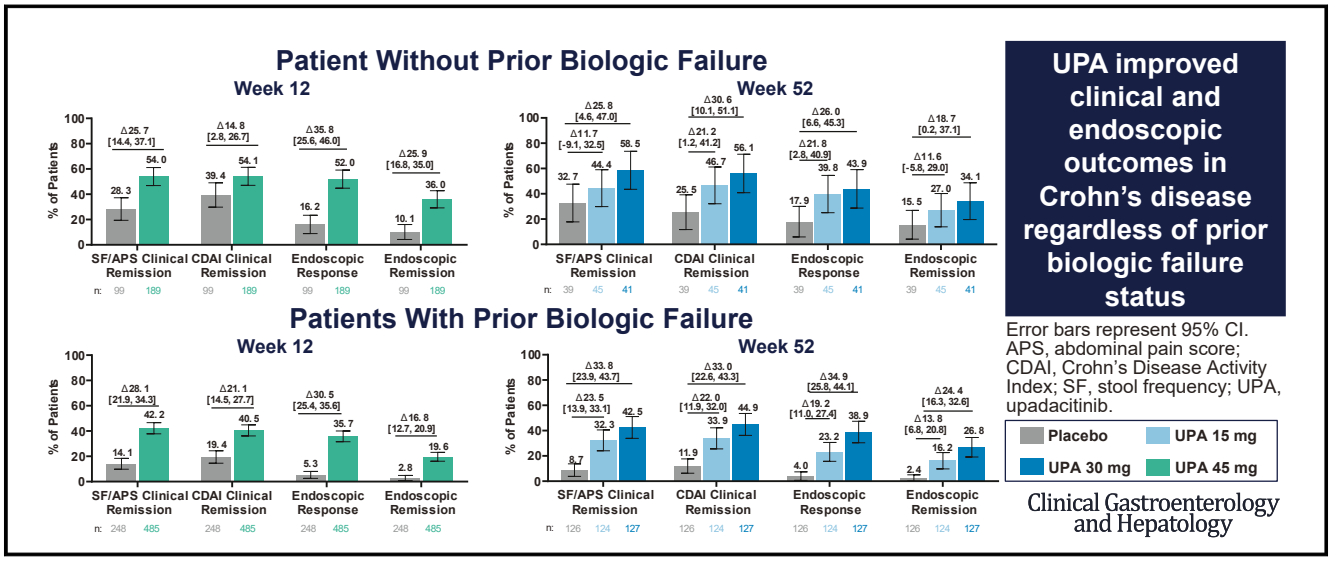
Upadacitinib Achieves Clinical and Endoscopic Outcomes in Crohn's Disease Regardless of Prior Biologic Exposure

Laurent Peyrin-Biroulet,[1,2,3,4,5] Remo Panaccione,[6] Edouard Louis,[7] Raja Atreya,[8] David T. Rubin,[9] James O. Lindsay,[10] Jesse Siffledeen,[11] Dana J. Lukin,[12] John Wright,[13] Kenji Watanabe,[14] Sharanya Ford,[15] Valencia P. Remple,[15] Ana P. Lacerda,[15] Elena Dubcenco,[15] Andrew Garrison,[15] Qian Zhou,[15] Sofie Berg,[15] Samuel I. Anyanwu,[15] and Stefan Schreiber[16]

[1]Department of Gastroenterology, Nancy University Hospital, Vandœuvre-lès-Nancy, France; [2]INSERM, NGERE, University of Lorraine, Nancy, France; [3]INFINY Institute, Nancy University Hospital, Vandœuvre-lès-Nancy, France; [4]FHU-CURE, Nancy University Hospital, Vandœuvre-lès-Nancy, France; [5]Groupe Hospitalier Privé Ambroise Paré - Hartmann, Paris IBD Center, Neuilly-sur-Seine, France; [6]Division of Gastroenterology and Hepatology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; [7]Hepato-Gastroenterology and Digestive Oncology Department, University Hospital CHU of Liège, Liège, Belgium; [8]First Department of Medicine, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; [9]Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, Illinois; [10]Centre for Immunobiology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; [11]Division of Gastroenterology, Covenant Health Grey Nuns Community Hospital, Edmonton, Alberta, Canada; [12]Department of Gastroenterology and Hepatology, New York Presbyterian/Weill Cornell Medical Center, New York, New York; [13]Kingsbury Hospital, Cape Town, South Africa; [14]Department of Internal Medicine for Inflammatory Bowel Disease, University of Toyama, Toyama, Japan; [15]AbbVie Inc, North Chicago, Illinois; and [16]Department Internal Medicine, University Hospital Schleswig-Holstein, Christian Albrechts University, Kiel, Germany



BACKGROUND & AIMS: **Upadacitinib, an oral Janus kinase inhibitor, achieved significantly higher rates of clinical remission and endoscopic response vs placebo during induction (U-EXCEL [NCT03345849], U-EXCEED [NCT03345836]) and maintenance (U-ENDURE [NCT03345823]) treatment in patients with moderate-to-severe Crohn's disease. Prior biologic failure is often associated with reduced**

Abbreviations used in this paper: AE, adverse events; APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; COVID-19, coronavirus disease 2019; CR-100, clinical response; FCP, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; MI, multiple imputation; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TNFα, tumor necrosis factor α.

Most current article

1542-3565
https://doi.org/10.1016/j.cgh.2024.02.026

responses to subsequent therapies. This post hoc analysis assessed upadacitinib efficacy by prior biologic failure status.

METHODS: **Patients were randomized to placebo or upadacitinib 45 mg (UPA45) for 12 weeks (induction). UPA45 clinical responders were enrolled in U-ENDURE and rerandomized to placebo, upadacitinib 15 mg, or upadacitinib 30 mg (UPA30) for 52 weeks. Assessments were by prior biologic failure.**

RESULTS: **Of 1021 patients, 733 (71.8%) had prior biologic failure. Across outcomes and subgroups, upadacitinib-treated patients achieved higher rates vs placebo. During induction, upadacitinib had higher rates vs placebo for clinical remission based on stool frequency/abdominal pain score (without failure: 54.0% vs 28.3%; with failure: 42.2% vs 14.1%) and endoscopic response (without failure: 52.0% vs 16.2%; with failure: 35.7% vs 5.3%). In maintenance, the greatest treatment effect (upadacitinib vs placebo) was among patients with prior biologic failure treated with UPA30 (clinical remission without failure: 58.5% vs 32.7%; with failure: 42.5% vs 8.7%; endoscopic response without failure: 43.9% vs 17.9%; with failure: 38.9% vs 4.0%). Patients without vs with prior biologic failure had fewer adverse events.**

CONCLUSIONS: **Upadacitinib led to higher absolutes rates of clinical and endoscopic outcomes in patients without vs with prior biologic failure. Patients treated with upadacitinib achieved greater rates of clinical and endoscopic improvements vs placebo, regardless of prior biologic exposure. ClinicalTrials.gov: NCT03345849, NCT03345836, NCT03345823.**

Keywords: Upadacitinib; JAK Inhibitor; Crohn's Disease; Biologic Naive; Biologic Failure.

After conventional therapy, biologics, in particular anti–tumor necrosis factor α (TNFα) agents, are often the first-line advanced treatment of Crohn's disease (CD). However, as many as 10%–30% of patients do not initially respond to anti-TNFα therapy, and approximately 23%–46% of those who do subsequently lose response.[1–3] In a meta-analysis of 6 clinical trials of patients with prior anti-TNFα therapy exposure, primary non-responders were 24% less likely to achieve clinical remission on subsequent therapy vs patients who discontinued an anti-TNFα therapy because of intolerance.[4] A need exists for therapies with a favorable benefit-risk profile that act rapidly and are capable of achieving mucosal healing irrespective of biologic treatment history.

The efficacy of upadacitinib, an oral Janus kinase inhibitor, was demonstrated in the phase 3 induction (U-EXCEL and U-EXCEED) and maintenance (U-ENDURE) trials.[5] Overall population data from these trials showed that patients treated with upadacitinib achieved and maintained symptomatic control, clinical remission (including steroid-free remission), and mucosal healing, which are short-, intermediate-, and long-term therapeutic targets for CD as recommended by STRIDE-II.[6,7] In some countries, including the United States, upadacitinib is indicated for patients who have had an inadequate response or intolerance to 1 or more anti-TNFα therapies.[8] Therefore, understanding the efficacy profile of upadacitinib in patients with prior biologic failure is important. In this post hoc analysis, we evaluated efficacy outcomes and safety for subgroups of patients with moderately to severely active CD by their prior biologic failure status.

Materials and Methods

Study Design and Treatment

The study design has been previously published.[5] Briefly, U-EXCEL (NCT03345849) and U-EXCEED (NCT03345836) were 12-week, phase 3, double-blind, randomized, placebo-controlled induction studies, in which patients were randomized 2:1 to receive placebo or upadacitinib 45 mg once daily (Supplementary Figure 1). Patients who achieved clinical response (defined as $\geq$30% decrease in average daily very soft/liquid stool frequency [SF] and/or $\geq$30% decrease in abdominal pain score [APS] and both not worse than baseline) after 12 weeks of induction treatment with upadacitinib in the U-EXCEL and U-EXCEED studies were eligible to enroll in the U-ENDURE (NCT03345823) maintenance study. In U-ENDURE, patients were rerandomized 1:1:1 to receive daily placebo, upadacitinib 15 mg, or upadacitinib 30 mg for 52 weeks (Supplementary Figure 1). Patients who were receiving steroids at baseline of the induction studies began a mandatory steroid taper at week 4 of the induction study. Patients who did not complete the taper during the induction studies continued tapering during the maintenance study.

All clinical trials were conducted in accordance with the International Council for Harmonisation guidelines,

applicable guidelines and regulations governing ethical principles, and study conduct originating in the Declaration of Helsinki. An independent ethics committee/institutional review board ensured the ethical, scientific, and medical appropriateness of the study before it was conducted and approved all relevant documentation. Written informed consent was obtained from all patients before enrollment. All authors had access to the study data and reviewed and approved the final manuscript.

Patients

Eligible patients were aged 18–75 years and had a prior diagnosis of CD that was moderately to severely active (defined as having an average daily very soft/liquid SF $\geq$4 and/or APS $\geq$2) in addition to a Simple Endoscopic Score for Crohn's Disease (SES-CD) of $\geq$6 (or a score of $\geq$4 for patients with isolated ileal disease) excluding the narrowing component. The U-EXCEL study enrolled patients with prior biologic failure (defined as intolerance or inadequate response to prior biological therapies) and patients without prior biologic failure (defined as intolerance or inadequate response to conventional therapies such as corticosteroids or immunosuppressants).[5] The U-EXCEED study enrolled only patients with prior biologic failure (Supplementary Table 1).

Assessments

Clinical endpoints. Clinical outcomes included clinical remission, defined by SF/APS (average daily very soft/liquid SF $\leq$2.8 and average daily APS $\leq$1.0 and both not greater than baseline) or Crohn's Disease Activity Index (CDAI) <150), clinical response (CR-100) $\geq$100-point decrease in CDAI from baseline), maintenance of SF/APS or CDAI clinical remission (clinical remission achieved at week 0 of maintenance and maintained at week 52), and steroid-free SF/APS or CDAI clinical remission.

Endoscopic endpoints. Endoscopic outcomes included endoscopic response (decrease in SES-CD >50% from baseline of the induction studies [or for patients with an SES-CD of 4 at baseline of the induction study, at least a 2-point reduction from baseline]), endoscopic remission (SES-CD $\leq$4 and $\geq$2-point reduction from baseline, with no subscore >1 in any individual variable), maintenance of endoscopic response and endoscopic remission (achieved at week 0 of maintenance and maintained at week 52), and mucosal healing (achievement of SES-CD ulcerated subscore of 0 in patients with SES-CD ulcerated surface subscore $\geq$1 at baseline). The SES-CD was assessed by a blinded central reader.

Markers of inflammation. The markers of inflammation (biomarkers) were assessed by normalization of high-sensitivity C-reactive protein (hs-CRP) $\leq$5 mg/L in patients with hs-CRP >5 mg/L at baseline) and normalization of fecal calprotectin (FCP) $\leq$250 mg/kg in patients with FCP >250 mg/kg at baseline).

What You Need to Know

Background

Patients with moderately to severely active Crohn's disease often experience reduced clinical effects after an inadequate response to prior biologic treatment with anti–tumor necrosis factor α agents.

Findings

This post hoc analysis demonstrated that patients with Crohn's disease treated with upadacitinib vs placebo achieved greater clinical and endoscopic improvements regardless of prior biologic exposure.

Implications for patient care

Upadacitinib may be a potential treatment option for patients with Crohn's disease, whether early in their treatment course or after having failed previous advanced therapies.

Safety. Incidence rates of adverse events (AEs) are reported for induction, and AEs per 100 patient-years are reported for maintenance.

Statistical Analysis

Data from the induction studies were pooled. Efficacy outcomes and safety were evaluated for all randomized patients who received $\geq$1 dose of study drug (in the U-ENDURE study, this was among the first 502 randomized patients completing the week 52 visit). Efficacy and safety outcomes were evaluated separately by subgroups of patients without and with prior biologic failure. Among patients with prior biologic failure, efficacy was also evaluated separately within each subpopulation of prior biologic failure (number [1, 2, >2] and type [anti-TNFα, ustekinumab, or vedolizumab/natalizumab]).

The 95% confidence interval was calculated using normal approximation to the binomial distribution for categorical endpoints. Treatment differences in categorical endpoints are shown as percentage points (induction: upadacitinib 45-mg group minus placebo group; maintenance: upadacitinib 15-mg group minus placebo group; upadacitinib 30-mg group minus placebo group) within each subgroup category. The analysis was not designed to perform statistical comparisons for baseline characteristics and safety results between treatment arms or subgroups; hence these data are presented descriptively. Similarly, the analysis was not designed to test for statistical differences in efficacy between subgroups by dose. Statistical comparisons of upadacitinib and placebo were conducted within each subgroup for key clinical and endoscopic endpoints. Calculations were based on non-responder imputation incorporating multiple imputation (MI) to handle missing data because of coronoavirus disease 2019 (COVID-19). If data were missing for any reason other than COVID-19, patients

were considered non-responders. However, missing data due to COVID-19 infection or logistical restrictions were imputed by MI. The probability of having missed visits and missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic can be reasonably assumed to be unrelated to the unobserved values. Therefore, for the purpose of statistical analysis, it is reasonable to assume that these missing data are missing at random, and the statistical models that require missing at random assumption are appropriate. The intent was to provide reliable estimates of the treatment effects under the scenario without the impact of COVID-19 pandemic.[5]

Results

Patients

A total of 1021 patients (288, 28.2% without and 733, 71.8% with prior biologic failure) were included in this analysis. Patients with prior biologic failure had higher rates of severe disease characteristics; all other baseline demographics were generally similar, regardless of prior biologic status (Table 1, Supplementary Table 2). Patient disposition was previously reported[5] and is highlighted in Supplementary Figure 2.

Efficacy Assessments

Key efficacy outcomes in patients without prior biologic failure. Among patients without prior biologic failure at induction week 12, greater proportions of patients treated with upadacitinib vs placebo achieved SF/APS clinical remission (54.0% vs 28.3%, respectively), CDAI clinical remission (54.1% vs 39.4%), and CR-100 (54.9% vs 46.5%; Figure 1*A*). Patients using corticosteroids at baseline who received upadacitinib achieved steroid-free clinical remission at higher rates vs placebo (SF/APS, 51.8% vs 21.4%; CDAI, 46.4% vs 25.0%; Supplementary Figure 3*A*). Patients treated with upadacitinib vs placebo also achieved higher rates of endoscopic response (52.0% vs 16.2%) and endoscopic remission (36.0% vs 10.1%; Figure 1*B*). Treatment with upadacitinib vs placebo led to higher rates of mucosal healing (32.5% vs 8.2%; Supplementary Figure 4*A*) and normalization of hs-CRP (57.3% vs 9.1%) and FCP (47.3% vs 10.3%; Supplementary Figure 5*A*).

At week 52 of maintenance, greater proportions of patients treated with upadacitinib (15 mg and 30 mg) vs placebo achieved SF/APS clinical remission (44.4% and 58.5% vs 32.7%), CDAI clinical remission (46.7% and 56.1% vs 25.5%), and CR-100 (51.1% and 61.0% vs 23.1%; Figure 2*A*). Among patients who achieved SF/APS clinical remission at week 0 of maintenance, upadacitinib (15 mg and 30 mg) maintained remission at higher rates vs placebo at week 52 (67.9% and 60.0% vs 40.7%). Similar results were observed for maintenance of CDAI clinical remission and steroid-free clinical remission (per SF/APS and CDAI; Figure 2*A*, Supplementary Figure 3*C*). At week 52, greater proportions of patients who received upadacitinib (15 mg and 30 mg) vs placebo achieved endoscopic response (39.8% and 43.9% vs 17.9%) and endoscopic remission (27.0% and 34.1% vs 15.5%; Figure 3*A*). Rates of maintenance of endoscopic response or endoscopic remission at week 52 were also higher for upadacitinib vs placebo. Rates of mucosal healing and normalization of hs-CRP and FCP were higher for upadacitinib vs placebo at week 52 of maintenance (Supplementary Figures 4*C* and 5*C*).

Key efficacy outcomes in patients with prior biologic failure. Among patients with prior biologic failure at induction week 12, patients treated with upadacitinib vs placebo achieved higher rates of SF/APS clinical remission (42.2% vs 14.1%, respectively), CDAI clinical remission (40.5% vs 19.4%), and CR-100 (53.2% vs 26.9%; Figure 1*C*). Patients receiving corticosteroids at baseline treated with upadacitinib achieved steroid-free clinical remission at higher rates vs placebo (SF/APS, 37.6% vs 6.3%; CDAI, 36.5% vs 10.5%; Supplementary Figure 3*B*). A greater proportion of patients who received upadacitinib vs placebo achieved endoscopic response (35.7% vs 5.3%) and endoscopic remission (19.6% vs 2.8%; Figure 1*D*). In addition, patients treated with upadacitinib vs placebo achieved higher rates of mucosal healing (16.6% vs 0.4%; Supplementary Figure 4*B*) and normalization of hs-CRP (48.6% vs 7.7%) and FCP (30.4% vs 7.4%; Supplementary Figure 5*B*).

At week 52 of maintenance, greater proportions of patients treated with upadacitinib (15 mg and 30 mg) vs placebo achieved SF/APS clinical remission (32.3% and 42.5% vs 8.7%), CDAI clinical remission (33.9% and 44.9% vs 11.9%), and CR-100 (37.9% and 48.0% vs 12.7%; Figure 2*B*). Among patients who achieved either SF/APS or CDAI clinical remission at week 0 of maintenance, greater proportions of patients who received upadacitinib (15 mg and 30 mg) vs placebo maintained SF/APS (44.2% and 60.0% vs 13.0%) or CDAI clinical remission (45.2% and 67.2% vs 15.9%) at week 52 (Figure 2*B*). Similarly, rates of steroid-free clinical remission (per SF/APS and CDAI) were higher for upadacitinib vs placebo (Supplementary Figure 3*D*). At week 52, patients who received upadacitinib (15 mg and 30 mg) vs placebo achieved higher rates of endoscopic response (23.2% and 38.9% vs 4.0%) and endoscopic remission (16.2% and 26.8% vs 2.4%; Figure 3*B*). Likewise, the rate of patients who maintained endoscopic response and endoscopic remission from week 0 to week 52 of the maintenance study was higher for upadacitinib vs placebo (Figure 3*B*). Patients treated with upadacitinib vs placebo achieved higher rates of mucosal healing (Supplementary Figure 4*D*) and normalization of hs-CRP or FCP (Supplementary Figure 5*D*).

Outcomes in patients with prior biologic failure stratified by number and type of prior biologics. Patients receiving upadacitinib as induction or maintenance treatment achieved clinical and endoscopic outcomes at higher rates vs placebo, regardless of the number of prior failed biologic therapies (Supplementary Figures 6 and 7). Patients who had failed fewer biologic therapies generally had higher rates of clinical remission, endoscopic response, and endoscopic remission at weeks 12 and 52.

Efficacy outcomes were also evaluated by subgroups stratified by type of prior biologics failed (anti-TNFα, ustekinumab, and/or vedolizumab/natalizumab; Supplementary Figures 6–8). These patients could have failed more than 1 type of biologic allowed per inclusion criteria, and because 96% of patients failed a prior anti-

Table 1. Baseline Demographics and Disease Characteristics

	Without prior biologic failure		With prior biologic failure	
Characteristic	PBO (n = 99)	UPA 45 mg (n = 189)	PBO (n = 248)	UPA 45 mg (n = 485)
Sex, n (%)				
Female	46 (46.5)	90 (47.6)	111 (44.8)	226 (46.6)
Age, y, mean (SD)	38.7 (14.1)	40.7 (14.3)	38.3 (12.5)	38.5 (13.5)
BMI, kg/m^2, mean (SD)	26.2 (7.6)	24.6 (5.7)	24.2 (6.1)	24.2 (6.1)
History of smoking, n (%)				
Current	21 (21.2)	45 (23.8)	60 (24.2)	93 (19.2)
Former	14 (14.1)	29 (15.3)	47 (19.0)	103 (21.2)
Never	63 (63.6)	115 (60.8)	141 (56.9)	288 (59.4)
Unknown	1 (1.0)	0	0	1 (0.2)
No. of prior biologic therapies failed[a]				
0	99 (100)	189 (100)	0	0
1	0	0	95 (38.3)	184 (37.9)
2	0	0	79 (31.9)	144 (29.7)
≥3	0	0	74 (29.8)	157 (32.4)
Type of prior biologic therapy failed				
Anti-TNFα	0	0	239 (96.4)	465 (95.9)
Ustekinumab	0	0	90 (36.3)	182 (37.5)
Vedolizumab/natalizumab	0	0	72 (29.0)	148 (30.5)
Corticosteroid use, n (%)	28 (28.3)	56 (29.6)	96 (38.7)	178 (36.7)
Crohn's disease duration, y, mean (SD)	6.1 (7.9)	7.1 (8.9)	10.8 (7.8)	12.0 (9.5)
Crohn's disease location per SES-CD, n (%)				
Ileal only	17 (17.2)	41 (21.7)	33 (13.3)	65 (13.4)
Colonic only	34 (34.3)	58 (30.7)	91 (36.7)	175 (36.1)
Ileal-colonic	48 (48.5)	90 (47.6)	124 (50.0)	245 (50.5)
FCP, μg/g, median (range)	724 (30–24,234)[b]	724 (30–27,716)[c]	1115 (30–19,104)[d]	1141 (30–28,800)[e]
hs-CRP, mg/L, median (range)	6.9 (0.2–110.0)	6.7 (0.2–94.4)[f]	8.2 (0.2–126.0)[g]	10.3 (0.2–144.0)[h]
CDAI, mean (SD)	289 (75)	284 (77)[i]	306 (89)	305 (88)[j]
Average daily very soft/liquid SF, mean (SD)	4.5 (2.3)	4.7 (2.3)	6.0 (3.3)	5.7 (3.2)[k]
Average daily APS, mean (SD)	2.0 (0.7)	2.0 (0.6)	1.8 (0.7)	1.8 (0.7)[k]
SES-CD, mean (SD)	12.4 (6.5)	12.4 (6.5)	15.0 (7.6)	15.2 (7.8)

BMI, body mass index; PBO, placebo; SD standard deviation; UPA, upadacitinib.
[a]Among patients with prior biologic therapy failure, 704/733 had received anti-TNFα, 272/733 had received ustekinumab, and 220/733 had received vedolizumab/natalizumab.
[b]n = 91.
[c]n = 174.
[d]n = 229.
[e]n = 443.
[f]n = 185.
[g]n = 240.
[h]n = 475.
[i]n = 188.
[j]n = 483.
[k]n = 484.

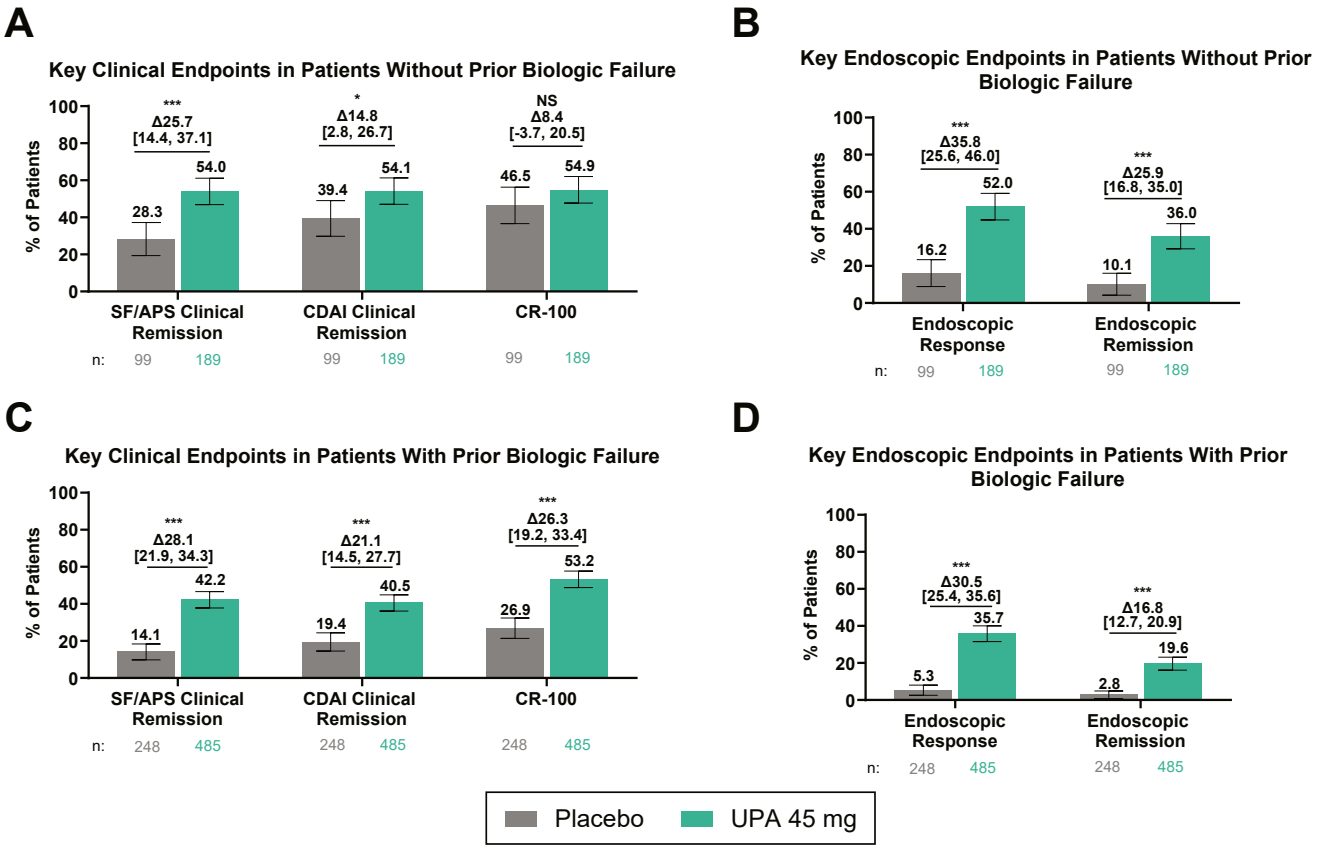


Figure 1. Achievement of key clinical and endoscopic endpoints at week 12 of induction. (*A*) Clinical endpoints in patients without prior biologic failure and (*B*) with prior biologic failure. (*C*) Endoscopic endpoints in patients without prior biologic failure and (*D*) with prior biologic failure. *Error bars* represent 95% confidence intervals. Δ values represent the percent difference between upadacitinib and placebo, with confidence intervals in brackets. *Nominal $P < .05$; ***nominal $P < .001$ vs placebo. UPA, upadacitinib.

TNFα, most patients exposed to ustekinumab or vedolizumab/natalizumab also had an inadequate response or intolerance to an anti-TNFα therapy. Across all these subgroups, higher rates of clinical and endoscopic outcomes were achieved with upadacitinib vs placebo during induction and maintenance. Rates were higher among patients who had not failed either of these prior treatments. Data for patients who had not failed anti-TNFα therapies should be interpreted with caution, because only 4% of patients had not failed this class of therapies before trial enrollment.

In addition, we further evaluated the efficacy of upadacitinib after patients received different regimens of prior therapies: 2 anti-TNFα therapies only; an anti-TNFα therapy and ustekinumab; or $\geq$1 anti-TNFα therapy, ustekinumab, and vedolizumab/natalizumab. Data for patients who received anti-TNFα therapy and vedolizumab/natalizumab were not included because of small sample sizes. Across all subgroups, achievement of clinical and endoscopic outcomes was greater for upadacitinib- vs placebo-treated patients at weeks 12 and 52 (Supplementary Figures 9 and 10). At week 12 of the induction studies, rates were lower for SF/APS or CDAI clinical remission and endoscopic response for patients who had been previously treated with all 3 different classes of biologics ($\geq$1 anti-TNFα therapy, ustekinumab, and vedolizumab/natalizumab) before receiving upadacitinib. These patients had higher baseline CD duration, corticosteroid use, SES-CD, hs-CRP, and SF compared with the total study population,[5] with all other clinical characteristics similar to the overall study patients. Caution should be exercised when interpreting results for this subgroup because of small sample sizes.

Safety assessments. Patients receiving upadacitinib 45 mg during induction experienced AEs at a similar rate to patients receiving placebo (without prior biologic failure: 59.8% vs 52.5%; with prior biologic failure: 67.2% vs 66.1%; Table 2). During the maintenance study, patients receiving upadacitinib across all subgroups of interest had similar or lower AE rates (events/100 patient-years) vs placebo (without prior biologic failure: placebo, 275.5; upadacitinib 15 mg, 249.8; upadacitinib 30 mg, 265.6; with prior biologic failure: placebo, 466.0; upadacitinib 15 mg, 353.0; upadacitinib 30 mg, 304.1; Table 3). The safety profile in these subgroups was consistent with that of the overall population and AEs of special interest. Serious infections, herpes zoster, neutropenia, and malignancies were rare.

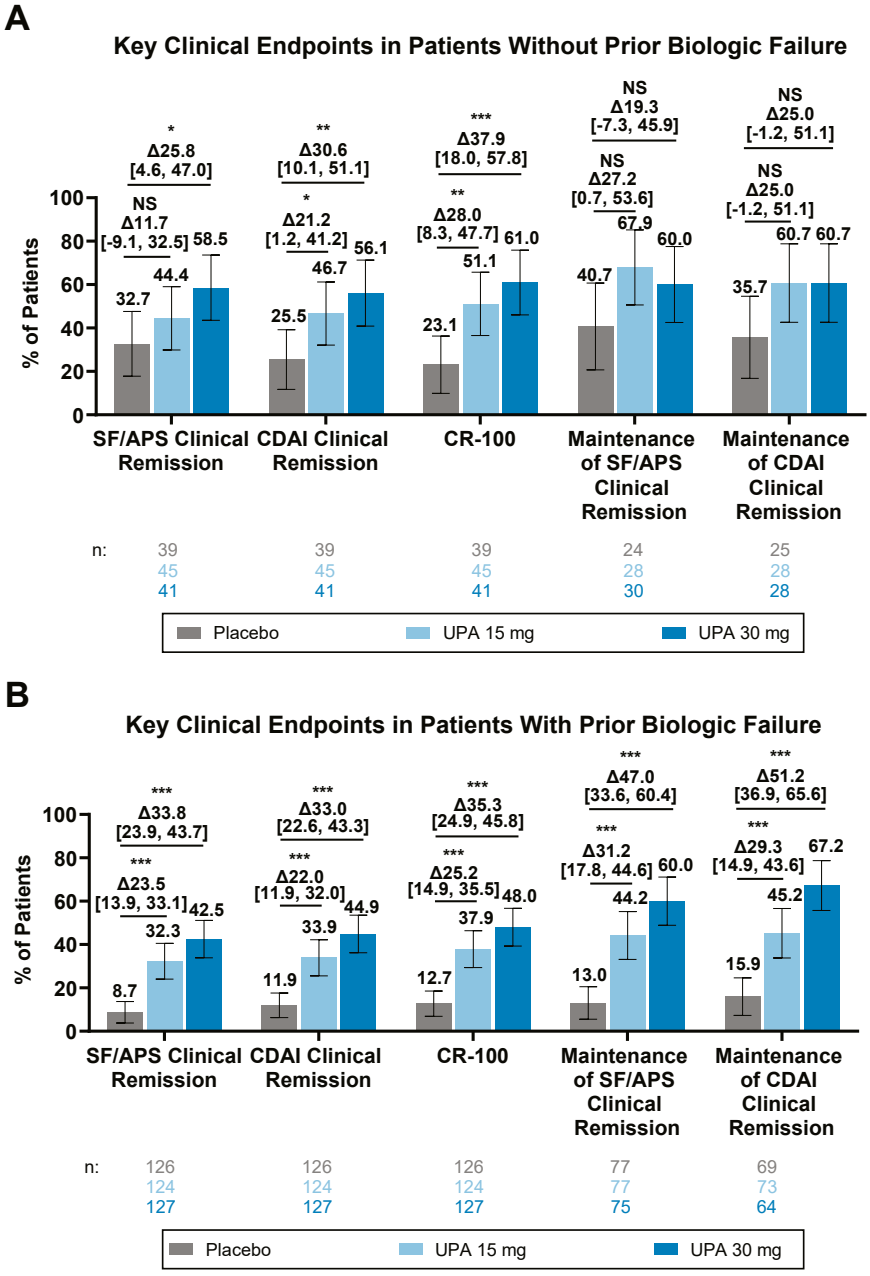


Figure 2. Achievement of key clinical endpoints at week 52 of maintenance in (*A*) patients without prior biologic failure and (*B*) with prior biologic failure. *Error bars* represent 95% confidence intervals. Δ values represent the percent difference between upadacitinib and placebo, with confidence intervals in brackets. *Nominal $P < .05$; **nominal $P < .01$; ***nominal $P < .001$ vs placebo. UPA, upadacitinib.

Discussion

In this post hoc analysis of the phase 3 U-EXCEL, U-EXCEED, and U-ENDURE trials, patients receiving upadacitinib achieved higher rates of clinical and endoscopic outcomes and biomarker normalization vs placebo, regardless of prior biologic exposure. Achievement of clinical, endoscopic, and biomarker outcomes occurred at higher absolute rates for patients without prior biologic failure vs patients with prior biologic failure. The achievement of these outcomes, particularly at week 12 of induction, may indicate an opportunity for patients to experience better outcomes when given upadacitinib earlier in the treatment course of CD, per local guidelines.[7]

The trend of higher efficacy response rates observed in patients without vs with prior biologic failure is consistent with other phase 3 results published for adalimumab (clinical remission at week 26), ustekinumab (UNITI-1/2, clinical remission at week 44), vedolizumab (GEMINI 2/3, clinical remission and clinical response at week 10), and risankizumab (ADVANCE, MOTIVATE, and FORTIFY, various clinical and endoscopic outcomes at weeks 12 and 52).[9–14] Differences in study designs and patient populations of these previous studies prevent direct comparisons with our current analysis.

The treatment effect of upadacitinib vs placebo for clinical and endoscopic outcomes was generally similar in both subgroups and remained consistently high in patients who had failed 1–2 prior biologic therapies.

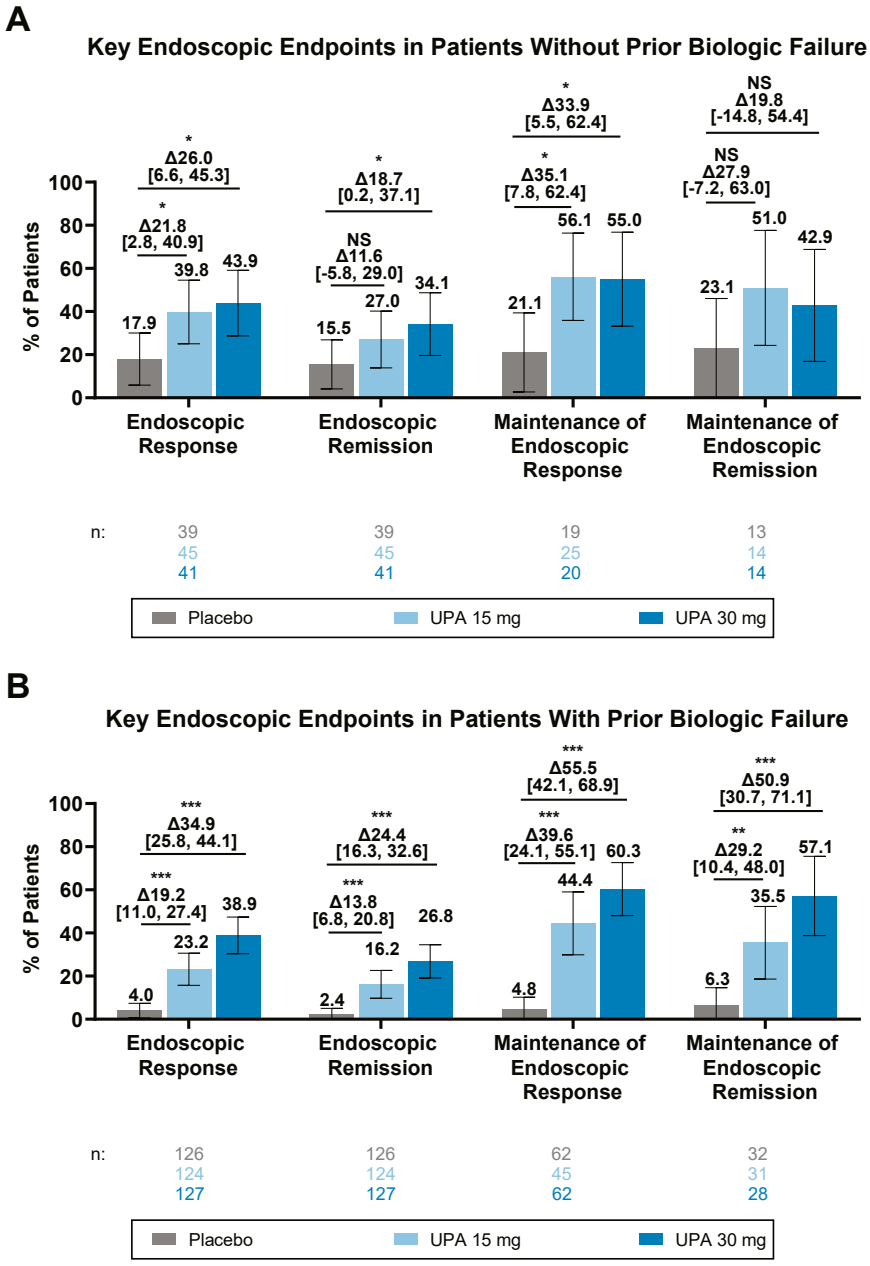


Figure 3. Achievement of key endoscopic endpoints at week 52 of maintenance in (*A*) patients without prior biologic failure and (*B*) with prior biologic failure. *Error bars* represent 95% confidence intervals. *Nominal $P < .05$; **nominal $P < .01$; ***nominal $P < .001$ vs placebo. Δ values represent the percent difference between upadacitinib and placebo, with confidence intervals in brackets. UPA, upadacitinib.

Rates of efficacy outcomes in patients with >2 prior biologic failures were generally lower. Evaluation of patients who had previously failed ≥1 anti-TNFα, ustekinumab, and vedolizumab/natalizumab, a population with more severe baseline disease characteristics, showed that upadacitinib still provided clinical benefit. However, the lower response rates for these patients who had failed all 3 of these prior biologic classes again support the use of upadacitinib earlier during treatment. During the maintenance study, a greater dose-response relationship was generally observed for patients receiving upadacitinib 30 mg vs upadacitinib 15 mg. This effect was more pronounced for patients with prior biologic failure, indicating a potential greater clinical benefit of upadacitinib 30 mg for patients with a higher disease burden or more refractory disease.

The safety profile for upadacitinib in these subgroups was consistent with the overall population, with no new safety risks identified.[5] Generally, the incidence of AEs in the induction and maintenance studies was lower for patients without vs with prior biologic failure, which may be due to higher baseline corticosteroid use, disease severity, and frequency of CD complications in this patient population. Venous thromboembolic events and malignancies were rare across both subgroups of upadacitinib-treated patients, and rates of serious infections were similar between upadacitinib and placebo groups. Notably, rates of any AEs observed during maintenance within each subgroup were lower for upadacitinib vs placebo. Although the results of this analysis suggest an overall favorable benefit-risk profile of upadacitinib in CD, use of upadacitinib should be based on

Table 2. Summary of Safety During the Induction Studies[a]

Adverse event, n (%)	Without prior biologic failure		With prior biologic failure	
	PBO (n = 99)	UPA 45 mg (n = 189)	PBO (n = 248)	UPA 45 mg (n = 485)
Any AE	52 (52.5)	113 (59.8)	164 (66.1)	326 (67.2)
Any serious AE	5 (5.1)	9 (4.8)	24 (9.7)	45 (9.3)
Any severe AE	5 (5.1)	14 (7.4)	30 (12.1)	43 (8.9)
Deaths[b]	0	0	0	1 (0.2)
AEs of special interest				
Serious infection	1 (1.0)	1 (0.5)	5 (2.0)	12 (2.5)
Opportunistic infection (excluding tuberculosis and herpes zoster)[c]	0	0	0	2 (0.4)
Herpes zoster	0	5 (2.6)	0	10 (2.1)
Anemia	6 (6.1)	17 (9.0)	13 (5.2)	33 (6.8)
Lymphopenia	5 (5.1)	2 (1.1)	3 (1.2)	9 (1.9)
Neutropenia	1 (1.0)	7 (3.7)	0	7 (1.4)
Creatine phosphokinase elevation	0	5 (2.6)	4 (1.6)	15 (3.1)
Hepatic disorder	3 (3.0)	5 (2.6)	7 (2.8)	13 (2.7)
Renal disorder	0	0	0	2 (0.4)
Venous thromboembolic events[d]	0	0	0	0
Adjudicated gastrointestinal perforation	0	0	0	1 (0.2)
Malignancies (all types)	0	0	0	0

PBO, placebo; UPA, upadacitinib.
[a]Safety population includes all patients who received ≥1 dose of study drug during induction.
[b]One non-treatment emergent death due to infectious shock (prior biologic failure, UPA 45 mg) occurred 159 days after the patient's premature discontinuation from the study.
[c]Opportunistic infections (excluding tuberculosis and herpes zoster) during the U-EXCEED study included 1 patient with cytomegalovirus infection and 1 patient with *Pneumocystis jirovecii* pneumonia (both UPA 45 mg).
[d]Defined as deep vein thrombosis and pulmonary embolism (fatal and non-fatal).

Table 3. Summary of Safety During the Maintenance Study[a]

AEs (events/100 PY)	Without prior biologic failure			With biologic failure		
	PBO (n = 53) PY = 47.6	UPA 15 mg (n = 57) PY = 70.0	UPA 30 mg (n = 59) PY = 71.5	PBO (n = 170) PY = 90.8	UPA 15 mg (n = 164) PY = 155.3	UPA 30 mg (n = 170) PY = 189.8
Any AE	131 (275.5)	175 (249.8)	190 (265.6)	423 (466.0)	548 (353.0)	577 (304.1)
Any serious AE	5 (10.5)	12 (17.1)	18 (25.2)	39 (43.0)	26 (16.7)	29 (15.3)
Any severe AE	5 (10.5)	13 (18.6)	13 (18.2)	39 (43.0)	25 (16.1)	29 (15.3)
Deaths	0	0	0	0	0	0
AEs of special interest						
Serious infection	1 (2.1)	4 (5.7)	3 (4.2)	9 (9.9)	5 (3.2)	12 (6.3)
Opportunistic infection (excluding tuberculosis and herpes zoster)[b]	0	1 (1.4)	1 (1.4)	0	0	0
Herpes zoster	2 (4.2)	2 (2.9)	2 (2.8)	3 (3.3)	7 (4.5)	12 (6.3)
Anemia	5 (10.5)	7 (10.0)	6 (8.4)	10 (11.0)	8 (5.2)	10 (5.3)
Lymphopenia	2 (4.2)	0	7 (9.8)	8 (8.8)	11 (7.1)	16 (8.4)
Neutropenia	0	0	1 (1.4)	1 (1.1)	7 (4.5)	5 (2.6)
Creatine phosphokinase elevation	1 (2.1)	2 (2.9)	4 (5.6)	3 (3.3)	7 (4.5)	6 (3.2)
Hepatic disorder	0	4 (5.7)	12 (16.8)	3 (3.3)	19 (12.2)	14 (7.4)
Renal disorder	1 (2.1)	0	1 (1.4)	2 (2.2)	0	0
Venous thromboembolic events[c]	0	0	1 (1.4)	0	0	0
Adjudicated gastrointestinal perforation	0	0	0	1 (1.1)	1 (0.6)	1 (0.5)
Malignancies (all types)	2 (4.2)	0	0	0	1 (0.6)	4 (2.1)

PBO, placebo; PY, patient-years; UPA, upadacitinib.
[a]Safety population includes all patients who received ≥1 dose of study drug during maintenance.
[b]Opportunistic infections (excluding tuberculosis and herpes zoster) during the U-ENDURE study were reported in 1 patient receiving UPA 15 mg (*Pneumocystis jirovecii* pneumonia) and 2 patients receiving UPA 30 mg (esophageal candidiasis and cytomegalovirus infection reactivation).
[c]Defined as deep vein thrombosis and pulmonary embolism (fatal and non-fatal).

individual patient-specific factors and adhere to local regulatory guidelines and the approved product label.

The limitations of this analysis include its post hoc nature and small sample sizes for certain subgroups, particularly for patients without biologic failure in the maintenance period, patients who had no prior anti-TNFα exposure, and for those with different failed prior biologic classes. Furthermore, efficacy outcomes were based on non-responder imputation incorporating MI to handle missing data due to COVID-19. Because there was only limited missing data due to COVID-19, the imputation of these missing data with MI did not have a substantial effect on the analysis compared with a traditional non-responder imputation analysis. Direct comparisons with other advanced therapies are not possible with the data from this placebo-controlled phase 3 clinical trial analysis. One network meta-analysis showed that upadacitinib ranked first and third for maintenance of remission and induction of clinical response, respectively, in patients with prior exposure to biologic therapy. However, the analysis did not report data for upadacitinib among patients naive to biologic therapy, only presented maintenance of remission data from clinical trials with a rerandomization design, and did not consider endoscopic outcomes.[15] Further indirect treatment comparisons are needed to integrate the newer data for upadacitinib presented in this article and evaluate across the CD treatment landscape.

Upadacitinib improved clinical and endoscopic outcomes across multiple lines of therapy and may help patients achieve the short-, intermediate-, and long-term goals of symptomatic control, remission, biomarker normalization, and endoscopic healing, respectively, as recommended by STRIDE-II.[7] The results of this analysis indicate that upadacitinib is an efficacious and tolerable treatment option for patients, whether early in their treatment course or after having failed previous advanced treatment regimens.

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.2024.02.026.

References

1. Roda G, Jharap B, Neeraj N, et al. Loss of response to anti-TNFs: definition, epidemiology, and management. Clin Transl Gastroenterol 2016;7:e135.
2. Barber GE, Yajnik V, Khalili H, et al. Genetic markers predict primary non-response and durable response to anti-TNF biologic therapies in Crohn's disease. Am J Gastroenterol 2016; 111:1816–1822.
3. Privitera G, Pugliese D, Rapaccini GL, et al. Predictors and early markers of response to biological therapies in inflammatory bowel diseases. J Clin Med 2021;10.
4. Singh S, George J, Boland BS, et al. Primary non-response to tumor necrosis factor antagonists is associated with inferior response to second-line biologics in patients with inflammatory bowel diseases: a systematic review and meta-analysis. J Crohns Colitis 2018;12:635–643.
5. Loftus EV Jr, Panes J, Lacerda AP, et al. Upadacitinib induction and maintenance therapy for Crohn's disease. N Engl J Med 2023;388:1966–1980.
6. Le Berre C, Peyrin-Biroulet L, group S-Is. Selecting end points for disease-modification trials in inflammatory bowel disease: the SPIRIT ocnsensus from the IOIBD. Gastroenterology 2021; 160:1452–1460.e1421.
7. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD)—determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology 2021;160:1570–1583.
8. RINVOQ (upadacitinib). Prescribing information. AbbVie Inc, 2023. Available at: https://www.rxabbvie.com/pdf/rinvoq_pi.pdf. Accessed Februrary 12, 2024.
9. Sands BE, Sandborn WJ, Van Assche G, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease in patients naive to or who have failed tumor necrosis factor antagonist therapy. Inflamm Bowel Dis 2017;23:97–106.
10. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007; 132:52–65.
11. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2016;375:1946–1960.
12. Ferrante M, Peyrin-Biroulet L, Dignass A, et al. Clinical and endoscopic improvements with risankizumab induction and maintenance dosing versus placebo are observed irrespective of number of prior failed biologics. Am J Gastroenterol 2022;117:e498–e499.
13. Ferrante M, Panaccione R, Baert F, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. Lancet 2022;399:2031–2046.
14. D'Haens G, Panaccione R, Baert F, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. Lancet 2022; 399:2015–2030.
15. Barberio B, Gracie DJ, Black CJ, et al. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. Gut 2023;72:264–274.

Correspondence
Address correspondence to: Laurent Peyrin-Biroulet, MD, PhD, Department of Gastroenterology, INFINY Institute, FHU-CURE, INSERME, NGERE, Nancy University Hospital, F-54500, Vandœuvre-lès-Nancy; Groupe Hospitalier Privé Ambroise Paré - Hartmann, Paris IBD Center, 92200 Neuilly-sur-Seine, France. e-mail: consultinglpb@gmail.com.

Acknowledgments
AbbVie and the authors thank all the trial investigators and the patients who participated in this clinical trial. Medical writing support was provided by Spencer Hughes, PhD, and Jay Parekh, PharmD, ISMPP CMPP, of JB Ashtin, and funded by AbbVie.

CRediT Authorship Contributions
Laurent Peyrin-Biroulet, MD, PhD (Conceptualization: Equal; Data Curation: Equal; Investigation: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)

Remo Panaccione, MD (Data Curation: Equal; Investigation: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Edouard Louis, MD (Data Curation: Equal; Investigation: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Raja Atreya, MD (Data Curation: Equal; Investigation: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
David T. Rubin, MD (Data Curation: Equal; Investigation: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
James O. Lindsay, PhD (Data Curation: Equal; Investigation: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Jesse Siffledeen, MD (Data Curation: Equal; Investigation: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Dana J. Lukin, MD (Data Curation: Equal; Investigation: Equal; Visualization: Equal Writing – original draft: Equal; Writing – review & editing: Equal)
John Wright, MD (Data Curation: Equal; Investigation: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Kenji Watanabe, MD, PhD (Data Curation: Equal; Investigation: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Sharanya Ford, PhD (Conceptualization: Lead; Supervision: Lead; Visualization: Lead; Writing – original draft: Equal; Writing – review & editing: Equal)
Valencia P. Remple, PhD (Conceptualization: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Ana P. Lacerda, MD (Conceptualization: Lead; Data Curation: Lead; Supervision: Lead; Visualization: Lead; Writing – original draft: Equal; Writing – review & editing: Equal)
Elena Dubcenco, MD (Conceptualization: Equal; Data Curation: Lead; Supervision: Lead; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Andrew Garrison, MS (Conceptualization: Lead; Formal Analysis: Lead; Validation: Lead; Visualization: Lead; Writing – original draft: Equal; Writing – review & editing: Equal)
Qian Zhou, PhD (Conceptualization: Lead; Formal Analysis: Lead; Validation: Lead; Visualization: Lead; Writing – original draft: Equal; Writing – review & editing: Equal)
Sofie Berg, PharmD, PhD (Conceptualization: Supporting; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Samuel I. Anyanwu, PhD (Conceptualization: Supporting; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)
Stefan Schreiber, MD (Data Curation: Equal; Investigation: Equal; Visualization: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)

Conflicts of interest

These authors disclose the following: Laurent Peyrin-Biroulet has received personal fees from AbbVie, Adacyte, Alimentiv, Alma Bio Therapeutics, Amgen, Applied Molecular Transport, Arena, Biogen, Bristol Myers Squibb, Celltrion, CONNECT Biopharm, Cytoki Pharma, Enthera, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead, Gossamer Bio, GlaxoSmithKline, HAC-Pharma, IAG Image Analysis, InDex Pharmaceuticals, Inotrem, Janssen, Lilly, Medac, Mopac, Morphic, MSD, Norgine, Nordic Pharma, Novartis, OM Pharma, ONO Pharma, OSE Immunotherapeutics, Pandion Therapeutics, Par'Immune, Pfizer, Prometheus, Protagonist, Roche, Sanofi, Sandoz, Takeda, Theravance, Thermo Fisher, Tigenix, Tillots, Viatris, Vifor, Ysopia, Abivax, Samsung, Ventyx, Roivant, and Vectivbio. Remo Panaccione has served as a consultant for Abbott, AbbVie, Abbivax, Alimentiv, Amgen, Arena Pharmaceuticals, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Eli Lilly, Ferring, Galapagos, Fresenius Kabi, Genentech, Gilead Sciences, Glaxo-Smith Kline, JAMP Bio, Janssen, Merck, Mylan, Novartis, Oppilan Pharma, Organon, Pandion Pharma, Pendopharm, Pfizer, Progenity, Prometheus Biosciences, Protagonist Therapeutics, Roche, Sandoz, Satisfai Health, Shire, Sublimity Therapeutics, Takeda Pharmaceuticals, Theravance Biopharma, Trellus, Viatris, Ventyx, and UCB and has received speaker's fees from AbbVie, Amgen, Arena Pharmaceuticals, Bristol-Myers Squibb, Celgene, Eli Lilly, Ferring, Fresenius Kabi, Gilead Sciences, Janssen, Merck, Organon, Pfizer, Roche, Sandoz, Shire, and Takeda Pharmaceuticals. 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. Raja Atreya has served as a speaker or consultant for or has received research grants from AbbVie, Arena Pharmaceuticals, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion Healthcare, Falk Foundation, Ferring, Fresenius Kabi, Galapagos, Gilead, InDex Pharmaceuticals, Janssen-Cilag, Lilly, MSD Sharp & Dohme, Pfizer, Roche Pharma, Samsung Bioepsis, and Takeda. David T. Rubin has received grant support from Takeda and has served as a consultant for AbbVie, Abgenomics, Allergan, Arena Pharmaceuticals, Bellatrix Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Celgene/Syneos, Checkcap, Dizal Pharmaceuticals, GalenPharma/Atlantica, Genentech/Roche, Gilead Sciences, Ichnos Sciences, InDex Pharmaceuticals, Iterative Scopes, Janssen, Lilly, Materia Prima, Narrow River Management, Pfizer, Prometheus Laboratories, Reistone, Takeda, and Techlab. James O. Lindsay has received consulting and/or speaker fees from AbbVie, Atlantic Healthcare, Bristol Myers Squibb, Celgene, Celltrion, Engytix, Ferring Pharmaceuticals, Galapagos, Gilead, GSK, Janssen, Lilly, MSD, Napp, Pfizer, Shire, Takeda, and Vifor Pharma and has received investigator-led research grants from AbbVie, Gilead, Pfizer, Shire, and Takeda. Jesse Siffledeen has received consultancy and/or speaking honoraria fees from AbbVie, BioJamp, Bristol Myers Squibb, Celltrion, Ferring, Fresenius Kabi, Janssen, Pfizer, Shire, and Takeda and has received educational grants from AbbVie and BioJamp. Dana J. Lukin has received consulting fees from AbbVie, Abgenomics, Boehringer Ingelheim, Bristol Myers Squibb, Fresenius Kabi, Janssen, Lilly, Magellan Health, Palatin Technologies, Pfizer, Prometheus Laboratories, PSI, and Takeda; has received research funding from AbbVie, Boehringer Ingelheim, Janssen, and Takeda; and has served on speaker's bureaus for AbbVie and Janssen. Kenji Watanabe has received consulting fees from AbbVie, EA Pharma, GlaxoSmithKline, Janssen, JIMRO, Kissei, Kyorin, Mitsubishi Tanabe, Mochida, Nippon Kayaku, Olympus, Pfizer, Sandoz, Takeda, and Zeria and has also received research grants from AbbVie, EA Pharma, EP CRSU, Helmsley Charitable Trust, JIMRO, Mitsubishi Tanabe, Mochida, Nippon Kayaku, and Takeda. Sharanya Ford, Valencia P. Remple, Ana P. Lacerda, Elena Dubcenco, Andrew Garrison, Qian Zhou, Sofie Berg, and Samuel I. Anyanwu are full-time employees of AbbVie and may hold AbbVie stock, stock options, and/or patents. Stefan Schreiber has received consulting fees from AbbVie, Amgen, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Falk Pharma, Ferring, Galapagos/Gilead, Genentech/Roche, GlaxoSmithKline, IMAB Biopharma, Lilly, MSD, Pfizer, Shire, and Takeda. The remaining authors disclose no conflicts.

Funding

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship.