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# Induction of Endoscopic Response, Remission, and Ulcer-Free Endoscopy With Upadacitinib Is Associated With Improved Clinical Outcomes and Quality of Life in Patients With Crohn's Disease

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**Background:** We evaluated the association of achieving endoscopic outcomes at week 12 of induction with improvements in clinical outcomes and quality of life (QoL) at week 52 of maintenance in patients with moderately to severely active Crohn's disease (CD) treated with upadacitinib (UPA).

**Methods:** This post hoc analysis evaluated data from 2 phase 3 induction trials (NCT03345836 and NCT03345849) and 1 maintenance (NCT03345823) trial. Clinical responders to 12-week induction therapy with UPA who also received 52-week maintenance treatment with UPA were included. Endoscopic response, remission, healing, and ulcer-free endoscopy were assessed at week 12. Meaningful improvements in clinical and QoL outcomes were evaluated at week 52.

**Results:** A significantly greater proportion of patients who achieved an endoscopic response at the end of induction, compared with patients who did not, attained Crohn's Disease Activity Index (CDAI) remission (52.0% vs 34.6%; $P \leq .01$), corticosteroid-free CDAI remission (50.0% vs 30.9%), Inflammatory Bowel Disease Questionnaire remission (52.6% vs 30.3%), and meaningful improvements in Functional Assessment of Chronic Illness Therapy—Fatigue response (46.7% vs 25.9%), overall work impairment (47.1% vs 26.5%), and daily activity impairment (53.3% vs 34.1%) (all $P < .05$) at week 52. Similar findings were observed for patients who achieved endoscopic remission, endoscopic healing, and ulcer-free endoscopy at the end of induction vs those who did not.

**Conclusions:** Early improvement in endoscopic outcomes after UPA induction treatment was associated with long-term meaningful improvements in clinical outcomes and QoL in patients with CD.

**Clinical Registration number:** U-EXCEED induction trial (NCT03345836), U-EXCEL induction trial (NCT03345849), and U-ENDURE maintenance trial (NCT03345823).

## Lay Summary

In patients with Crohn's disease treated with 12 weeks of upadacitinib, a greater proportion with early improvements in endoscopic response, remission, healing, and ulcer-free endoscopy, vs those without improvements, attained long-term meaningful improvements in clinical outcomes and quality of life.

**Key Words:** Crohn's disease, clinical trials, endoscopy, quality of life, upadacitinib

## Introduction

Crohn's disease (CD) is characterized by chronic inflammation of the gastrointestinal tract, resulting in symptoms of diarrhea, abdominal pain (AP), weight loss, anemia, and fatigue.[1-3] As a consequence, patients with CD experience reduced quality of life (QoL) and disease-related impact on work productivity, contributing to a high disease burden.[2,4,5]

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) Initiative of the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) recommends endoscopic healing and normalization of QoL as important long-term treatment goals in CD.[6] Treatment targets are important for disease management as they help patients and physicians to assess and monitor disease progression, optimize therapy, and work toward goals

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**Key Messages**

**What is already known?**

Early endoscopic improvements in patients with Crohn's disease have been associated with favorable long-term outcomes, such as a decreased risk of disease progression and achievement of clinical remission.

**What is new here?**

This study demonstrates the association between early endoscopic response, remission, and ulcer-free endoscopy after 12-week induction treatment with upadacitinib and long-term meaningful improvements in clinical outcomes at week 52, in patients with Crohn's disease.

**How can this study help patient care?**

The findings illustrate the importance of achieving improvements in intestinal inflammation early during treatment, to attain endoscopic healing and long-term improvement in quality of life for patients with moderate to severe Crohn's disease.

of improving outcomes and decreasing the risk of long-term bowel damage and disability.[7,8]

In phase 3 trials of patients with CD, treatment with upadacitinib (UPA), an oral, reversible, and selective Janus kinase inhibitor, resulted in endoscopic remission, along with clinical and endoscopic responses, and improvements in fatigue and QoL, during a 12-week induction and a 52-week maintenance period, compared with placebo (PBO).[9] Additionally, real-world evidence of patients with moderate to severe CD confirmed the effectiveness of UPA in inducing a clinical response and remission at 3-month follow-up.[10] Findings from phase 2b and 3 trials suggested that patients with moderate to severe CD who received UPA vs PBO had meaningful improvements in QoL and work productivity at week 52.[11,12]

Early endoscopic improvements in patients with CD have been associated with favorable long-term outcomes, such as a decreased risk of disease progression and achievement of clinical remission.[13-15] The relationship between early endoscopic response, remission, and ulcer-free endoscopy after UPA induction treatment, and long-term improvement in symptoms, inflammatory biomarkers, and QoL in patients with CD has not been fully characterized.

The aim of this study was to evaluate the relationship between achieving endoscopic outcomes at week 12 and attaining clinical outcomes and improvement in QoL at week 52 in patients with moderately to severely active CD who were treated with UPA.

## Materials and Methods

### Study Design and Participants

This was a post hoc analysis of data from phase 3 clinical trials, 2 UPA induction (U-EXCEED [NCT03345836] and U-EXCEL [NCT03345849]) trials and 1 maintenance (U-ENDURE [NCT03345823]) trial. These trials evaluated the efficacy and safety of UPA in patients with moderate to severe CD who had inadequately responded to or were intolerant to conventional or biologic therapy.[9] Patients 18-75 years of age with a confirmed diagnosis of CD ≥3 months before baseline were included. Eligible patients had a Simple Endoscopic Score for CD (SES-CD; excluding the presence of narrowing component) ≥6 (or ≥4 for patients with isolated ileal disease), as confirmed by a central reader. Further details on inclusion and exclusion criteria for U-EXCEED and U-EXCEL are published elsewhere.[9]

Patients who had a clinical response to 12-week induction therapy with UPA (45 mg once daily [QD]) in U-EXCEED or U-EXCEL and received maintenance therapy with UPA (15 or 30 mg QD) in U-ENDURE for up to 52 weeks were included in this study (Figure 1). Patients receiving PBO during maintenance were excluded from this analysis. A clinical response was defined as a ≥30% decrease in average daily very soft or liquid stool frequency (SF) and/or ≥30% decrease in average daily AP score, both not worse than baseline.

### Outcomes

#### Endoscopic endpoints

At the end of induction, all patients underwent an endoscopy to serve as the reference for all subsequent visits. The following definitions of endoscopic improvement were used:

- Endoscopic response: a decrease in SES-CD >50% from baseline (or for patients with isolated ileal disease and an SES-CD of 4, at least a 2-point reduction from baseline).
- Endoscopic remission: SES-CD ≤4 and at least a 2-point reduction from baseline and no subscore >1 in any individual variable.
- Endoscopic healing: SES-CD ≤2.
- Ulcer-free endoscopy (absence of ulceration): SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥1 at baseline of the induction study.

#### Clinical outcomes

Clinical outcomes evaluated at week 52 were CD Activity Index (CDAI) remission (CDAI <150), CDAI response (≥100-point decrease from baseline), corticosteroid-free CDAI remission (discontinuation of corticosteroid use within 90 days before week 52 and achievement of clinical remission [CDAI <150] among patients receiving corticosteroids at baseline), SF remission (average daily SF ≤2.8 and not worse than baseline), AP remission (average daily AP score ≤1 and not worse than baseline), high-sensitivity C-reactive protein (hs-CRP) level ≤5 mg/L, and fecal calprotectin level (f-cal) (≤250 µg/g).

#### QoL outcomes

Meaningful improvements evaluated at week 52 in QoL outcomes included the Inflammatory Bowel Disease Questionnaire (IBDQ) remission (IBDQ total score ≥170 points),[16] IBDQ response (defined as ≥16-point increase from induction baseline),[17] and improvements in Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-Fatigue) (clinically meaningful improvement defined as ≥9-point increase from induction baseline),[18] in 36-Item Short Form Health Survey (SF-36) Physical Component Score (PCS) and Mental Component Score (MCS) (clinically meaningful improvement defined as ≥5-point increase from induction baseline),[19] and in Work Productivity and Activity Impairment Questionnaire (WPAI) domains of overall work impairment,

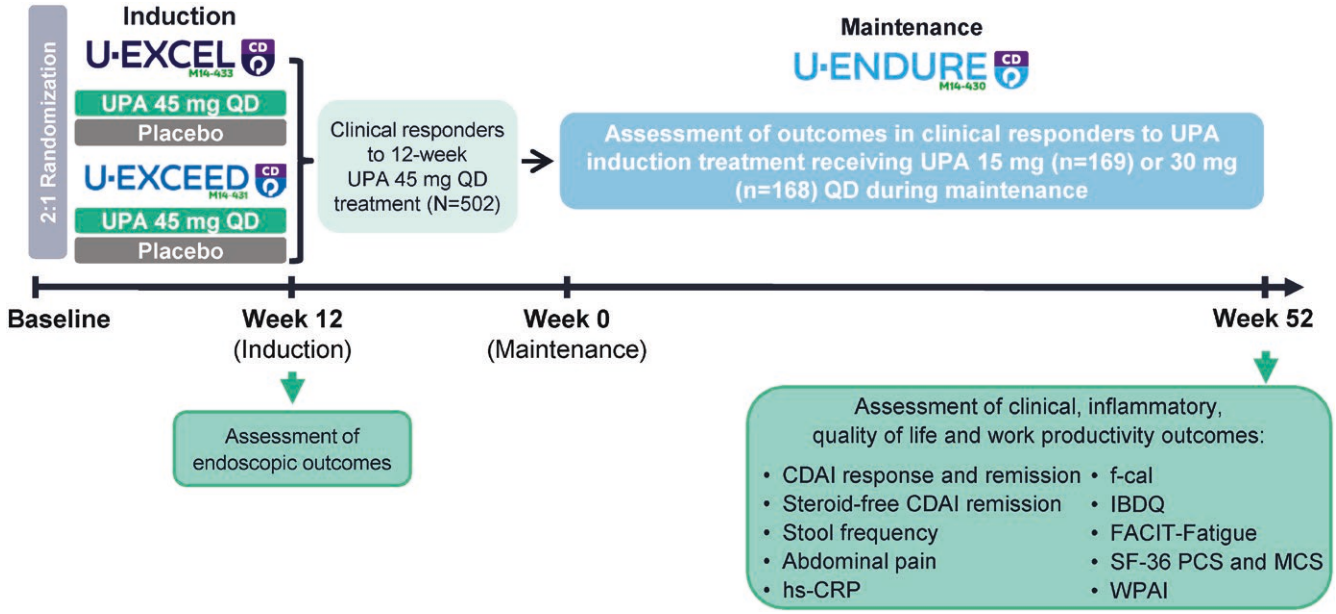


**Figure 1.** Study design. Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy—Fatigue; f-cal, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Score; PCS, Physical Component Score; QD, once daily; SF-36, Short Form 36; UPA, upadacitinib; WPAI, Work Productivity and Activity Impairment Questionnaire.

absenteeism, presenteeism, and activity impairment (clinically meaningful improvement defined as a ≥7% reduction in each domain from induction baseline).[20]

### Statistical Analyses

Baseline characteristics were reported using descriptive statistics. Clinical and QoL outcomes were compared between patients who did or did not achieve endoscopic outcomes at the end of the induction period week 12 (after 12 weeks of UPA). Differences between groups were analyzed using the Chi-square test and reported as nominal *P* values ($P \leq .05$).

### Ethical Requirements

All randomized controlled trials were conducted in compliance with the protocol, International Conference on Harmonisation guidelines, and the ethical principles of the Declaration of Helsinki. As per Good Clinical Practice, the study protocol, informed consent forms, and all other explanatory materials were approved by the relevant ethics committees or institutional review board at all study sites. All patients provided informed consent before study participation.

## Results

### Baseline Characteristics

A total of 502 clinical responders to the 12-week UPA induction treatment were re-randomized to 15 mg UPA ($n = 169$), 30 mg UPA ($n = 168$), or PBO ($n = 165$) in the maintenance study. We assessed endoscopic outcomes at induction week 12, and clinical and patient-reported outcomes at maintenance week 52 in the 337 patients who received UPA (15 or 30 mg daily) during the maintenance study (Figure 1).

Of the 337 UPA-treated patients included in this post hoc analysis, 152 (45.1%) had an endoscopic response at week 12 of induction (Table 1). Patients who achieved an endoscopic response were younger (35.0 ± 12.3 vs 39.6 ± 13.9 years), had the CD for a shorter period of time (8.5 ± 8.6 vs 11.1 ± 8.6 years), and were more likely to have the ileal–colonic disease (59.2% vs 39.5%) than patients who did not achieve an endoscopic response.

Disease activity measures at baseline differed between groups. Mean f-cal and SES-CD for patients with an endoscopic response following induction were lower (f-cal: 431.5 ± 715.2 µg/g, SES-CD: 3.5 ± 3.6) than in patients with no endoscopic response (f-cal:1079.9 ± 1824.4 µg/g, SES-CD: 11.6 ± 6.2). Mean baseline values for QoL outcomes were similar between patients who achieved an endoscopic response and those who did not.

Of 337 UPA-treated patients, 87 (25.8%), 62 (18.4%), and 75 (22.3%) achieved endoscopic remission, endoscopic healing, and ulcer-free endoscopy, respectively, at induction week 12. Baseline characteristics in patients who achieved endoscopic remission, endoscopic healing, and ulcer-free endoscopy were similar to patients who achieved an endoscopic response (Table 1).

### Clinical Outcomes

A significantly greater proportion of patients who achieved an endoscopic response at the end of induction, compared with patients who did not achieve an endoscopic response, attained CDAI remission (52.0% vs 34.6%; $P \leq .01$), CDAI response (54.6% vs 39.5%; $P \leq .01$), corticosteroid-free CDAI remission (50.0% vs 30.9%; $P \leq .05$), SF remission (57.9% vs 36.8%; $P \leq .001$), AP remission (53.3% vs 38.4%; $P \leq .01$), hs-CRP ≤5 mg/L (52.0% vs 30.8%; $P \leq .001$), and f-cal ≤250 µg/g (42.1% vs 21.6%; $P \leq .001$) at week 52 (Figure 2A).

Similar findings were observed for all clinical outcomes in patients who achieved endoscopic remission ($P \leq .01$), endoscopic healing ($P \leq .05$), or ulcer-free endoscopy ($P \leq .05$), compared with those who did not, at the end of induction (Figure 2B–D).

**Table 1.** Demographics and baseline characteristics of patients in the maintenance study.[a]

| Baseline characteristic | Endoscopic response | | Endoscopic remission | | Endoscopic healing | | Ulcer-free endoscopy | |
|---|---|---|---|---|---|---|---|---|
| | Yes (*n* = 152) | No (*n* = 185) | Yes (*n* = 87) | No (*n* = 250) | Yes (*n* = 62) | No (*n* = 275) | Yes (*n* = 75) | No (*n* = 262) |
| Male, *n* (%) | 93 (61.2) | 102 (55.1) | 50 (57.5) | 145 (58.0) | 36 (58.1) | 159 (57.8) | 45 (60.0) | 150 (57.3) |
| Age (y), mean ± SD | 35.0 ± 12.3 | 39.6 ± 13.9 | 33.9 ± 11.6 | 38.8 ± 13.7 | 35.2 ± 12.2 | 38.1 ± 13.6 | 36.2 ± 12.5 | 38.0 ± 13.6 |
| Race, *n* (%) | | | | | | | | |
| White | 87 (57.2) | 145 (78.4) | 53 (60.9) | 179 (71.6) | 37 (59.7) | 195 (70.9) | 45 (60.0) | 187 (71.4) |
| Black or African American | 6 (4.0) | 7 (3.8) | 3 (3.5) | 10 (4.0) | 3 (4.8) | 10 (3.6) | 4 (5.3) | 9 (3.4) |
| Asian | 56 (36.8) | 32 (17.3) | 30 (34.5) | 58 (23.2) | 22 (35.5) | 66 (24.0) | 25 (33.3) | 63 (24.1) |
| Multiple | 3 (2.0) | 1 (0.5) | 1 (1.2) | 3 (1.2) | 0 (0.0) | 4 (1.5) | 1 (1.3) | 3 (1.2) |
| Ethnicity, *n* (%) | | | | | | | | |
| Hispanic or Latino | 11 (7.2) | 13 (7.0) | 8 (9.2) | 16 (6.4) | 6 (9.7) | 18 (6.6) | 7 (9.3) | 17 (6.5) |
| Disease duration (y), *n* | 152 | 185 | 87 | 250 | 62 | 275 | 75 | 262 |
| Mean ± SD | 8.5 ± 8.6 | 11.1 ± 8.6 | 8.4 ± 8.7 | 10.5 ± 8.6 | 8.9 ± 9.3 | 10.2 ± 8.5 | 9.2 ± 9.6 | 10.2 ± 8.4 |
| Disease location, *n* (%) | | | | | | | | |
| Ileal only | 1 (0.7) | 41 (22.2) | 3 (3.5) | 39 (15.6) | 1 (1.6) | 41 (14.9) | 1 (1.3) | 41 (15.7) |
| Colonic only | 61 (40.1) | 71 (38.4) | 43 (49.4) | 89 (35.6) | 36 (58.1) | 96 (34.9) | 43 (57.3) | 89 (34.0) |
| Ileal-colonic | 90 (59.2) | 73 (39.5) | 41 (47.1) | 122 (48.8) | 25 (40.3) | 138 (50.2) | 31 (41.3) | 132 (50.4) |
| Prior biologic use, *n* (%) | | | | | | | | |
| Bio-IR | 107 (70.4) | 144 (77.8) | 59 (67.8) | 192 (76.8) | 44 (71.0) | 207 (75.3) | 52 (69.3) | 199 (76.0) |
| CDAI, *n* | 152 | 185 | 87 | 250 | 62 | 275 | 75 | 262 |
| Mean ± SD | 131.1 ± 74.7 | 144.7 ± 80.7 | 129.4 ± 83.9 | 141.8 ± 76.1 | 138.1 ± 91.6 | 138.7 ± 75.1 | 139.6 ± 87.0 | 138.3 ± 75.7 |
| Abdominal pain score, *n* | 152 | 185 | 87 | 250 | 62 | 275 | 75 | 262 |
| Mean ± SD | 0.6 ± 0.6 | 0.7 ± 0.6 | 0.6 ± 0.6 | 0.7 ± 0.6 | 0.7 ± 0.6 | 0.7 ± 0.6 | 0.7 ± 0.6 | 0.7 ± 0.6 |
| Stool frequency, *n* | 152 | 185 | 87 | 250 | 62 | 275 | 75 | 262 |
| Mean ± SD | 1.0 ± 1.7 | 1.9 ± 1.9 | 1.1 ± 1.8 | 1.7 ± 1.8 | 1.2 ± 2.0 | 1.6 ± 1.8 | 1.3 ± 2.0 | 1.6 ± 1.8 |
| SES-CD, *n* | 152 | 166 | 87 | 231 | 62 | 256 | 75 | 243 |
| Mean ± SD | 3.5 ± 3.6 | 11.6 ± 6.2 | 1.1 ± 1.4 | 10.2 ± 6.0 | 0.3 ± 0.6 | 9.5 ± 6.1 | 0.9 ± 1.3 | 9.9 ± 6.1 |
| hs-CRP, *n* | 152 | 184 | 87 | 249 | 62 | 274 | 75 | 261 |
| Mean ± SD | 4.2 ± 12.0 | 8.8 ± 14.9 | 2.3 ± 5.3 | 8.3 ± 15.5 | 1.4 ± 2.3 | 7.9 ± 15.0 | 2.9 ± 6.8 | 7.8 ± 15.1 |
| f-cal, *n* | 148 | 181 | 86 | 243 | 62 | 267 | 75 | 254 |
| Mean ± SD | 431.5 ± 715.2 | 1079.9 ± 1824.4 | 167.8 ± 401.9 | 1007.8 ± 1638.8 | 96.1 ± 156.9 | 949.0 ± 1587.6 | 257.8 ± 527.7 | 944.9 ± 1615.8 |
| IBDQ total score, *n* | 151 | 184 | 86 | 249 | 62 | 273 | 75 | 260 |
| Mean ± SD | 179.0 ± 28.8 | 172.9 ± 30.9 | 182.3 ± 25.0 | 173.3 ± 31.3 | 180.6 ± 25.8 | 174.5 ± 30.9 | 179.4 ± 25.4 | 174.5 ± 31.2 |
| FACIT-Fatigue, *n* | 151 | 184 | 86 | 249 | 62 | 273 | 75 | 260 |
| Mean ± SD | 39.2 ± 10.4 | 37.2 ± 10.9 | 40.6 ± 9.3 | 37.3 ± 11.1 | 39.8 ± 9.6 | 37.8 ± 10.9 | 39.2 ± 9.8 | 37.8 ± 10.9 |
| SF-36 PCS, *n* | 151 | 184 | 86 | 249 | 62 | 273 | 75 | 260 |

**Table 1.** Continued

| Baseline characteristic | Endoscopic response | | Endoscopic remission | | Endoscopic healing | | Ulcer-free endoscopy | |
|---|---|---|---|---|---|---|---|---|
| | Yes ($n$ = 152) | No ($n$ = 185) | Yes ($n$ = 87) | No ($n$ = 250) | Yes ($n$ = 62) | No ($n$ = 275) | Yes ($n$ = 75) | No ($n$ = 262) |
| Mean ± SD | 50.8 ± 7.0 | 48.9 ± 7.7 | 51.3 ± 6.8 | 49.2 ± 7.6 | 50.9 ± 7.3 | 49.5 ± 7.4 | 50.9 ± 7.0 | 49.5 ± 7.5 |
| SF-36 MCS, $n$ | 151 | 184 | 86 | 249 | 62 | 273 | 75 | 260 |
| Mean ± SD | 47.6 ± 10.5 | 47.2 ± 10.4 | 48.5 ± 10.6 | 47.0 ± 10.4 | 48.0 ± 11.3 | 47.2 ± 10.3 | 48.1 ± 10.6 | 47.2 ± 10.4 |
| WPAI, $n$ | | | | | | | | |
| Mean ± SD | | | | | | | | |
| Absenteeism[b] | 89<br>7.1 ± 16.8 | 113<br>8.0 ± 19.7 | 58<br>6.8 ± 15.7 | 144<br>7.9 ± 19.5 | 43<br>8.1 ± 16.8 | 159<br>7.5 ± 18.9 | 50<br>7.0 ± 15.8 | 152<br>7.8 ± 19.3 |
| Presenteeism[b] | 88<br>21.3 ± 23.0 | 110<br>21.5 ± 19.8 | 58<br>18.3 ± 21.6 | 140<br>22.6 ± 21.0 | 43<br>20.2 ± 22.3 | 155<br>21.7 ± 21.0 | 50<br>21.2 ± 24.1 | 148<br>21.4 ± 20.2 |
| Activity impairment | 151<br>23.7 ± 25.4 | 184<br>25.7 ± 22.5 | 86<br>19.2 ± 22.1 | 249<br>26.7 ± 24.1 | 62<br>20.8 ± 22.7 | 273<br>25.7 ± 24.0 | 75<br>23.1 ± 24.7 | 260<br>25.3 ± 23.6 |
| Overall work impairment[b] | 89<br>25.5 ± 26.9 | 113<br>27.2 ± 25.4 | 58<br>22.2 ± 25.3 | 144<br>28.1 ± 26.1 | 43<br>24.7 ± 26.1 | 159<br>26.9 ± 26.0 | 50<br>25.0 ± 27.1 | 152<br>26.9 ± 25.7 |

Abbreviations: Bio-IR, inadequate response to biologics; CDAI, Crohn's Disease Activity Index; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy—Fatigue; f-cal, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Score; PCS, Physical Component Score; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF-36, Short Form 36; WPAI, Work Productivity and Activity Impairment Questionnaire.
[a]Gender, age, race, disease duration, disease location, and prior biological use are based on the patient information collected at the induction baseline; other characteristics are based on the maintenance baseline in U-ENDURE.
[b]Reported only to patients who were employed.

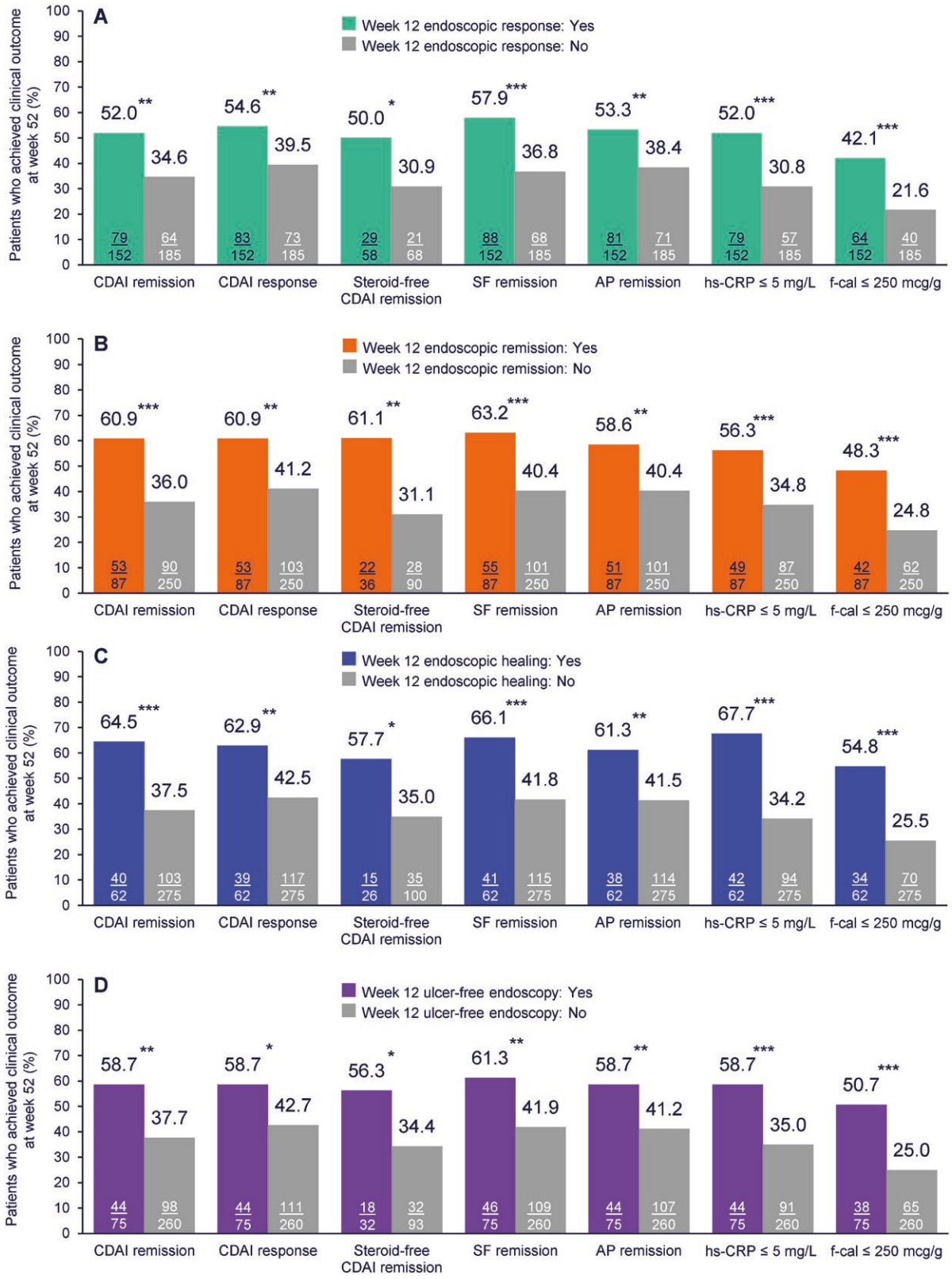


**Figure 2.** Clinical outcomes at week 52 among patients who achieved (A) an endoscopic response, (B) endoscopic remission, (C) endoscopic healing, or (D) ulcer-free endoscopy at the end of induction, compared with patients who did not. *Nominal *P*-value ≤.05; **nominal *P*-value ≤.01; ***nominal *P*-value <.001. Abbreviations: AP, abdominal pain; CDAI, Crohn's Disease Activity Index; f-cal, fecal calprotectin level; hs-CRP, high-sensitivity C-reactive protein; SF, stool frequency.

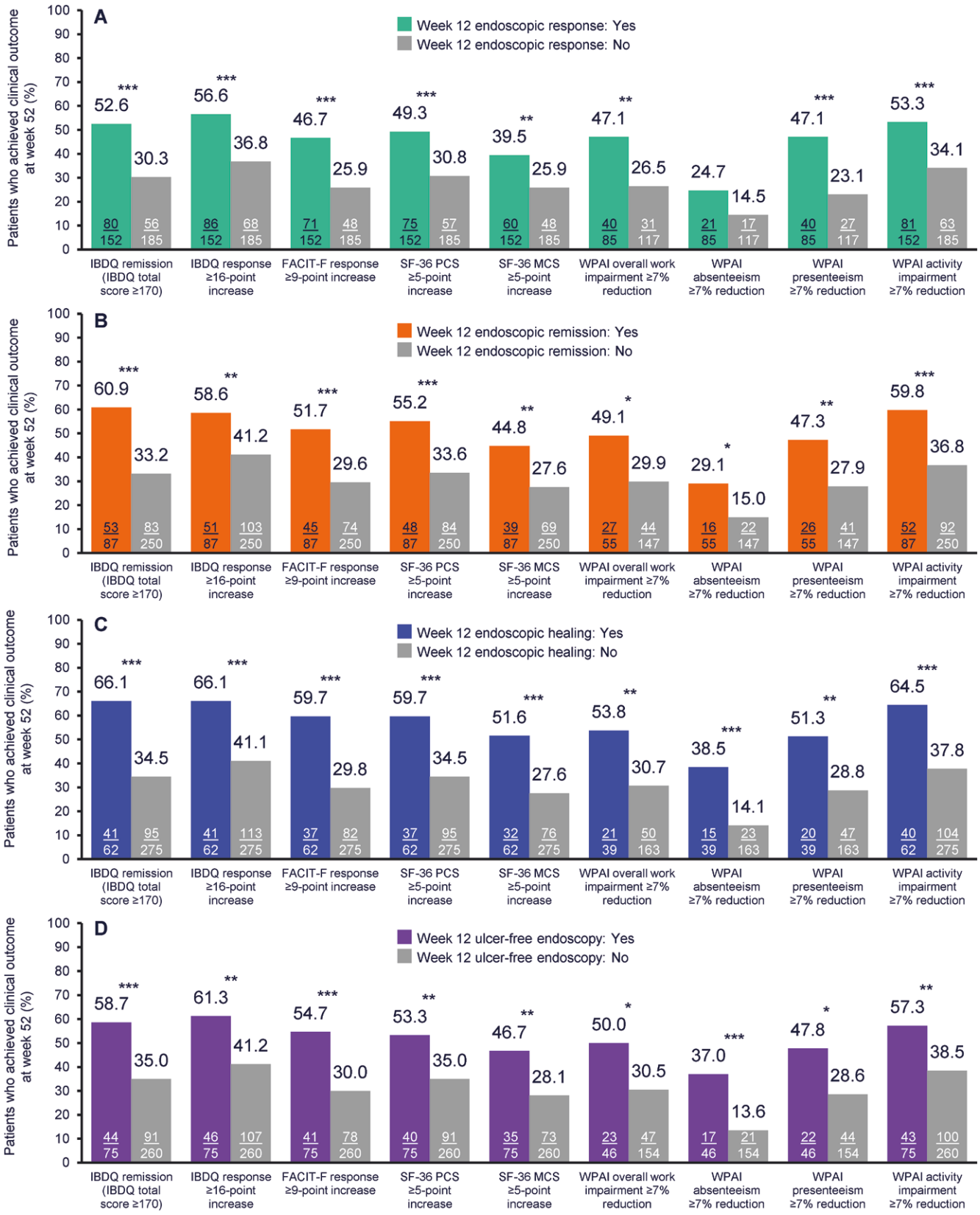


**Figure 3.** Meaningful improvement in QoL outcomes at week 52 among patients who achieved (A) an endoscopic response, (B) endoscopic remission, (C) endoscopic healing, or (D) ulcer-free endoscopy at the end of induction, compared with patients who did not. *Nominal *P*-value ≤.05; **nominal *P*-value ≤.01; ***nominal *P*-value <.001. WPAI was reported for employed patients only. Abbreviations: FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy—Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Score; PCS, Physical Component Score; QoL, quality of life; SF-36, Short Form 36; WPAI, Work Productivity and Activity Impairment Questionnaire.

### QoL Outcomes

A significantly greater proportion of patients who achieved an endoscopic response at the end of induction, compared with patients who did not, attained IBDQ remission (52.6% vs 30.3%; $P \leq .001$), IBDQ response (56.5% vs 36.8%; $P \leq .001$), and meaningful improvements in FACIT-Fatigue (46.7% vs 25.9%; $P \leq .001$), SF-36 PCS (49.3% vs 30.8%; $P \leq .001$), SF-36 MCS (39.5% vs 25.9%; $P \leq .01$), WPAI overall work impairment (47.1% vs 26.5%; $P \leq .01$), presenteeism (47.1% vs 23.1%; $P \leq .001$), and activity impairment (53.3% vs 34.1%; $P \leq .001$) (Figure 3A). A trend of improvement in patients who achieved endoscopic response at the end of induction, compared with patients who did not, was observed in the WPAI domain of absenteeism (24.7 vs 14.5%) ($P = .068$).

Similar improvements were observed across all QoL outcomes in patients who achieved endoscopic remission (all $P \leq .05$, Figure 3B), endoscopic healing (all $P \leq .01$, Figure 3C), and ulcer-free endoscopy (all $P \leq .05$, Figure 3D) at the end of induction vs those who did not.

## Discussion

The results of this study show that early achievement of endoscopic outcomes at the end of UPA induction treatment is associated with meaningful improvement in symptoms, inflammatory biomarkers, QoL, fatigue, and overall work productivity at week 52 of UPA maintenance treatment in patients with moderate to severe CD, compared with those who did not achieve early endoscopic outcomes. Meaningful long-term improvements were observed across all definitions of endoscopic improvement, including endoscopic response, endoscopic remission, endoscopic healing, and ulcer-free endoscopy.

Previous research has shown that patients with CD who achieved mucosal healing were less likely to suffer disease flares and clinical relapse after 1 year compared with patients without healing.[21,22] In a study of patients with small bowel CD, a lack of endoscopic healing was a risk factor for clinical and serological relapses.[23] Additionally, complete mucosal healing in patients with CD was associated with steroid-free remission 4 years after treatment initiation.[24] In particular, the results of our study suggest that early endoscopic improvement or healing of the intestinal mucosa could be pivotal in the adequate long-term control of clinical symptoms, markers of inflammation, QoL, and return to daily life activities. We can hypothesize that these improved outcomes may be associated with a decreased likelihood of disease flares.

Endoscopic healing and QoL have been recommended as long-term treatment goals by STRIDE-II in patients with CD.[6] Although STRIDE-II considers endoscopic healing as a long-term treatment goal and symptom improvement short-term, our findings demonstrate the benefit of achieving endoscopic improvements early in the treatment course. Improvements in symptoms and QoL outcomes are important treatment goals from the patient's perspective,[25] as CD has a substantial negative impact on daily life, including work, education, as well as social and psychological wellbeing.[25] Specifically, reduced health-related QoL and fatigue observed in patients with CD have been correlated with higher percentages of work impairment.[26] This illustrates that the disease burden associated with CD can be debilitating, and that normalization of QoL and improvements in symptoms negatively impacting daily activities are important treatment goals for patients with CD.

Well-defined and standardized definitions of endoscopic outcomes in CD are necessary to prescribe appropriate treatment and monitor treatment goals in clinical practice. In this study, multiple definitions were used, including a 50% improvement in the endoscopic lesions (endoscopic response), SES-CD score of 0-2 (endoscopic healing), reflecting normal mucosal or minimal residual inflammation, and absence of ulcers (ulcer-free endoscopy). Altogether, these measures can help inform the treating physician about the response to treatment when evaluating patients with CD. Interestingly, endoscopic response and remission, and ulcer-free endoscopy were associated with similar levels of improvement in long-term benefits, regardless of the stringency of definition utilized at week 12.

The findings of this study highlight the importance of achieving improvements in intestinal inflammation early during treatment, to attain not only endoscopic healing but also long-term improvement in QoL for patients with moderate to severe CD. Moreover, the clinical and endoscopic benefits of UPA induction treatment were also further enhanced by the 52-week maintenance treatment, illustrating the importance of continued therapy with UPA. Future analyses may evaluate data for longer periods of time to understand whether early endoscopic outcomes are associated with improvements beyond 1 year. In addition, future research can further explore and validate endoscopic definitions to standardize these outcomes across CD trials and studies, and improve patient care,[27] and perhaps find a noninvasive objective measure to define endoscopic changes early in treatment.

A strength of this study is the novelty of analyzing the association between endoscopic outcomes and clinical symptoms and QoL in patients with CD using large phase 3 clinical trial data. The use of multiple endoscopic endpoints to assess the association is a strength of this study. The inclusion of biomarkers and QoL measures makes the evaluation of the association of these outcomes with endoscopic endpoints more stringent. A limitation is that the results may not be generalizable beyond this clinical trial population of patients with CD. For example, a smaller number of patients in this analysis had the ileal-only disease, therefore findings may be less applicable to this patient subgroup. Furthermore, this trial was not designed to address the research question discussed in this analysis, as such, patient groups were not mutually exclusive. However, this trial does provide data that are not limited by some of the biases of real-world evidence.

In conclusion, early improvement in endoscopic outcomes after 12-week induction treatment with UPA was associated with meaningful improvements in long-term clinical outcomes and QoL under continued treatment with UPA.

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## Author Contributions

Study design: A.P.L. Patient recruitment and data collection: E.V.L. Data analysis and interpretation of data: A.P.L., S.X.,

W.-J.L., N.J., K.K., and N.S. Critically reviewed/revised the manuscript for important intellectual content: A.P.L., W.-J.L., N.J., and K.K. All authors approved the final version of the manuscript before submission.

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## Conflicts of Interest

J.P. received financial support for research from AbbVie and Pfizer; received consultancy fees/honorarium from AbbVie, Arena, Athos, Atomwise, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Galapagos, Genentech/Roche, GlaxoSmithKline, Janssen, Mirum, Morphic, Nestlé, Origo, Pandion, Pfizer, Progenity, Protagonist, Revolo, Robarts, Takeda, Theravance, and Wasserman; reports payment for lectures including service on speaker bureau from Abbott, Ferring, Janssen, Pfizer, and Takeda; and reports payment for development of educational presentations from Abbott, Janssen, Pfizer, Roche, and Takeda. E.L. received research grants from Janssen, Pfizer, and Takeda; educational grant from AbbVie, Janssen, MSD, and Takeda; speaker fees for AbbVie, Falk, Ferring, Hospira, Janssen, MSD, Pfizer, and Takeda; served on an advisory board for AbbVie, Celgene, Ferring, Hospira, Janssen, MSD, Pfizer, Takeda, Galapagos, Gilead, and Arena; and served as a consultant for AbbVie. P.B. received research grants from AbbVie, Amgen, Celltrion, Mylan, Pfizer, and Takeda; received lecture fees from AbbVie, Celltrion, Janssen, Lilly, and Takeda; and served as a consultant for AbbVie, Arena Pharmaceuticals, BMS, Celltrion, Dr Falk, Galapagos, Janssen, Lilly, Pentax, PSI-CRO, Roche, Takeda, and Tetrameros. N.J., W.-J.L., A.P.L., K.K., and S.X. are full-time salaried employees of AbbVie and may own stock/options. N.S. is a contractor of AbbVie. E.V.L. served as a consultant for AbbVie, Alvotech, Amgen, Arena, Astellas, Avalo Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion Healthcare, Eli Lilly, Fresenius Kabi, Genentech, Gilead, GlaxoSmithKline, Gossamer Bio, Iota Biosciences, Iterative Scopes, Janssen, KSL Diagnostics, Morphic Therapeutics, Ono Pharma, Protagonist, Surrozen, Sun Pharma, Takeda, TR1X Bio, and UCB; received research grants from AbbVie, AstraZeneca, Bristol Myers Squibb, Celgene, Genentech, Gilead, Gossamer Bio, Janssen, Pfizer, Receptos, Takeda, Theravance, and UCB; and is a shareholder of Exact Sciences.

## Ethical Considerations

All randomized controlled trials were conducted in compliance with the protocol, International Conference on Harmonisation guidelines, and the ethical principles of the Declaration of Helsinki. As per Good Clinical Practice, the study protocol, informed consent forms, and all other explanatory materials were approved by the relevant ethics committees or institutional review board at all study sites. All patients provided informed consent before study participation.

## Data Availability

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis datasets), as well as other information (eg, protocols, clinical study reports, or analysis plans), 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, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. 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.abbvieclinicaltrials.com/hcp/data-sharing/.

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