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Upadacitinib Treatment Improves Symptoms of Bowel Urgency and Abdominal Pain, and Correlates With Quality of Life Improvements in Patients With Moderate to Severe Ulcerative Colitis

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ABSTRACT

Background and Aims: Bowel urgency and abdominal pain are impactful, yet underappreciated ulcerative colitis symptoms and not commonly assessed in clinical trials. We evaluated how these symptoms may improve with upadacitinib treatment and correlate with clinical and health-related quality of life (HRQOL) outcomes in the phase 2b U-ACHIEVE study.

Methods: Patients aged 18–75 years with moderately to severely active ulcerative colitis were randomised to receive placebo or upadacitinib (7.5, 15, 30, or 45 mg QD). Bowel urgency and abdominal pain were evaluated at baseline and Weeks 2, 4, 6, and 8. Week 8 correlations were evaluated between bowel urgency/abdominal pain with clinical (Mayo subscores, and high-sensitivity C-reactive protein and faecal calprotectin measurements) and HRQOL outcomes (Inflammatory Bowel Disease Questionnaire and 36-Item Short Form Health Survey scores).

Results: A greater proportion of patients (N = 250) reported no bowel urgency and less abdominal pain with upadacitinib treatment compared to placebo, with improvements observed as early as 2 weeks. At Week 8, patients receiving the 45-mg QD dose had the greatest improvements versus placebo, with 46% reporting no bowel urgency (vs 9%; $P \leq 0.001$) and 38% reporting no abdominal pain (vs 13%; $P = 0.015$). At Week 8, moderate correlations were found between bowel urgency or abdominal pain and most clinical and HRQOL outcomes.

Conclusions: Induction treatment with upadacitinib demonstrated significant reductions in bowel urgency and abdominal pain compared to placebo. These symptoms also correlate to clinical and HRQOL outcomes, supporting their use to monitor disease severity and other treatment outcomes.

Trial Registration: ClinicalTrials.gov identifier, NCT02819635

Key Words: abdominal pain, bowel urgency, upadacitinib

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INTRODUCTION

Ulcerative colitis (UC) is a chronic, relapsing inflammatory disease of the large intestine characterised by inflammation and ulceration of the colonic mucosa.[1] The reported prevalence of UC is highest in Europe (505 per 100,000 in Norway) and North America (286 per 100,000 in the United States).[2] The goals of medical treatment in UC are to control inflammation, reduce symptoms, and maintain remission, as well as improve health-related quality of life (HRQOL).[3,4] Despite the availability of various therapies, many patients are not able to achieve or maintain clinical remission, indicating a significant medical need.[5,6]

Upadacitinib, an oral selective Janus kinase (JAK)-1 inhibitor, is currently being assessed in patients with UC and Crohn's disease.[7,8] In the phase 2b study of the U-ACHIEVE program for UC (NCT02819635), clinical remission was achieved after 8 weeks of treatment with upadacitinib once daily (QD).[7] Adverse events with upadacitinib were consistent with those observed from other clinical trials with JAK inhibitors for moderate to severe inflammatory bowel disease and rheumatoid arthritis.[7,9-18]

One of the challenges in the development of new treatments for UC is the identification of measures reflecting symptoms which are important to patients and can serve as relevant tools for determining disease severity and assessment of treatment success.[19] Current treatment guidelines utilise tools such as the Mayo score to define UC severity, which includes evaluations of stool frequency, rectal bleeding, endoscopic findings, and Physician Global Assessment.[4,20]

However, these tools do not incorporate bowel urgency and abdominal pain symptoms in their assessments.[20] Both bowel urgency and abdominal pain are reported by more than 50% of patients with UC and are meaningful symptoms considered by patients in their treatment decisions.[21-23] Bowel urgency is particularly distressing to patients as it can lead to incontinence and inability to distinguish liquid and gas from solid stool.[24] Tools commonly used in observational studies, such as

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the Simple Clinical Colitis Activity Index (SCCAI) and patient-SCCAI, include bowel urgency but not abdominal pain.[25,26]

In this study we evaluated bowel urgency and abdominal pain in patients with moderately to severely active UC who received upadacitinib or placebo from the U-ACHIEVE study. We assessed improvements in bowel urgency and abdominal pain with upadacitinib treatment versus placebo and performed similar analyses for rectal bleeding, stool frequency, and HRQOL. Correlation of bowel urgency and abdominal pain improvements with clinical outcomes, HRQOL, and biomarker levels were also determined.

MATERIALS AND METHODS

The methods for the U-ACHIEVE study have been described in detail elsewhere[7] and are summarised briefly below.

Study design and participants

This was a *post hoc* analysis of the phase 2b, double-blind, placebo-controlled, randomised, dose-ranging, 8-week induction therapy portion of the U-ACHIEVE study. Patients were randomised to receive placebo or upadacitinib at doses of 7.5, 15, 30, or 45 mg QD.

Included in the study were patients aged 18–75 years old with moderately to severely active UC defined as an adapted Mayo score (Mayo score without Physician's Global Assessment) of 5 to 9 points and Mayo endoscopic subscore of 2 to 3 (confirmed by central reader). Patients also had to have UC for ≥90 days prior to baseline, confirmed by colonoscopy, and to have demonstrated an inadequate response to, loss of response to, or intolerance to corticosteroids, immunosuppressants, and/or biologic therapies. Patients were excluded if they had a diagnosis of Crohn's disease or indeterminate colitis, UC limited to the rectum, clinical signs of fulminant colitis, toxic megacolon, or a history of colectomy. Patients were permitted to concomitantly receive oral corticosteroids,

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inhaled or topical dermatologic corticosteroids, aminosalicylates, topical non-steroidal anti-inflammatory drugs, or methotrexate but could not receive biologics, cyclosporine, intravenous corticosteroids, tacrolimus, azathioprine, 6-mercaptopurine, or topical rectal therapies.

Bowel urgency and abdominal pain symptoms

Bowel urgency and abdominal pain symptoms were collected by the patient in an electronic diary (e-diary) using a handheld device and recorded daily using a 24-hour recall period. Data from e-diary entries over the most recent consecutive 3-day period within 10 days before each study visit were calculated for study symptoms.

Bowel urgency was reported by the patient (yes or no) from their daily diary, with the total number of days experiencing bowel urgency measured over 3 consecutive days before each study visit, within a range of 0–3. Patients were divided into two groups, those with any bowel urgency (1, 2, or 3 days) and those with no bowel urgency (0 days). Abdominal pain was scored as 0 (no pain), 1 (mild pain), 2 (moderate pain), and 3 (severe pain), with average abdominal pain calculated over 3 consecutive days before each study visit, with a range of 0–3.

Bowel urgency and abdominal pain were collected from the patient daily diary and evaluated at baseline and at Weeks 2, 4, 6, and 8. UC symptoms evaluated across trial arms were the percentage of patients reporting the absence of bowel urgency and an average abdominal pain of 0 over the 3 examined days and the mean change from baseline to Weeks 2, 4, and 8 in abdominal pain.

Additional UC symptoms

Rectal bleeding was assessed using Mayo rectal bleeding subscore[27] with 0 meaning no blood seen; 1, streaks of blood with stool less than half the time; 2, obvious blood with stool most of the time; and 3, blood alone passed. Stool frequency was determined using Mayo stool frequency subscore,[27] with 0 meaning normal number of stools for respective patient; 1 meaning 1–2 stools

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more than normal; 2 meaning 3–4 stools more than normal; and 3 meaning ≥5 stools more than normal. The average values over the most recent consecutive 3-day period within 10 days before each study visit were calculated for rectal bleeding and stool frequency symptoms.

Rectal bleeding and stool frequency symptoms evaluated across trial arms were the percentage of patients reporting a Mayo rectal bleeding subscore of 0 and Mayo stool frequency subscore of ≤1 over the 3 examined days and the mean change from baseline to Weeks 2, 4, 6, and 8 in Mayo rectal bleeding subscore, and Mayo stool frequency subscore.

Clinical outcomes

The full Mayo score was used to assess UC severity with all the subscores: stool frequency subscore, rectal bleeding subscore, endoscopy subscore, and Physician's Global Assessment subscore. Clinical remission was determined per adapted Mayo score (defined as stool frequency subscore ≤1, rectal bleeding subscore of 0, and endoscopic subscore ≤1) at Week 8. Clinical response was defined as a decrease from baseline of ≥2 points in the adapted Mayo score and ≥30% from baseline PLUS a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore ≤1.

Biomarkers assessed were high-sensitivity C-reactive protein (hs-CRP) and faecal calprotectin at baseline and Weeks 2, 4 (hs-CRP only), and 8.

HRQOL measures

HRQOL measures assessed were Inflammatory Bowel Disease Questionnaire (IBDQ) and 36-Item Short Form Health Survey (SF-36)**.** IBDQ is a disease-specific instrument composed of 32 items graded on a 7-point Likert scale.[28,29] For IBDQ, total score ranges from 32 to 224, with higher scores indicating better HRQOL. SF-36 is composed of a Physical Component Summary (PCS) and Mental Component Summary (MCS).[30,31] PCS and MCS scores range from 0 to 50, with higher scores indicating better HRQOL.

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HRQOL measures were assessed at baseline and at Weeks 2, 4, and 8. HRQOL measure outcomes evaluated across trial arms were the percentage of patients with IBDQ remission (defined as IBDQ score ≥170 points) and with IBDQ response (defined as an increase of ≥16 points from baseline) at Weeks 2, 4, and 8.

Statistical analyses

Analyses were performed in the intent-to-treat population, which consists of all patients who were randomised and received one dose of study drug. Comparisons between bowel urgency and abdominal pain with clinical outcomes and HRQOL measures were determined using the Mann-Whitney test at Week 8. Correlations between bowel urgency and abdominal pain with clinical outcomes, HRQOL measures, and biomarker levels were evaluated with Spearman's correlation coefficients at Week 8. Estimates of correlation coefficient between 0 and 0.3 (−0.3) indicate weak correlation, >0.3 to 0.7 (<−0.3 to −0.7) indicate moderate correlation, >0.7 to 0.9 (<−0.7 to −0.9) indicate strong correlation, and >0.9 to 1.0 (<−0.9 to −1.0) indicate very strong correlation.[32]

Comparisons between upadacitinib dose groups and placebo for percentage of patients with bowel urgency and abdominal pain symptoms, other UC symptoms, IBDQ response, and IBDQ remission were based on Cochran-Mantel-Haenszel tests, adjusting for prior biologic use, baseline corticosteroid use, and adapted Mayo score (≤7, >7). Missing data were reported using non-responder imputation. For abdominal pain, Mayo rectal bleeding subscore, and Mayo stool frequency subscore, mean changes from baseline to Weeks 2, 4, and 8 were assessed using analysis of covariance. Missing data were reported using last observation carried forward. All data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

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Ethical requirements

This study was conducted per the International Conference on Harmonization guidelines, applicable regulations, and the Declaration of Helsinki and was approved by respective institutional review committees.[7] All patients provided informed consent before study participation.

RESULTS

Study population

Of the 250 patients randomised between treatment groups, baseline UC symptoms were generally similar between treatment cohorts, although there was some variability in the percentage of patients with a given number of bowel urgency days (**Table 1**). Bowel urgency was reported by 83% of patients over 3 days at baseline (71% for 3 days, 8% for 2 days, 4% for 1 day), while 7% experienced no bowel urgency. Abdominal pain was experienced at some level by 82% of patients at baseline (7% severe, 34% moderate, 41% mild), while 8% had no abdominal pain. The percentage of patients with missing data for bowel urgency and abdominal pain was 10% and ranged from 4% for the 7.5-mg QD cohort to 16% for the 45-mg QD cohort.

Change in bowel urgency and abdominal pain with upadacitinib treatment

A greater proportion of patients who received upadacitinib reported no bowel urgency during the study compared with those who received placebo, with improvements observed by 2 weeks (**Figure 1**). Improvements in bowel urgency with upadacitinib were dose dependent. Patients receiving upadacitinib 45 mg QD had the greatest improvements, with 46.4% reporting no bowel urgency at Week 8 compared with 8.7% for placebo, a 37.7% difference (95% CI, 18.1–54.0; $P \leq 0.001$) versus placebo).

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Similarly, patients receiving upadacitinib reported lower abdominal pain scores during the study compared with those receiving placebo, with differences observed by Week 2 (**Figure 2**). With upadacitinib 45 mg QD, a 24.5% difference (95% CI, 4.0–37.9; *P* = 0.015) in the percentage of patients reporting an abdominal pain score of 0 was observed compared with placebo (37.5% vs 13.0%) at Week 8 (**Figure 2A**). Mean abdominal pain score was reduced with upadacitinib treatment by 2 weeks and continued over the course of the study, with reductions significant for most doses and time points versus placebo (*P* ≤0.01, **Figure 2B**).

Change in other UC symptoms and IBDQ with upadacitinib treatment

Significantly greater percentages of patients reported a Mayo rectal bleeding subscore of 0 in the upadacitinib 30- and 45-mg QD groups compared with placebo from Week 2 to Week 8 (*P* ≤0.05, **Supplemental Figure S1A**). Reductions in mean Mayo rectal bleeding subscore with upadacitinib were also noted throughout the study, with changes occurring as early as Week 2 (**Supplemental Figure S1B**).

Stool frequency was also substantially reduced with upadacitinib treatment, with a significantly greater percentage of patients at Week 8 reporting a Mayo stool frequency score of ≤1 for upadacitinib 30 mg and 45 mg QD compared with placebo (*P* ≤0.01, **Supplemental Figure S2A**). Mean Mayo stool frequency subscore reductions were observed with upadacitinib as early as Week 2, which continued during the study (**Supplemental Figure S2B**).

At Week 8, IBDQ remission was reported by a significantly greater percentage of patients treated with upadacitinib 15 mg, 30 mg, and 45 mg QD than with placebo (*P* ≤0.05, **Supplemental Figure S3A**). IBDQ response at Week 2 through Week 8 was also reported by a significantly greater percentage of patients treated with upadacitinib 15 mg, 30 mg, and 45 mg QD than with placebo (*P* ≤0.05, **Supplemental Figure S3B).**

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Correlation of bowel urgency and abdominal pain with clinical outcomes, HRQOL measures, and biomarker levels

Patients who achieved clinical remission per adapted Mayo score at Week 8 had significantly fewer bowel urgency days than those who did not achieve remission ($P \leq 0.01$, **Figure 3A**). At baseline, significantly lower IBDQ and SF-36 PCS scores were obtained for patients with any bowel urgency compared with those with no bowel urgency ($P \leq 0.05$, **Figure 3B**). When outcomes were correlated with bowel urgency at Week 8, a moderate correlation was found for most clinical outcomes, HRQOL measures, abdominal pain, and biomarker levels, except for the SF-36 MCS (**Table 2**).

For abdominal pain, patients who achieved clinical remission per adapted Mayo score at Week 8 had lower mean scores versus those who did not achieve remission ($P \leq 0.01$, **Figure 4A**). A trend of increasing abdominal pain severity with greater HRQOL impairment at baseline was also demonstrated (**Figure 4B**). At baseline, patients with severe abdominal pain had significantly lower IBDQ, SF-36 PCS, and SF-36 MCS scores compared with those with no abdominal pain ($P \leq 0.001$, **Figure 4B**). At Week 8, moderate correlations were observed between abdominal pain and most clinical outcomes, HRQOL measures, bowel urgency, and biomarker levels, except for Mayo endoscopic score and faecal calprotectin (**Table 2**).

DISCUSSION

In this report, we demonstrated that eight weeks of induction therapy with upadacitinib resulted in statistically significant improvements in patient symptoms, including bowel urgency and abdominal pain, in patients with moderately to severely active UC. Upadacitinib treatment also resulted in significant and clinically meaningful positive changes in IBDQ. Both symptom and IBDQ improvements with upadacitinib occurred as early as Week 2. These results extend the positive findings that were recently reported for the primary and key secondary endpoints from the phase 2b

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study of the U-ACHIEVE program.[7] At Week 8, clinical remission (defined based on the adapted Mayo score as a stool frequency subscore ≤1, rectal bleeding subscore = 0, and endoscopic subscore ≤1) was achieved by 8.5%, 14.3%, 13.5%, and 19.6% of patients receiving upadacitinib 7.5 mg, 15 mg, 30 mg, or 45 mg, respectively, with none in the placebo group (P = 0.052, P = 0.013, P = 0.011, and P = 0.002, compared with placebo, respectively). Endoscopic improvement (defined as endoscopic subscore ≤1) at Week 8 was also obtained by a greater percentage of patients receiving upadacitinib (14.9%, 30.6%, 26.9%, and 35.7% for the 7.5 mg, 15 mg, 30 mg, and 45 mg doses, respectively) compared with placebo (2.2%) (P = 0.033, P <0.001, P <0.001, P <0.001, respectively).

There is a considerable need for novel treatments and measurement tools for UC, particularly as current therapeutic options, including mesalamine, glucocorticoids, immunosuppressants, and biologics, are ineffective in a substantial percentage of patients.[33,34] For those patients who have a response, it can be inadequate or may not be maintained.[33,34] Additionally, these treatments can be associated with adverse effects that can limit their use.[33,34]

Bowel urgency and abdominal pain are highly prevalent in patients with UC and have a serious impact on their mental and physical quality of life.[21-23,35,36] In a study of 501 patients with UC, bowel urgency and abdominal pain were reported in 63% and 58%, respectively, of patients with active disease.[23] This resulted in a significant impact on the daily life of approximately 40% of these patients.[23] Bowel urgency and abdominal pain have also been defined as meaningful attributes from a patient perspective for treatment.[21]

However, to our knowledge, the use of bowel urgency and abdominal pain to measure disease severity or treatment effectiveness have never been evaluated in comparison with other more commonly used UC measurement tools such as Mayo score. In this phase 2b study of patients with moderately to severely active UC treated with upadacitinib or placebo for 8 weeks, we found a moderate correlation of improvements in bowel urgency and abdominal pain with positive

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outcomes for most clinical outcomes, IBDQ measures, and biomarker level changes. Furthermore, we observed statistically significant improvements with upadacitinib versus placebo in bowel urgency and abdominal pain at Week 8 with improvements seen as early as Week 2. Similar results were also seen for rectal bleeding, stool frequency, and disease-specific and general HRQOL. Therefore, bowel urgency and abdominal pain are relevant, related to clinical outcomes, and responsive to upadacitinib treatment.

Previously, the validated Monitor Inflammatory bowel disease At Home (MIAH) questionnaire, which included questions on bowel urgency and abdominal pain, was used with the combination of a calprotectin home test and shown to be highly accurate in predicting endoscopic inflammation.[37] In the current study, Mayo endoscopic subscore was moderately correlated with bowel urgency but weakly with abdominal pain. The findings in this current study provide further support for the use of bowel urgency and abdominal pain evaluations in patient-reported outcome measurements, in addition to the commonly used stool frequency and rectal bleeding assessments.

This study reported the important, but underappreciated patient-reported outcome measurements of bowel urgency and abdominal pain from a patient perspective in the context of a phase 2b clinical trial. We observed that upadacitinib can significantly relieve symptoms that are highly prevalent and burdensome to these patients compared with placebo by 2 weeks of treatment, with the caveat that this study was not pre-specified to statistically power the evaluation of changes in bowel urgency and abdominal pain. One limitation of this study was that this was a post-hoc analysis which was not designed to directly evaluate the association of improvements in these individual symptoms with HRQOL. Although this analysis was based on data collected in a phase 2b study with a limited sample size, the reported positive findings provide an incentive to confirm this association in a larger phase 3 trial.

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Additional avenues of research that could not be addressed in this current study are the long-term outcomes for patients based on bowel urgency and abdominal pain response and the characterization of patients with differential improvements in bowel urgency and abdominal pain relative to other measures, including the Mayo score, rectal bleeding, and stool frequency. These will be addressed in future studies, including the larger phase 3 portion of the U-ACHIEVE study and its long-term follow-up.

Increasingly, patient-reported outcomes in UC are including bowel urgency and abdominal pain questions, such as for the paediatric daily UC signs and symptoms scale (DUCS).[38] Consequently, as part of the UC patient-reported outcomes, bowel urgency and abdominal pain results would need to be incorporated for use in clinical trials. These findings are relevant as the association between symptoms of bowel urgency and abdominal pain and quality of life in patients with UC tends to be underestimated by healthcare professionals.[39,40]

In conclusion, we found that improvements with upadacitinib in bowel urgency and abdominal pain correlate with positive changes in various clinical outcomes, HRQOL measures, and biomarker levels, including those that are commonly used to measure disease severity in clinical trials. These results support the use of bowel urgency and abdominal pain measurements to monitor disease severity and treatment outcomes. As patients treated with upadacitinib had superior IBDQ remission and response rates compared with those given placebo, these results indicate a potential HRQOL benefit with symptom relief for patients with UC. These results support the further evaluation of upadacitinib for patients with moderate to severe UC in phase 3 trials.

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Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Conflict of Interest

S Ghosh received lecture fee(s) from AbbVie, Janssen, Takeda, Pfizer, Celltrion, Eli Lilly, Shield, Ferring, Falk Pharma; is steering/advisory committee member for Pfizer, Janssen, AbbVie, Bristol Myers Squibb, Celgene, Boehringer Ingelheim, Celltrion, Gilead, Galapagos, Eli Lilly, Takeda; and received research support from GSK, AbbVie, and Vertex.

Y Sanchez Gonzalez, W Zhou, R Clark, and W Xie are AbbVie employees and may own AbbVie stock/stock options.

E Louis received financial support for research from Takeda, Pfizer, and Janssen; received lecture fee(s) from AbbVie, Celgene, Falk, Ferring, MSD, Takeda, Janssen, and Pfizer; received consultancy fees from AbbVie; received educational grants from AbbVie, Takeda, and Janssen; and served on

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Author Contributions

SG contributed to the concept, draft structure, data interpretation, writing of manuscript, final revision and approved the final version.

YSG contributed to the concept, draft structure, data interpretation, writing of manuscript, final revision and approved the final version.

WZ contributed to data acquisition, data interpretation, statistical analyses, revising the manuscript, and approved the final version.

RC contributed to data interpretation, revising the manuscript, and approved the final version.

WX contributed to data acquisition, data interpretation, statistical analyses, revising the manuscript, and approved the final version.

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EVL contributed to data acquisition, data interpretation, revising the manuscript, and approved the final version.

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FIGURE LEGENDS

Figure 1. Percentage of patients reporting no bowel urgency over time with upadacitinib.

*P ≤0.05, **P ≤0.01, ***P ≤0.001 compared with placebo. NRI, ITT population.

ITT, intent-to-treat; NRI, non-responder imputation.

Figure 2. Improvements in abdominal pain with upadacitinib.

A. Percentage of patients reporting an abdominal pain score of 0 from Weeks 2 to 8.

B. Reduction in mean abdominal pain from Weeks 2 to 8.

*P ≤0.05, **P ≤0.01, ***P ≤0.001 compared with placebo. Panel A is analysed NRI. Panel B is analysed LOCF. ITT population.

ITT, intent-to-treat; LOCF, last observation carried forward; NRI, non-responder imputation.

Figure 3. Association of bowel urgency with clinical outcomes and HRQOL measures.

A. Bowel urgency severity in patients who attained clinical remission per adapted Mayo score at Week 8.

B. Burden associated with bowel urgency based on HRQOL measures at baseline.

Adapted Mayo score defined as stool frequency subscore ≤1, RBS of 0, and endoscopic subscore ≤ 1.

*P ≤0.05, **P ≤0.01, using Mann–Whitney U test for patients between groups (panel A) or with any bowel urgency vs no bowel urgency (panel B). Observed data. ITT population.

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HRQOL, health-related quality of life; IBDQ, Inflammatory Bowel Disease Questionnaire; ITT, intent-to-treat; MCS, Mental Component Summary; PCS, Physical Component Summary; RBS, rectal bleeding subscore; SF-36, 36-Item Short Form Health Survey.

Figure 4. Association of abdominal pain with clinical outcomes and HRQOL measures.

A. Abdominal pain severity in patients who attained clinical remission per adapted Mayo score at Week 8.

B. Burden associated with abdominal pain based on HRQOL measures at baseline.

*$P \leq 0.01$, **$P \leq 0.001$ using Mann–Whitney U test for patients between groups (panel A) or with abdominal pain vs no pain (panel B). ITT population. Observed data.

HRQOL, health-related quality of life; IBDQ, Inflammatory Bowel Disease Questionnaire; ITT, intent-to-treat; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-36, 36-Item Short Form Health Survey.

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TABLES

Table 1. Patient demographics and baseline characteristics

Variable	Placebo (n = 46)	Upadacitinib 7.5 mg QD (n = 47)	Upadacitinib 15 mg QD (n = 49)	Upadacitinib 30 mg QD (n = 52)	Upadacitinib 45 mg QD (n = 56)
Age (years), median (range)	40.0 (21–67)	41.0 (18–75)	47.0 (22–71)	42.0 (20–72)	37.0 (19–74)
Female, n (%)	17 (37.0)	24 (51.1)	19 (38.8)	21 (40.4)	19 (33.9)
White, %	37 (80.4)	36 (76.6)	37 (75.5)	37 (71.2)	38 (67.9)
Disease duration (years), mean ± SD	7.5 ± 6.7	9.0 ± 7.9	9.3 ± 9.8	7.3 ± 5.7	7.9 ± 6.8
Prior biologic use, %	35 (76.1)	36 (76.6)	38 (77.6)	42 (80.8)	43 (76.8)
Adapted Mayo score, mean ± SD*	7.0 ± 1.1	7.0 ± 1.2	7.0 ± 1.1	7.0 ± 1.2	6.7 ± 1.2
Number of bowel urgency days, n (%)					
0 day	2 (4.3)	5 (10.6)	4 (8.2)	4 (7.7)	3 (5.4)
1 day	3 (6.5)	2 (4.3)	2 (4.1)	1 (1.9)	3 (5.4)
2 days	3 (6.5)	3 (6.4)	5 (10.2)	1 (1.9)	8 (14.3)

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3 days	33 (71.7)	35 (74.5)	34 (69.4)	42 (80.8)	33 (58.9)
Missing	5 (10.9)	2 (4.3)	4 (8.2)	4 (7.7)	9 (16.1)
Abdominal pain score, n (%)[†]					
0 to 1	24 (52.2)	23 (48.9)	24 (49.0)	26 (50.0)	26 (46.4)
>1 to 2	14 (30.4)	17 (36.2)	17 (34.7)	19 (36.5)	18 (32.1)
>2 to 3	3 (6.5)	5 (10.6)	4 (8.2)	3 (5.8)	3 (5.4)
Missing	5 (10.9)	2 (4.3)	4 (8.2)	4 (7.7)	9 (16.1)
Rectal bleeding subscore, mean ± SD[*]	1.7 ± 1.0	1.6 ± 1.0	1.5 ± 0.9	1.5 ± 1.0	1.4 ± 0.9
Stool frequency score, mean ± SD[*]	2.6 ± 0.7	2.6 ± 0.6	2.7 ± 0.6	2.6 ± 0.7	2.6 ± 0.6
IBDQ, mean ± SD[*]	129.0 ± 36.0	120.6 ± 36.9	121.3 ± 34.7	123.0 ± 31.0	128.4 ± 29.3
SF-36 PCS, mean ± SD*	43.9 ± 8.0	40.0 ± 9.4	42.7 ± 9.0	41.5 ± 7.3	43.0 ± 7.0
SF-36 MCS, mean ± SD*	41.6 ± 10.4	41.9 ± 11.1	40.1 ± 12.5	40.8 ± 11.9	42.1 ± 10.4
HS-CRP, n (%)					
≤0.5 mg/L	21 (45.7)	24 (51.1)	11 (22.4)	18 (34.6)	24 (42.9)

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>0.5 mg/L	25 (54.3)	23 (48.9)	38 (77.6)	34 (65.4)	32 (57.1)
Faecal calprotectin (mg/kg), mean ± SD	3299 ± 4901	2713 ± 3644	4153 ± 5009	3031 ± 3575	2954 ± 3503

*n values different from those listed in header: placebo: 45 (IBDQ, SF-36); upadacitinib 7.5 mg: 44 (IBDQ, SF-36); upadacitinib 15 mg: 48 (IBDQ, SF-36); upadacitinib 30 mg: 49 (IBDQ) and 48 (SF-36); upadacitinib 45 mg: 55 (IBDQ, adapted Mayo, rectal bleeding, stool frequency) and 54 (SF-36). †Abdominal pain was scored as 0 (no pain), 1 (mild pain), 2 (moderate pain), and 3 (severe pain).

HS-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Summary; PCS, Physical Component Summary; QD, once a day; SD, standard deviation; SF-36, 36-Item Short Form Health Survey.

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Table 2. Correlation of bowel urgency days and abdominal pain at Week 8 with clinical outcomes, HRQOL measures, and biomarker levels

Measures	Bowel urgency days		Abdominal pain	
	N	Spearman correlation (95% CI)	N	Spearman correlation (95% CI)
Full Mayo score	206	0.59 (0.49, 0.68)	206	0.41 (0.28, 0.53)
Mayo rectal bleeding subscore	210	0.40 (0.27, 0.51)	210	0.43 (0.31, 0.54)
Mayo stool frequency subscore	210	0.55 (0.45, 0.65)	210	0.35 (0.21, 0.47)
Mayo Physician Global Assessment subscore	210	0.50 (0.38, 0.60)	210	0.42 (0.29, 0.53)
Mayo endoscopic subscore	222	0.42 (0.30, 0.54)	222	0.20 (0.05, 0.33)
Abdominal pain	189	0.54 (0.43, 0.63)	–	–
Bowel urgency	–	–	189	0.54 (0.43, 0.63)
IBDQ	214	−0.50 (−0.61, −0.38)	214	−0.55 (−0.64, −0.20)
SF-36 PCS	214	−0.41 (−0.53, −0.28)	214	−0.52 (−0.62, −0.41)
SF-36 MCS	214	−0.27 (−0.41, −0.13)	214	−0.31 (−0.44, −0.16)
HS-CRP	231	0.34 (0.21, 0.46)	231	0.32 (0.18, 0.44)

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Faecal calprotectin	211	0.41 (0.28, 0.53)	211	0.22 (0.08, 0.36)

Estimates between 0 and 0.3 (−0.3) indicate weak correlation (orange) and >0.3 to 0.7 (<−0.3 to −0.7) indicate moderate correlation (blue).[32]

All correlations in the table were statistically significant.

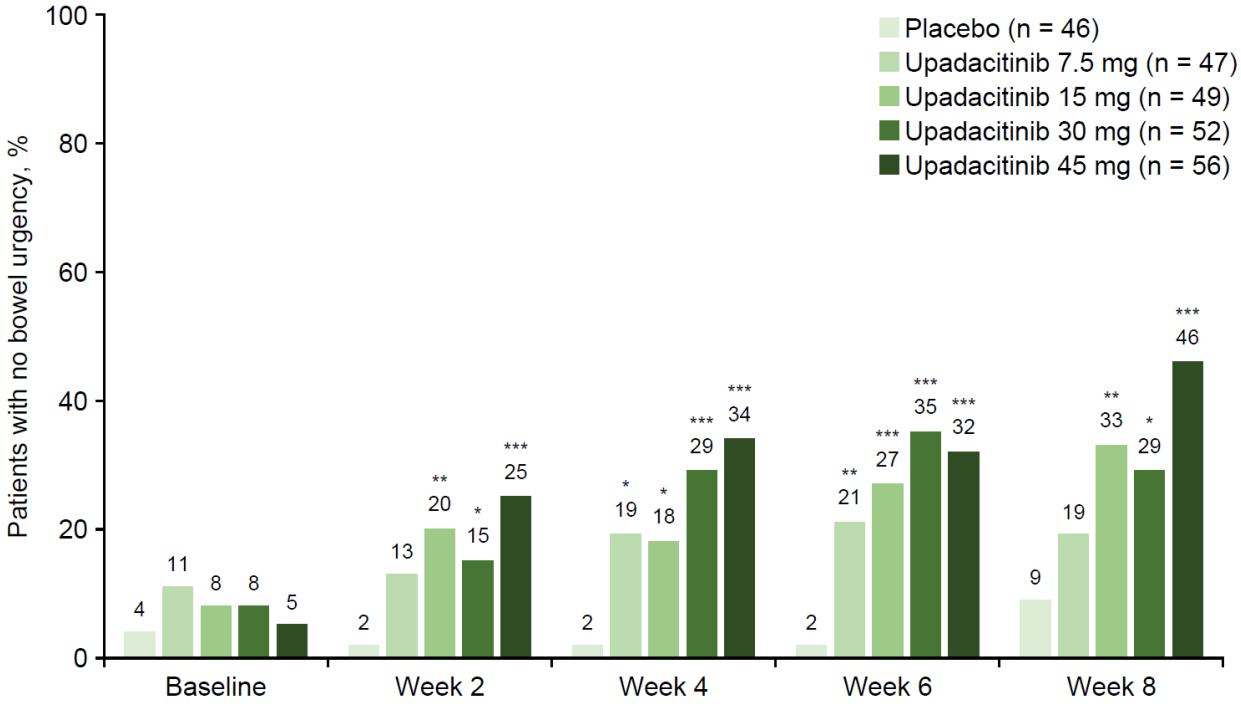
CI, confidence interval; HRQOL, health-related quality of life; HS-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-36, 36-Item Short Form Health Survey.

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FIGURES

Figure 1. Percentage of patients reporting no bowel urgency over time with upadacitinib



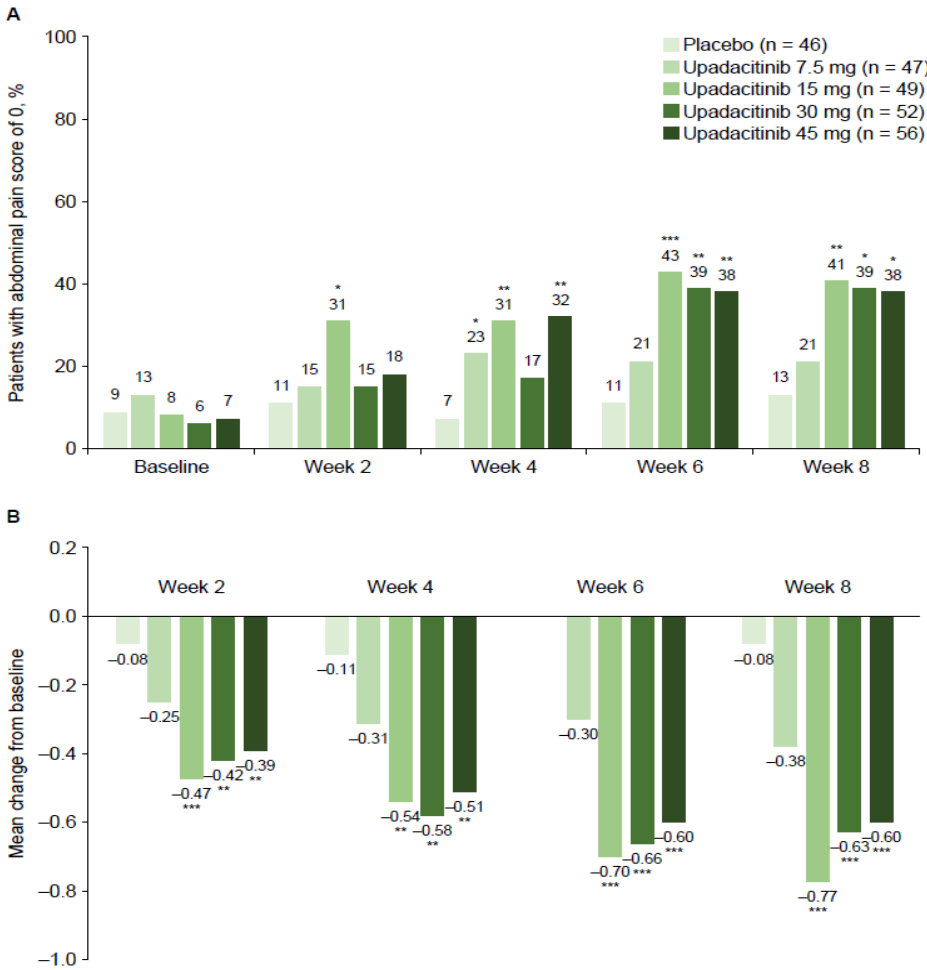
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Figure 2. Improvements in abdominal pain with upadacitinib



A. Percentage of patients reporting an abdominal pain score of 0 from Weeks 2 to 8.

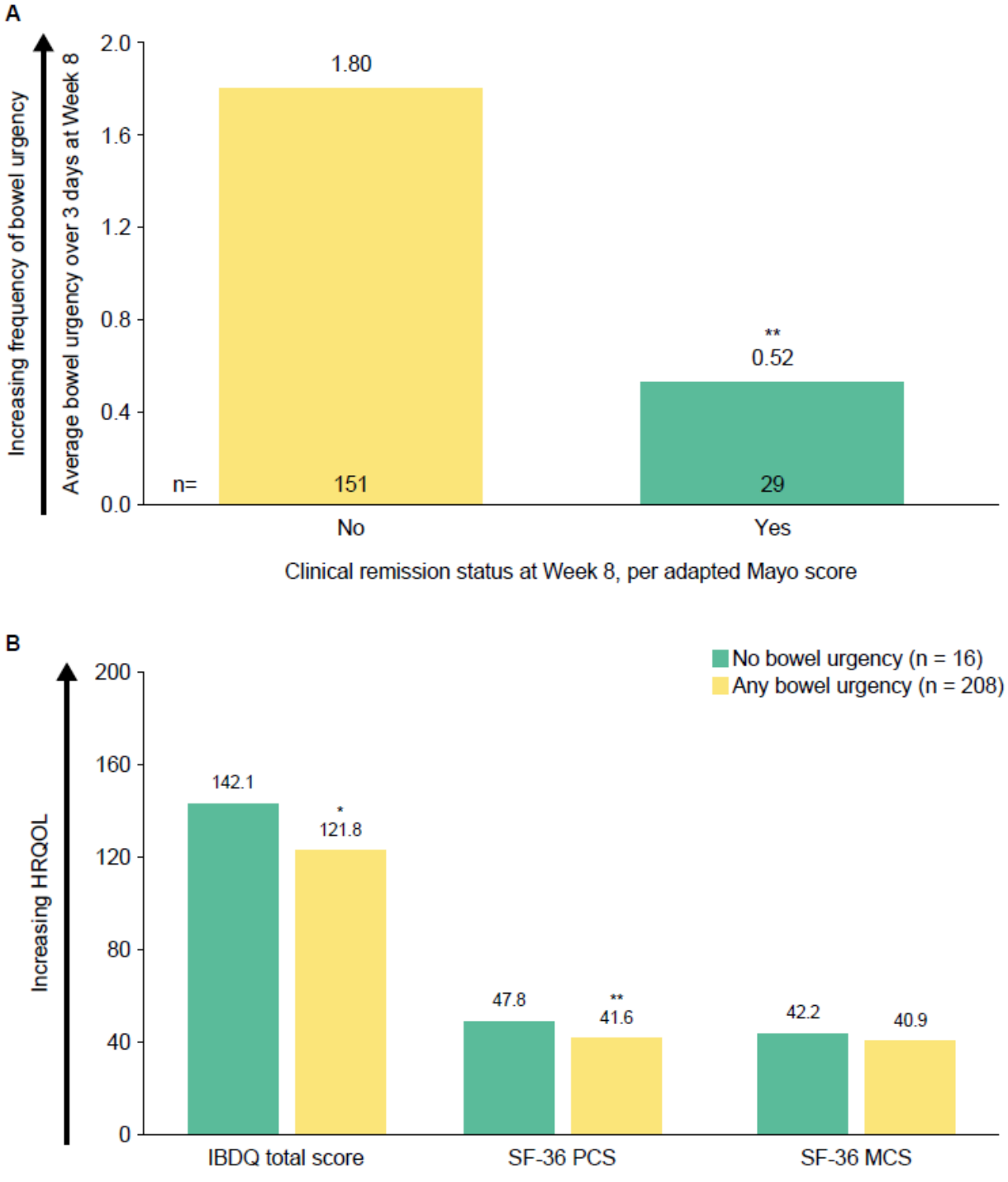
B. Reduction in mean abdominal pain from Weeks 2 to 8.

*P ≤0.05, **P ≤0.01, ***P ≤0.001 compared with placebo. Panel A is analysed NRI. Panel B is analysed LOCF. ITT population.

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Figure 3. Association of bowel urgency with clinical outcomes and HRQOL measures



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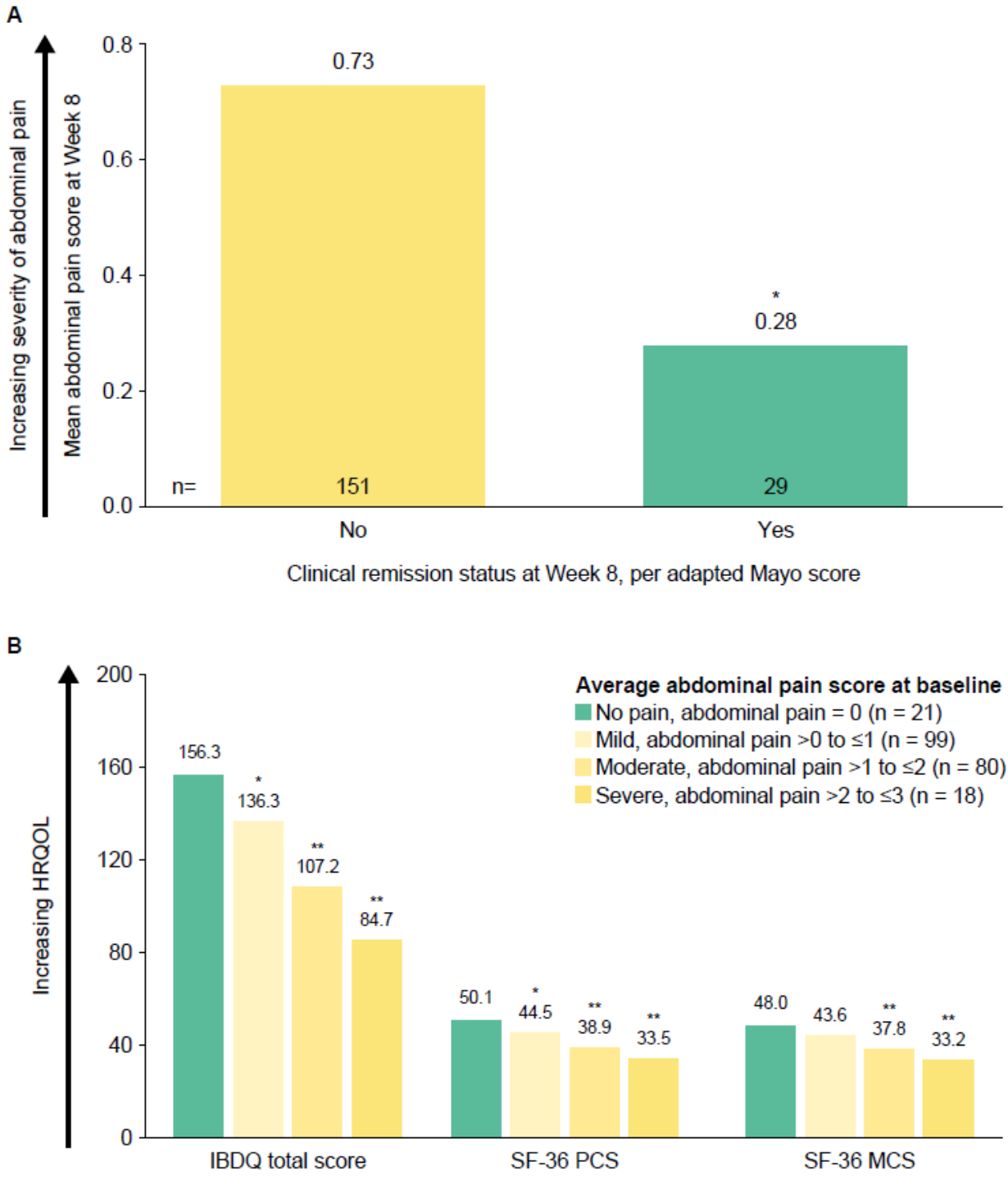
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