (coded using preferred terms from the Medical Dictionary for Regulatory Activities, version 23.0 or later). Treatment-emergent AEs were defined as AEs with onset or worsening after the first dose of study drug in CELEST OLE and within 30 days after the last dose of study drug. Relationship to study drug was assessed by the investigator.

Statistical Analyses

All efficacy outcomes were assessed in the intent-to-treat population. For analysis, patients were divided into 3 groups: those who initiated the CELEST OLE study with upadacitinib 15 mg QD and did not escalate their dose; patients who initiated the study with upadacitinib 30 mg QD; and patients who initiated the study with upadacitinib 15 mg QD but received the escalated dose of 30 mg QD at or after week 4 (upadacitinib 30 mg QD dose-escalated). The safety population included all enrolled patients who received $\geq$1 dose of upadacitinib during CELEST OLE. Missing data were imputed via last observation carried forward for all endpoints, with the exception of endoscopic outcomes, for which observed-case analysis was used. Efficacy variables were summarized using descriptive statistics.

Results

Enrollment of the CELEST OLE study commenced on August 3, 2017, and of the 129 patients who completed CELEST, 107 entered CELEST OLE (upadacitinib 15 mg, n = 53; upadacitinib 30 mg, n = 31; dose-escalated to upadacitinib 30 mg, n = 23) and were included in this analysis (Supplementary Figure 2). Baseline demographics were broadly similar across groups (Table 1). The median CD duration was 10 years, and the median upadacitinib exposure was 900, 749, and 789 days in the upadacitinib 15-mg, 30-mg, and dose-escalated groups, respectively. At week 0, 9 patients (8.4%) were being treated with corticosteroids, and 14 patients (13.1%) were receiving methotrexate. Overall, the patients in the 30-mg QD and dose-escalated groups had numerically higher median CDAI, SF, AP, hsCRP, and FCP and used more concomitant steroids or

Table 1. Patient Demographic and Clinical Characteristics at Week 0

	Upadacitinib					
	15 mg QD (n = 53)		30 mg QD (n = 31)		30 mg QD dose-escalated (n = 23)	
Parameter	Baseline[a]	Week 0[b]	Baseline[a]	Week 0[b]	Baseline[a]	Week 0[b]
Age, *y*	41.0 (19.0–64.0)	43.0 (20–65)	37.0 (20.0–65.0)	38.0 (21–66)	39.0 (22.0–76.0)	40.0 (23–77)
Sex, female	29 (54.7)		17 (54.8)		10 (43.5)	
Disease duration, *y*	10.1 (0.36–41.59) n = 53	11.1 (1.4–42.6) n = 53	8.6 (1.91–28.22) n = 31	9.6 (2.9–29.2) n = 31	9.5 (1.07–46.41) n = 23	11.1 (2.5–47.4) n = 22
Upadacitinib exposure, *d*	900 (8–900)		749 (10–900)		789 (91–900)	
CDAI	287 (162–447)	100 (0–383)	288 (229–400)	122 (5–287)	278 (234–430)	158 (0–332)
SES-CD	12 (4–37) n = 53	5 (0–15) n = 49	16 (4–36) n = 31	6 (0–23) n = 28	11 (4–30) n = 23	7 (0–18) n = 20
Daily SF, *n*	5.7 (0.1–14.0)	1.1 (0–6.0)	5.6 (2.7–13.1)	2.0 (0–9.6)	5.3 (2.6–10.7)	2.4 (0–11.7)
Daily AP	2.0 (0.9–3.0)	0.6 (0–2.4)	1.9 (0.7–3.0)	0.7 (0–2.0)	1.9 (0.9–3.0)	1.0 (0–2.3)
hsCRP, *mg/L*	6.1 (0.23–88.92)	1.4 (0.10–29.31)	16.2 (0.76–93.77)	3.2 (0.13–63.38)	9.0 (0.11–53.13)	4.0 (0.13–179.6)
FCP, *μg/g*	1018 (11–9600) n = 53	166 (19–4037) n = 51	1277 (90–8087) n = 31	581 (10–9600) n = 26	1340 (87–9600) n = 23	287 (14–8310) n = 21
Immunosuppressant use	6 (11.3)	5 (9.4)	6 (19.4)	5 (16.1)	3 (13.0)	4 (17.4)
Corticosteroid use	14 (26.4)	2 (3.8)	14 (45.2)	5 (16.1)	13 (56.5)	2 (8.7)

Note: Data are presented as number (%) or median (range).
Note: ITT population.
AP, Abdominal pain; CDAI, Crohn's Disease Activity Index; FCP, fecal calprotectin; hsCRP, high-sensitivity C-reactive protein; ITT, intent to treat; QD, once daily; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency.
[a]Baseline of CELEST study.
[b]Week 0 of the CELEST OLE study.

immunosuppressants at week 0 than patients in the 15-mg QD group. Two patients in the dose-escalated group de-escalated their upadacitinib dose (one each at 18 and 30 months of this OLE).

Efficacy Endpoints

Clinical remission 2.8/1.0 at the time of entry into CELEST OLE (week 0) was achieved by 61%, 57%, and 45% of patients in the upadacitinib 15-mg, 30-mg, and dose-escalated groups, respectively. In the upadacitinib 15- and 30-mg groups, this was sustained to month 30 in 61% and 54% of patients, respectively). In the dose-escalated group, 55% achieved clinical remission at month 30 (Figure 1*A*), with a median time to dose escalation of 254 days (range, 31-824 days).

Although the proportion of patients achieving CDAI remission was similar with clinical remission 2.8/1.0 across the 3 treatment groups, CDAI remission showed more variability and decreased slightly between week 0 and month 30 (from 72% to 60% in the 15-mg group and from 65% to 55% in the 30-mg group) (Figure 1*C*). In the dose-escalated group, 48% and 35% of patients achieved CDAI remission at week 0 and month 30, respectively (Figure 1*C*).

At week 0, 83% and 77% of patients receiving upadacitinib 15 and 30 mg, respectively, achieved enhanced clinical response, and these proportions were sustained throughout CELEST OLE (85% and 74% at 30 months, respectively [last observation carried forward imputation]) (Figure 1*B*). Likewise, enhanced clinical response was maintained throughout the 30 months in the dose-escalated group (65% and 70% at week 0 and month 30, respectively) (Figure 1*B*).

The proportion of patients achieving endoscopic remission (44%–55%) and endoscopic response 50% (56%–77%) increased during the first 12 months of CELEST OLE in all 3 groups (observed-case analysis); this was sustained to 24 months in patients receiving upadacitinib 15 and 30 mg QD, whereas it decreased in patients in the dose-escalated group (Figure 2).

The mean SES-CD remained stable from CELEST OLE baseline to month 24 in patients treated with upadacitinib 15 mg and those in the dose-escalated group, whereas a small decrease was noted in patients receiving upadacitinib 30 mg (Supplementary Figure 3).

Among patients who were taking steroids at CELEST study baseline and who were steroid-free for ≥90 days before months 12, 24, and 30, the majority of those receiving upadacitinib 15 and 30 mg QD achieved steroid-free clinical remission 2.8/1.0 or CDAI remission at week 0 and months 12, 24, and 30; similar results were noted in the dose-escalated group, with the exception of steroid-free CDAI remission at month 24 (Supplementary Figure 4). At month 30, 57% (8/14) of patients receiving upadacitinib 15 mg, 50% (7/14) receiving upadacitinib 30 mg, and 38% (5/13) in the dose-escalated group were steroid-free.

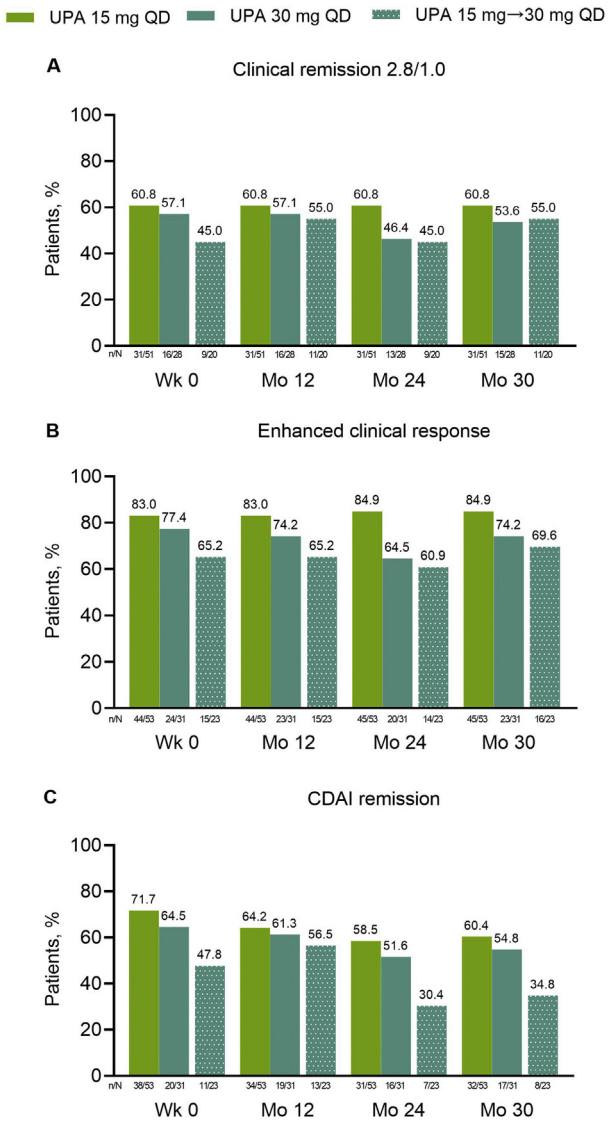

Figure 1. Clinical remission (*A*), enhanced clinical response (*B*), and CDAI remission (*C*) over time. Clinical remission defined as SF ≤2.8 and AP score ≤1.0, both not worse than baseline of CELEST study in patients with SF ≥4 or AP score ≥2.0 at baseline. Enhanced clinical response defined as ≥65% reduction from baseline of CELEST study in SF and AP not worse than baseline or ≥35% reduction from baseline in AP and SF not worse than baseline. CDAI remission defined as CDAI <150. AP, Abdominal pain; CDAI, Crohn's Disease Activity Index; Mo, month; QD, once daily; SF, stool frequency; UPA, upadacitinib; Wk, week.

At week 0, 14% of patients enrolled in the 15-mg and 30-mg groups were in clinical and endoscopic remission (ie, remission); this proportion increased at month 12 (38% and 33%, respectively) and remained stable at month 24 (34% and 43%, respectively). Among patients who dose-escalated, 15%, 24%, and 0% were in remission (ie, achieved clinical remission 2.8/1.0 and endoscopic remission) at week 0 and months 12 and 24, respectively (Figure 3*A*).

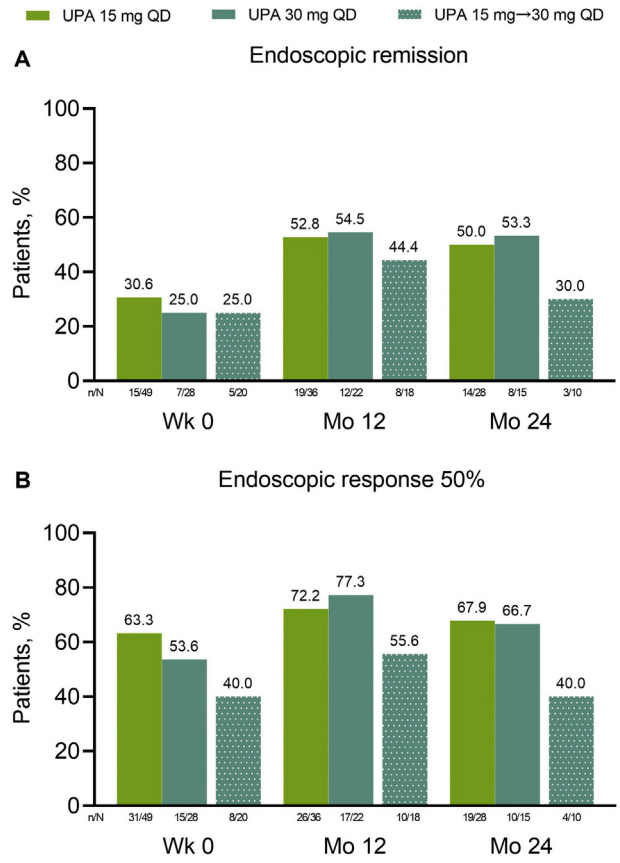

Figure 2. Endoscopic remission (*A*) and endoscopic response 50% (*B*) over time. Observed-case analysis. Mo, Month; QD, once daily; UPA, upadacitinib; Wk, week.

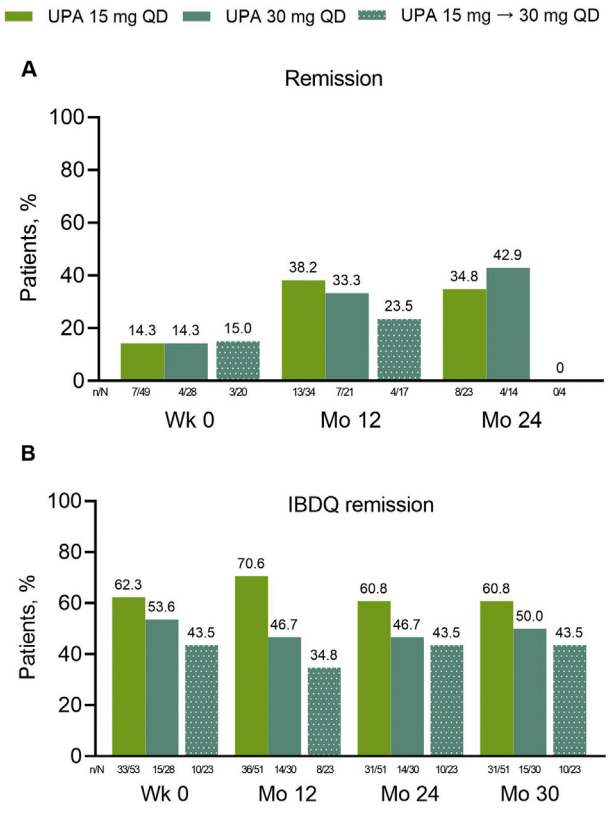

Figure 3. Remission (*A*) and IBDQ remission (*B*) over time. Remission defined as clinical remission 2.8/1.0 and endoscopic remission. IBDQ remission defined as IBDQ ≥170. IBDQ, Inflammatory Bowel Disease Questionnaire; Mo, month; QD, once daily; UPA, upadacitinib; Wk, week.

The IBDQ remission generally remained stable within groups from week 0 to month 30 of CELEST OLE. A larger proportion of patients receiving upadacitinib 15 mg achieved IBDQ remission compared with those receiving upadacitinib 30 mg and those in the dose-escalated group (Figure 3*B*).

The median levels of the inflammatory marker hsCRP decreased between the CELEST study baseline and week 0 of CELEST OLE and were sustained thereafter in the 15-mg group (Figure 4*A*). Patients allocated to upadacitinib 30 mg and the dose-escalated group showed a small increase in hsCRP levels, but they remained below baseline values. The median FCP improved from CELEST study baseline to week 0 of CELEST OLE, and improvements were generally sustained or continued to improve thereafter across all treatment groups (Figure 4*B*).

Safety

In the overall safety population (n = 107), AEs were reported by 96 patients (89.7%) and serious AEs by 20 patients (18.7%), corresponding to 374.6 E/100 PY and 15.3 E/100 PY, respectively (Table 2). A higher proportion of patients treated with upadacitinib 30 mg QD (96.8%; 465.4 E/100 PY) and the dose-escalated group (95.7%; 378.8 E/100 PY) experienced an AE compared with patients in the upadacitinib 15-mg QD group (83.0%; 326.8 E/100 PY) (Table 2). Serious AEs were reported in 10 patients (10.8 E/100 PY) in the upadacitinib 15-mg QD group, 6 patients (21.2 E/100 PY) in the upadacitinib 30-mg QD group, and 4 patients (18.8 E/100 PY) in the dose-escalated group (Table 2). The most frequently reported serious AEs were CD (8 patients [7.5%]), AP, and abdominal abscess and anal fistula (2 patients [1.9%] each).

Infections were reported by 72 patients (67.3%; 103.8 E/100 PY) and serious infections by 4 patients (3.7%; 2.0 E/100 PY), including 2 abdominal abscesses (1 each in the 30-mg and dose-escalated groups; 1 was considered possibly study-drug related), 1 anal abscess (30-mg group; possibly study-drug related), and 1 influenza A virus infection (15-mg group, possibly study-drug related). The intra-abdominal abscess in the dose escalation group (a 23-year-old woman) was adjudicated as an intestinal perforation; the patient had a concurrent event of urinary tract infection and a serious AE of CD flare; all events but the urinary tract infection were considered study-drug-related, and the patient was discontinued from the study. Six reports of herpes zoster in 5 patients (4.7%; 3.1 E/100 PY): 2 in one patient in the 15-mg group (AEs of shingles and post-herpetic neuralgia), 3 in 3 patients in the 30-mg group, and 1 in 1 patient in the dose-escalated group, representing 2.0, 5.8,

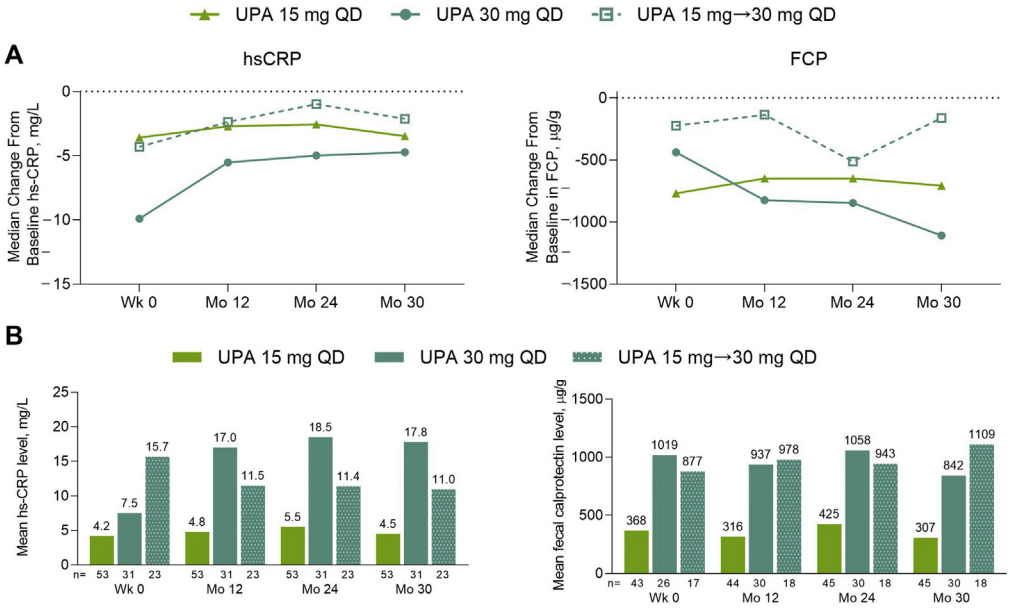

Figure 4. Median change from CELEST study baseline (*A*) and absolute mean (*B*) in hsCRP and FCP over time. FCP, Fecal calprotectin; hsCRP, high-sensitivity C-reactive protein; Mo, month; QD, once daily; UPA, upadacitinib; Wk, week.

and 2.4 E/100 PY, respectively (Table 2). All herpes zoster AEs were non-serious and of mild or moderate severity, involving 1 dermatome in 4 patients and more than 2 dermatomes in 1 patient.

One adjudicated cardiovascular event (coronary artery occlusion) was reported in a 56-year-old woman receiving upadacitinib 15 mg QD. This patient had a medical history of hypertension, diabetes mellitus, osteoporosis, obesity, hypercholesterolemia, and was also a current smoker; the event was considered unrelated to treatment. Two deep vein thrombosis events were reported, one in a 41-year-old woman in the 15-mg group with a 20-year history of smoking and Factor V Leiden mutation (possibly study-drug related; the patient was discontinued from the study), and the other in a 64-year-old man in the dose-escalated group who had been a smoker for 33 years with a history of coronary artery disease, hyperlipidemia, obesity (the event occurred 2 weeks after removal of basal cell carcinoma, was unrelated to study drug; the patient was discontinued from the study).

In addition to the single case of basal cell carcinoma, 1 report of squamous cell carcinoma of the skin was in the 15-mg group (Table 2). No other reports of malignancies, active tuberculosis, or renal dysfunction were reported. One non-treatment-emergent death was reported during the study in a 35-year-old man who died after postsurgical infectious complications 15 months after discontinuation from the study.

Creatine phosphokinase elevation was reported more frequently in patients who received upadacitinib 30 mg, whereas anemia was reported more frequently among patients who received upadacitinib 15 mg compared with the other groups (Table 2). The changes from baseline to month 30 in laboratory parameters were of small magnitude and were not considered clinically meaningful (Supplementary Table 1).

Discussion

The CELEST study was the first study to evaluate the efficacy, safety, and dose response of immediate-release formulation with upadacitinib, a JAK 1 inhibitor, in patients with moderate-to-severe CD who were refractory to TNF antagonists.[8] The CELEST OLE study reports long-term upadacitinib data (a total of 3.5 years with the CELEST study) with the extended-release formulation. The interim results demonstrated sustained long-term effect of upadacitinib and a safety profile consistent with previous upadacitinib studies[9,10] and that of other JAK inhibitors.[5] Rates of clinical remission, enhanced clinical response, and CDAI remission achieved during the 52-week CELEST study were, in general, sustained for an additional 30 months of open-label treatment. In addition, endoscopic remission and response were sustained from week 0 of the extension study to month 24.

The majority of patients (n = 76; 71%) enrolled in the study received upadacitinib 15 mg, and one-third of these (n = 23) lost response at or after week 4 and required dose escalation to 30 mg. Nevertheless, compared with patients receiving upadacitinib 30 mg or who increased dosage to 30 mg, a higher proportion of patients receiving upadacitinib 15 mg achieved clinical remission 2.8/1.0 and an enhanced clinical response, suggesting that this dose is an effective dose as maintenance treatment for long-term use in patients with a sustained response in the first year of treatment. Patients assigned to upadacitinib 30 mg at the start of CELEST OLE had received rescue therapy during the CELEST study and were therefore likely to have more severe or refractory disease. Despite this, the majority of patients in this group achieved clinical remission or response, and >53% achieved endoscopic remission or response at month 30. Consistent with the observed sustained clinical remission and improvement in endoscopic outcomes,

Table 2. Occurrence and Rate of Treatment-emergent AEs and AEs of Special Interest in the Overall Study Population

Treatment-emergent AEs, n (%) [E (E/100 PY)]	15 mg QD (n = 53; 101.9 PY)	30 mg QD (n = 31; 52.0 PY)	30 mg QD dose-escalated (n = 23; 42.5 PY)	Overall (N = 107; 196.5 PY)
AEs	44 (83.0) [333 (326.8)]	30 (96.8) [242 (465.4)]	22 (95.7) [161 (378.8)]	96 (89.7) [736 (374.6)]
Serious AEs	10 (18.9) [11 (10.8)]	6 (19.4) [11 (21.2)]	4 (17.4) [8 (18.8)]	20 (18.7) [30 (15.3)]
AE leading to discontinuation of study drug	10 (18.9) [11 (10.8)]	9 (29.0) [11 (21.2)]	3 (13.0) [4 (9.4)]	22 (20.6) [26 (13.2)]
AEs with reasonable possibility of being related to study drug[a]	29 (54.7) [107 (105.0)]	20 (64.5) [74 (142.3)]	10 (43.5) [44 (103.5)]	59 (55.1) [225 (114.5)]
Serious AE with reasonable possibility of being related to study drug[a]	3 (5.7) [3 (2.9)]	2 (6.5) [3 (5.8)]	1 (4.3) [3 (7.1)]	6 (5.6) [9 (4.6)]
Infections	33 (62.3) [97 (95.2)]	23 (74.2) [67 (128.8)]	16 (69.6) [40 (94.1)]	72 (67.3) [204 (103.8)]
Serious infection[b]	1 (1.9) [1 (1.0)]	2 (6.5) [2 (3.8)]	1 (4.3) [1 (2.4)]	4 (3.7) [4 (2.0)]
Herpes zoster	1 (1.9) [2 (2.0)]	3 (9.7) [3 (5.8)]	1 (4.3) [1 (2.4)]	5 (4.7) [6 (3.1)]
Active tuberculosis	0 [0]	0 [0]	0 [0]	0 [0]
Opportunistic infection excluding herpes zoster and tuberculosis	0 [0]	0 [0]	0 [0]	0 [0]
Malignancy other than NMSC	0 [0]	0 [0]	0 [0]	0 [0]
NMSC	1 (1.9) [1 (1.0)]	0 [0]	1 (4.3) [3 (7.1)]	2 (1.9) [4 (2.0)]
CPK elevation	6 (11.3) [7 (6.9)]	5 (16.1) [5 (9.6)]	3 (13.0) [3 (7.1)]	14 (13.1) [15 (7.6)]
Anemia	4 (7.5) [6 (5.9)]	2 (6.5) [3 (5.8)]	0 [0]	6 (5.6) [9 (4.6)]
Neutropenia	1 (1.9) [1 (1.0)]	1 (3.2) [1 (1.9)]	0 [0]	2 (1.9) [2 (1.0)]
Adjudicated gastrointestinal perforation	0 [0]	0 [0]	1 (4.3) [1 (2.4)]	1 (0.9) [1 (0.5)]
Adjudicated cardiovascular event[c]	1 (1.9) [1 (1.0)]	0 [0]	0 [0]	1 (0.9) [1 (0.5)]
Death[d]	1 (1.9) [1 (1.0)]	0 [0]	0 [0]	1 (0.9) [1 (0.5)]

AE, Adverse event; CPK, creatine phosphokinase; E, event; NMSC, non-melanoma skin cancer; PY, patient-year; QD, once daily.

[a]As assessed by the investigator.

[b]Included 2 abdominal abscesses (1 considered possibly study-drug related by investigator and led to discontinuation of study drug), 1 anal abscess, and 1 influenza virus A infection (both possibly study-drug related).

[c]A 56-year-old woman was reported with left anterior descending coronary artery occlusion; not considered related to treatment.

[d]A 35-year-old man died after surgery for dysplasia of the colon 15 months after premature discontinuation from the study; was not considered to have reasonable possibility of being related to the study drug and was considered non-treatment-emergent.

reductions of the levels of the inflammatory markers hsCRP and FCP were noted throughout the study, indicating a sustained anti-inflammatory effect of upadacitinib. Importantly, improvements in clinical, endoscopic, and biological parameters achieved in CELEST were maintained throughout CELEST OLE in the upadacitinib 15-mg QD group. Likewise benefits in quality of life (QoL) as assessed by the IBDQ were maintained.

The AEs reported in this study were consistent with those reported in the CELEST study,[8] with infections being the most frequently reported. Serious infections and herpes zoster were reported more frequently among patients who received upadacitinib 30 mg. This is in line with reports from the CELEST study[8] and other studies of JAK inhibitors in CD[11–13] as well as larger upadacitinib and tofacitinib phase III studies in rheumatoid arthritis.[14–16] Two patients experienced deep vein thrombosis, and both had multiple comorbidities or an inherited hypercoagulability risk factor. Thromboembolic events have been reported with JAK inhibitors, and patients with inflammatory bowel diseases, including CD, are at a 2- to 3-fold higher risk of developing a venous thromboembolism compared with the general population.[17] In addition, 1 patient with multiple cardiovascular risk factors had a coronary artery occlusion. Of note, patients with CD have an increased risk of developing cardiovascular disorders.[18,19]

Strengths of this study are treatment follow-up period that is the longest reported to date in patients with CD receiving a JAK inhibitor and the comprehensive set of clinical, endoscopic, QoL, and inflammatory markers data. Although the ability to detect rare AEs is limited by the small number of patients—and a considerable number of patients were lost to follow-up—CELEST OLE showed that long-term treatment with upadacitinib leads to sustained clinical and endoscopic improvements, decreased serum markers of inflammation, and increased patient-reported QoL benefits in patients with CD who are mostly refractory to TNF therapy.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2021.12.030.

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Conflicts of interest

The authors disclose the following: Geert D'Haens has served as advisor for AbbVie, Ablynx, Active Biotech AB, Agomab Therapeutics, Alimentiv, Allergan, Alphabiomics, Amakem, Amgen, AM Pharma, Applied Molecular Therapeutics, Arena Pharmaceuticals, AstraZeneca, Avaxia, Biogen, Bristol Myers Squibb/Celgene, Boehringer Ingelheim, Celltrion, Cosmo, Dr Falk Pharma, DSM Pharma, Echo Pharmaceuticals, Eli Lilly, Engene, Exeliom Biosciences, Ferring, Galapagos, Genentech/Roche, Gilead, GlaxoSmithKline, Gossamerbio, Immunic, Johnson and Johnson, Kintai Therapeutics, Lument, Lycera, Medimetrics, Medtronic, Mitsubishi Pharma, Merck Sharp & Dohme, Mundipharma, Nextbiotics, Novonordisk, Otsuka, Pfizer, Photopill, ProciseDx, Prodigest, Prometheus Laboratories/Nestle, Progenity, Protagonist, RedHill, Salix, Samsung Bioepis, Sandoz, Seres/Nestec/Nestle, Setpoint, Shire, Takeda, Teva, Tigenix, Tillotts, Topivert, Versant, and Vifor; and has received speaker fees from AbbVie, Biogen, Ferring, Galapagos/Gilead, Johnson and Johnson, Merck Sharp & Dohme, Millenium/Takeda, Mundipharma, Norgine, Pfizer, Samsung Bioepis, Shire, Tillotts, and Vifor. Julian Panés has served as consultant and/or speaker for AbbVie, Arena, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Genentech, GlaxoSmithKline, Janssen, Origo, Pandion, Pfizer, Progenity, Robarts, Roche, Takeda, Theravance, and Wassermann; and has received research grants from AbbVie and Pfizer. Edouard Louis has received research grants from Janssen, Pfizer, and Takeda; has received educational grants from AbbVie, Janssen, MSD, and Takeda; has received speaker fees from AbbVie, Falk, Ferring, Hospira, Janssen, MSD, Pfizer, and Takeda; has served on advisory boards for AbbVie, Arena, Celgene, Ferring, Galapagos, Gilead, Hospira, Janssen, MSD, Pfizer, and Takeda; and has served as a consultant for AbbVie. Edward V. Loftus Jr has served as a consultant for AbbVie, Allergan, Amgen, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Calibr, Celgene, Celltrion Healthcare, Eli Lilly, Genentech, Gilead, Gossamer Bio, Iterative Scopes, Janssen, Ono Pharma, Pfizer, Scipher Medicine, Sun Pharma, Takeda, and UCB; and has received research grants from AbbVie, Bristol-Myers Squibb, Celgene, Genentech, Gilead, Gossamer Bio, Janssen, Pfizer, Receptos, Robarts Clinical Trials, Takeda, Theravance, and UCB. John Liu, Qian Zhou, and Ana Lacerda are AbbVie employees and may own AbbVie stock and/or options.

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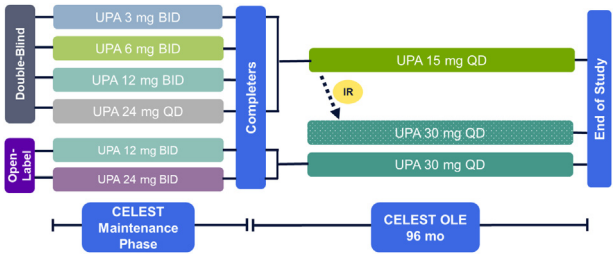
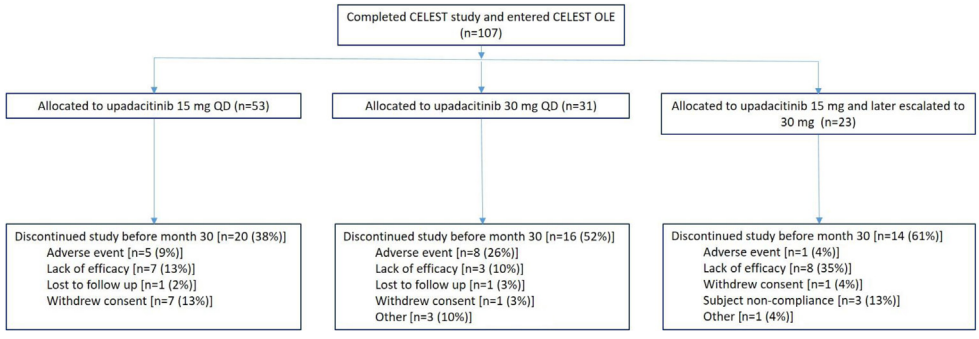
Data transparency statement

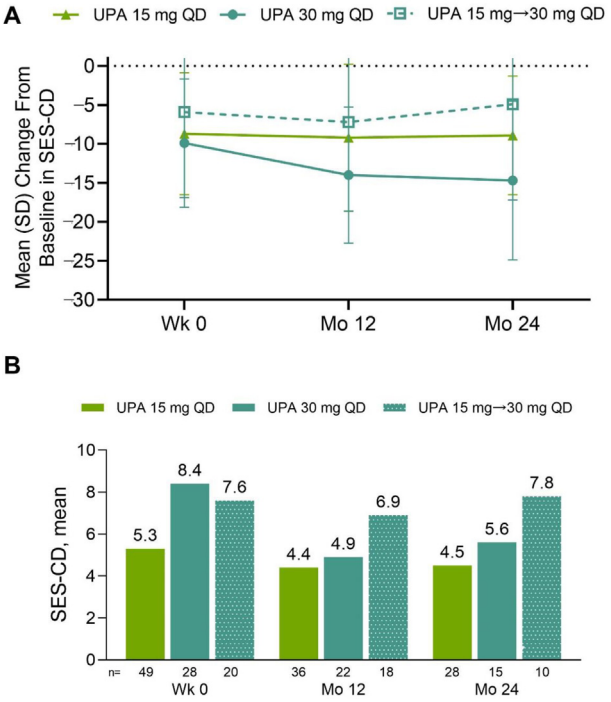
AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing 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 following 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 the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.



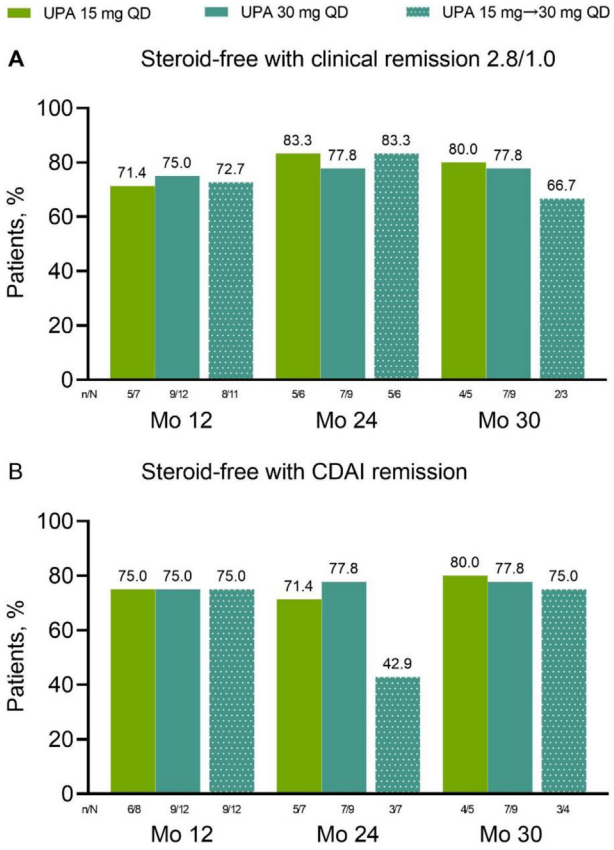
Supplementary Figure 1. Study designs for CELEST maintenance phase and CELEST OLE. Patients who completed the primary CELEST study and initiated the OLE received upadacitinib 15 or 30 mg QD. At or after week 4, patients receiving upadacitinib 15 mg QD who had an inadequate response and no safety concerns identified by the investigator could escalate the dose of upadacitinib to 30 mg QD. BID, twice daily; IR, inadequate response; OLE, open-label extension; QD, once daily; UPA, upadacitinib.



Supplementary Figure 2. Patient disposition during CELEST OLE.



Supplementary Figure 3. Mean change from CELEST study baseline (*A*) and absolute mean values (*B*) in SES-CD score to week 0, month 12, and month 24. SES-CD, Simple Endoscopic Score for Crohn's Disease; Mo, month; QD, once daily; SD, standard deviation; UPA, upadacitinib; Wk, week.



Supplementary Figure 4. Endpoints of steroid-free remission with clinical remission 2.8/1.0[a] (*A*) and with CDAI remission[b] (*B*) for months 12, 24, and 30. AP, abdominal pain; CDAI, Crohn's Disease Activity Index; Mo, month; QD, once daily; SF, stool frequency; UPA, upadacitinib. [a]Defined as steroid-free for 90 days before months 12, 24, and 30 with SF $\leq$2.8 and AP score $\leq$1.0, both not worse than baseline of the CELEST study in patients with SF $\geq$4 or AP score $\geq$2.0 at baseline. [b]Defined as steroid-free for 90 days before months 12, 24, and 30 with CDAI $<$150.

Supplementary Table 1. Change From CELEST Baseline in Laboratory Values to Final Analysis

Parameter	Upadacitinib		
	15 mg QD (n = 53)	30 mg QD (n = 31)	30 mg QD dose-escalated (n = 23)
ALT, *U/L*			
Mean (SD)	7.9 (23.4)	7.0 (21.6)	12.3 (34.5)
Median	8.0	5.0	4.0
AST, *U/L*			
Mean (SD)	7.2 (16.3)	5.2 (12.6)	9.0 (14.1)
Median	6.0	7.0	7.0
Creatinine, *μmol/L*			
Mean (SD)	0.9 (10.0)	0.3 (7.9)	−1.2 (8.6)
Median	1.8	0.8	−1.8
CPK, *U/L*			
Mean (SD)	111.1 (191.8)	126.2 (163.7)	53.8 (127.5)
Median	56.0	100.0	58.0
Hemoglobin, *g/L*			
Mean (SD)	3.0 (17.3)	−1.9 (15.6)	−3.3 (12.5)
Median	2.0	–1.0	−6.0
Lymphocytes, *cells* $\times 10^9$*/L*			
Mean (SD)	−0.42 (0.86)	−0.34 (1.78)	−0.38 (0.83)
Median	−0.37	−0.41	−0.50
Neutrophils, *cells* $\times 10^9$*/L*			
Mean (SD)	−1.13 (3.71)	−1.75 (4.18)	−2.75 (3.33)
Median	−1.19	−1.38	−1.87
Platelet count, $\times 10^9$*/L*			
Mean (SD)	−37.7 (113.2)	−4.1 (168.2)	–7.4 (84.5)
Median	−19.0	11.5	–5.0
Total cholesterol, *mmol/L*			
Mean (SD)	0.50 (0.97)	0.36 (0.86)	0.06 (1.1)
Median	0.62	0.45	0.00
HDL cholesterol, *mmol/L*			
Mean (SD)	0.21 (0.35)	0.09 (0.44)	–0.01 (0.36)
Median	0.26	0.40	0.00
LDL cholesterol, *mmol/L*			
Mean (SD)	0.27 (0.87)	0.32 (0.64)	0.20 (0.79)
Median	0.34	0.39	0.26
Triglycerides, *mmol/L*			
Mean (SD)	0.12 (0.80)	−0.10 (0.56)	−0.21 (0.93)
Median	0.11	–0.05	−0.18

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; QD, once daily; SD, standard deviation.