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Efficacy and Safety of Upadacitinib Maintenance Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Final Results From the Phase 3 U-ACHIEVE Maintenance Study

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OBJECTIVE

To report further efficacy and safety data on upadacitinib (UPA) 15 mg and 30 mg once daily (QD) in moderately to severely active ulcerative colitis (UC) from U-ACHIEVE Maintenance, from a larger population than has been previously analyzed[1]

CONCLUSIONS

Consistent with the primary analysis,[1] UPA 15 mg QD and 30 mg QD showed significantly greater efficacy than placebo as maintenance therapy across all primary and assessed secondary endpoints at 52 weeks

Both UPA doses were well tolerated and no new safety signals were observed compared with the smaller, primary analysis set[1] or other non-UC indications[5,6]

These Phase 3 results from a larger patient population than previously reported[1] support the favorable benefit–risk profile of UPA as maintenance therapy in patients with moderately to severely active UC

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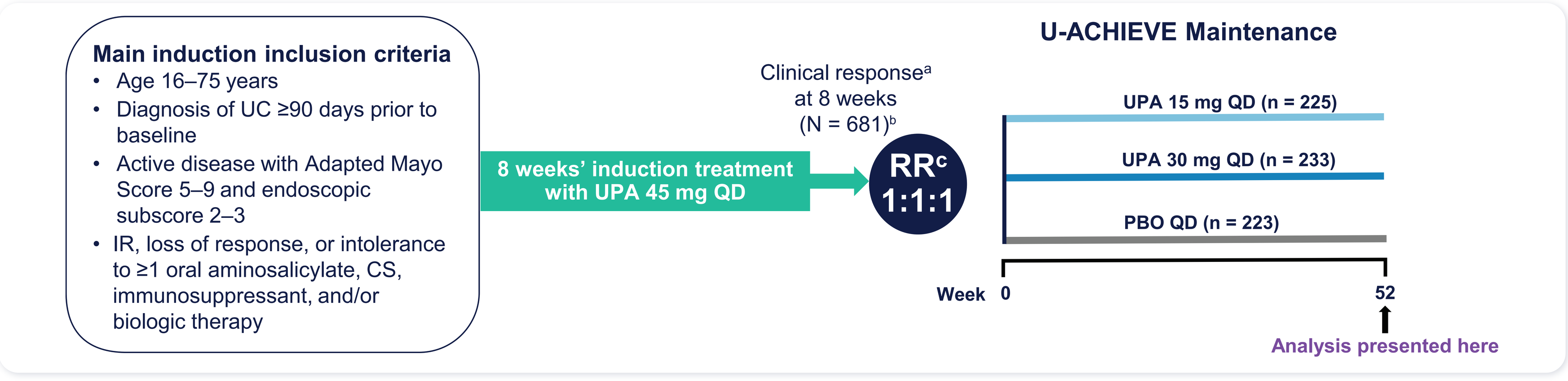
BACKGROUND

- The Phase 3 program for UPA, an oral, selective, and reversible Janus kinase inhibitor, included 2 identical induction studies of UPA 45 mg QD (U-ACCOMPLISH [NCT03653026] and U-ACHIEVE Induction [NCT02819635]), and a maintenance study of UPA 15 mg QD and 30 mg QD (U-ACHIEVE Maintenance [NCT02819635]), for moderately to severely active UC
- Results from the placebo (PBO)-controlled induction studies and the primary analysis of the PBO-controlled maintenance study, which included the first 451 randomized patients, have been reported previously[1]
  - Clinical, endoscopic, and histologic outcomes were significantly improved with both UPA 15 mg QD and 30 mg QD maintenance doses vs PBO after 52 weeks' maintenance treatment[1]

METHODS

- This analysis included all treated patients in the Phase 3, double-blind, PBO-controlled clinical trial program who responded to 8 weeks' UPA 45 mg QD induction therapy (**Figure 1**), including the first 451 previously analyzed[1]
  - Patients who received 16 weeks' extended induction therapy were not included in this analysis
- Efficacy endpoints were analyzed post-hoc in the full intent-to-treat (ITT) population, defined as all patients who achieved a clinical response after 8 weeks' UPA 45 mg QD induction treatment and were re-randomized to UPA 15 mg QD or 30 mg QD, or PBO, under 52-week protocol
- Safety analyses were pre-specified and performed in the full safety population, defined as the ITT population plus patients who received up to 44 weeks' maintenance therapy under earlier versions of protocol amendments

Figure 1. Study Design



CS, corticosteroid; IR, inadequate response; PBO, placebo; QD, once daily; RBS, rectal bleeding subscore; RR, re-randomized; UC, ulcerative colitis; UPA, upadacitinib.
[a]Defined as a decrease in Adapted Mayo Score of ≥2 points and ≥30% from baseline, plus a decrease in RBS of ≥1 or an absolute RBS of ≤1. [b]21 patients entered from the Phase 2b study.
[c]Re-randomization stratified by history of biologic failure, clinical remission status post-induction, and CS use at maintenance study baseline.

RESULTS

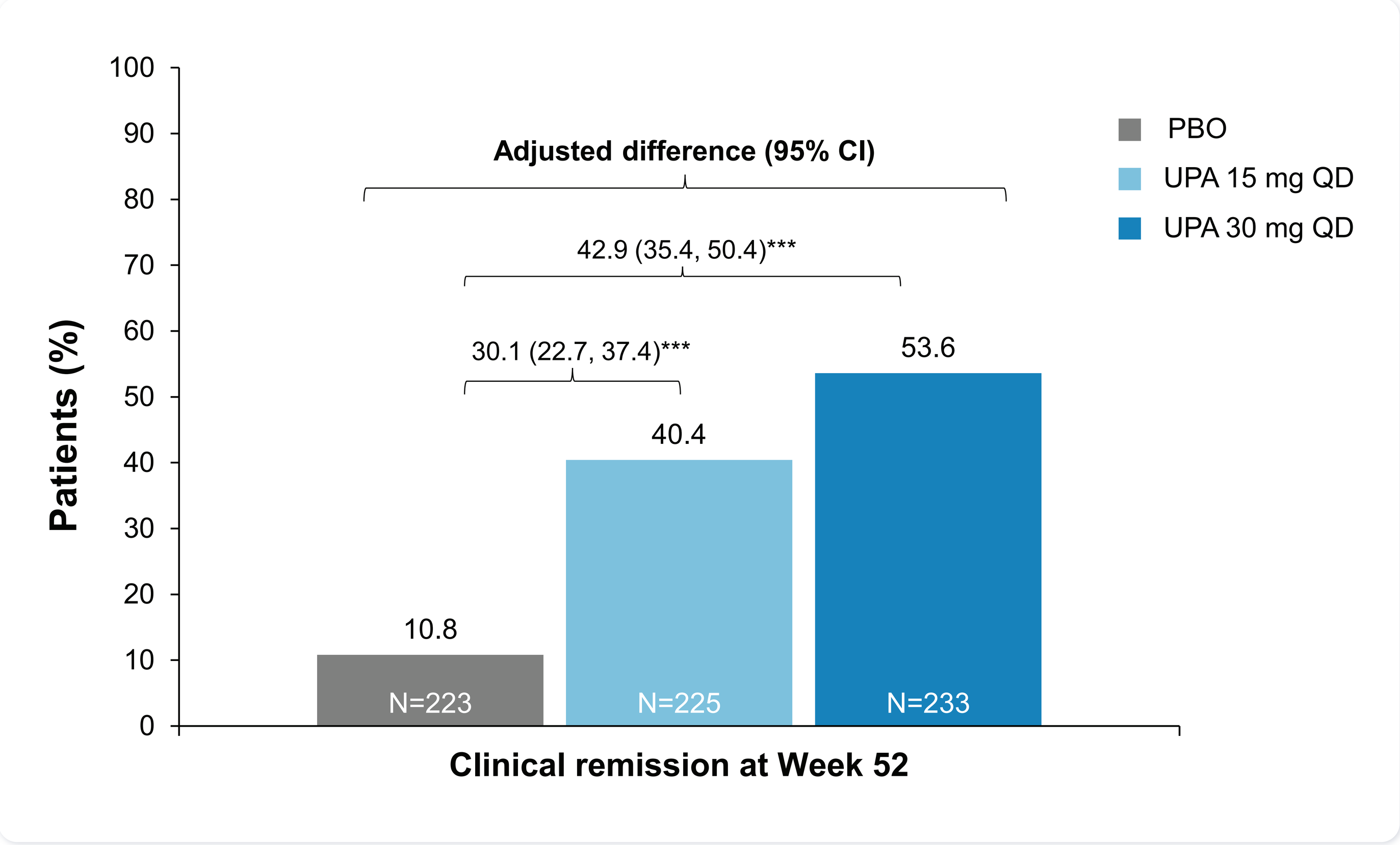
- Baseline characteristics were similar across treatment groups in the ITT population (**Figure 2**)
- A significantly greater proportion of patients achieved the primary endpoint (**Figure 2**), and all analyzed key secondary efficacy endpoints (**Figures 3** and **4**) with both doses of UPA vs PBO
- A summary of adverse events in the safety population is shown in **Table 2**

Table 1. Baseline Characteristics Were Generally Similar Across Treatment Groups

	All patients in ITT population (N = 681)		
	PBO (n = 223)	UPA 15 mg QD (n = 225)	UPA 30 mg QD (n = 233)
Female, n (%)	100 (44.8)	79 (35.1)	92 (39.5)
Age, years	42.4 (14.5)	41.7 (14.2)	43.0 (14.6)
Weight, kg	72.1 (18.2)	72.7 (19.7)	72.8 (19.1)
Disease duration, years	8.4 (7.8)	8.2 (7.3)	7.9 (6.9)
CS use, n (%)	84 (37.7)	84 (37.3)	84 (36.1)
5-aminosalicylate use, n (%)	146 (65.5)	160 (71.1)	168 (72.1)
Adapted Mayo Score	7.0 (1.2)	6.9 (1.2)	7.0 (1.3)[a]
≤7, n (%)	131 (58.7)	140 (62.2)	137 (59.3)[a]
>7, n (%)	92 (41.3)	85 (37.8)	94 (40.7)[a]
Fecal calprotectin, mg/kg, median (range)	1679 (30, 28,800)[b]	1707 (30, 28,800)[c]	1580 (30, 28,800)[d]
hs-CRP, mg/L, median (range)	3.9 (0.2, 105.0)	3.6 (0.2, 83.3)	4.1 (0.2, 107.0)
Bio-IR, n (%)	116 (52.0)	109 (48.4)	111 (47.6)
Prior TNFi exposure, n (%)	107 (48.0)	104 (46.2)	107 (45.9)
IBDQ total score	123.3 (34.7)[e]	126.8 (34.6)[e]	122.9 (35.1)[f]
FACIT-F score	30.2 (11.5)[g]	31.9 (11.1)[e]	30.5 (11.8)[h]

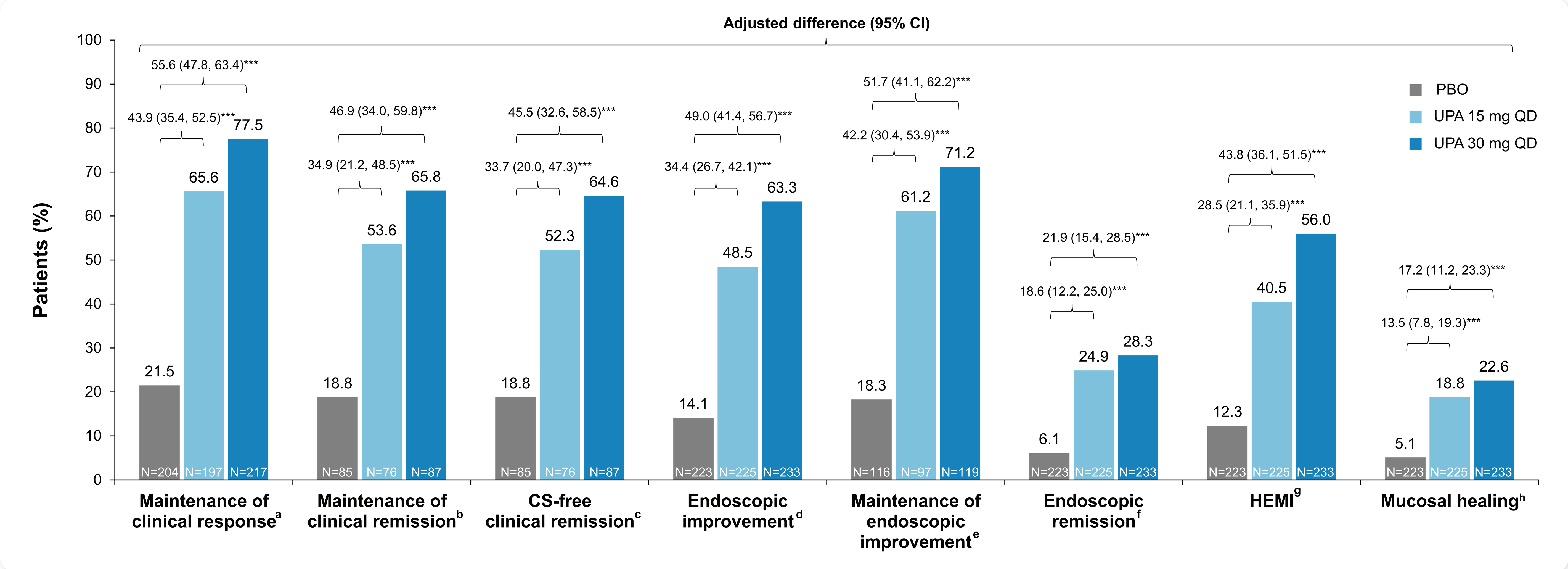
bio-IR, biologic-inadequate response; CS, corticosteroid; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; ITT, intent-to-treat; PBO, placebo; QD, once daily; TNFi, tumor necrosis factor inhibitor; UPA, upadacitinib.
All values are mean (standard deviation) unless otherwise stated.
[a]n = 231. [b]n = 195. [c]n = 197. [d]n = 193. [e]n = 222. [f]n = 229. [g]n = 221. [h]n = 228.

Figure 2. Primary Endpoint: Clinical Remission Rates at Week 52[a] Were Significantly Better With Both UPA Doses vs PBO



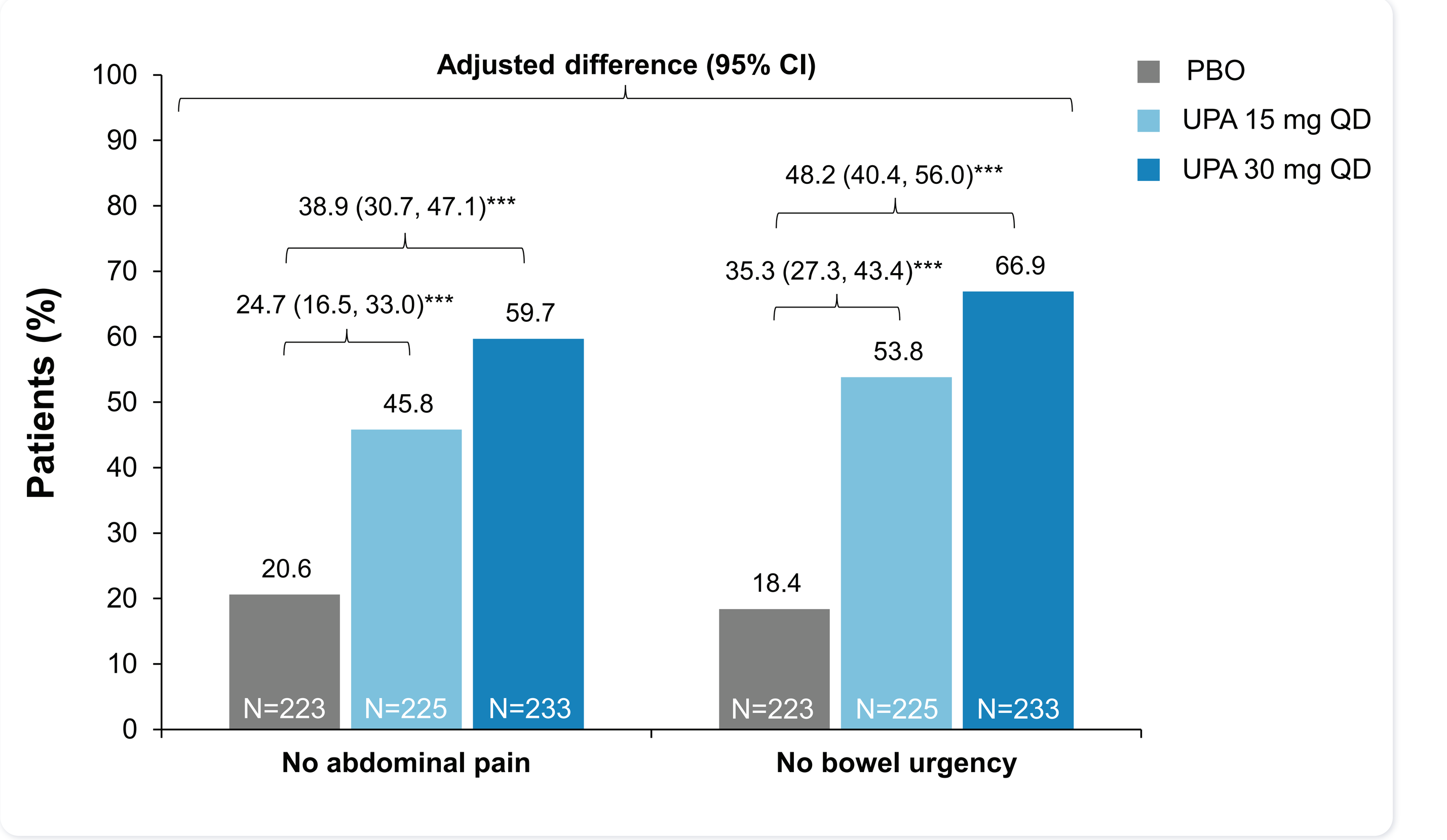
CI, confidence interval; PBO, placebo; QD, once daily; UPA, upadacitinib.
****P* <.001.
[a]Defined as Adapted Mayo Score ≤2, with stool frequency subscore ≤1 and not greater than baseline, rectal bleeding subscore = 0, and endoscopic subscore ≤1 without friability.

Figure 3. Key Secondary Clinical, Endoscopic, and Mucosal Endpoints Were Achieved at Week 52 by a Significantly Greater Proportion of Patients With Both UPA Doses vs PBO



CI, confidence interval; CS, corticosteroid; ES, endoscopic subscore; HEMI, histologic–endoscopic mucosal improvement; PBO, placebo; QD, once daily; RBS, rectal bleeding subscore; UPA, upadacitinib.
****P* <.001.
[a]Clinical response (decrease in Adapted Mayo Score of ≥2 points and ≥30% from baseline, plus a decrease in RBS of ≥1 or an absolute RBS of ≤1) at week 52 among patients who achieved a clinical response at the end of induction therapy. [b]Clinical remission (defined as Adapted Mayo Score ≤2, with stool frequency subscore ≤1 and not greater than baseline, RBS = 0, and ES ≤1 without friability) at week 52 among patients who achieved clinical remission at the end of induction therapy. [c]Clinical remission (defined as Adapted Mayo Score ≤2, with stool frequency subscore ≤1 and not greater than baseline, RBS = 0, and ES ≤1 without friability) at week 52 and CS-free for ≥90 days immediately prior to week 52 among patients who achieved clinical remission at the end of induction therapy. [d]ES ≤1. [e]ES ≤1 among patients who achieved endoscopic improvement (defined as ES ≤1) at the end of induction therapy. [f]ES = 0. [g]ES ≤1 without friability and Geboes score ≤3.1. [h]ES = 0 and Geboes score <2.

Figure 4. Key Secondary Symptom Endpoint Achievement at Week 52 Was Significantly Increased With Both UPA Doses vs PBO



CI, confidence interval; PBO, placebo; QD, once daily; UPA, upadacitinib.
****P* <.001.

Table 2. Overview of AEs

	N = 746		
Events/100 PY	PBO (n = 245) 135.0 PY	UPA 15 mg QD (n = 250) 199.4 PY	UPA 30 mg QD (n = 251) 218.5 PY
Any AE	494.1	314.1	315.6
Any serious AE	20.8	12.0	10.0
AEs leading to discontinuation	19.1	5.5	8.7
AEs leading to death	0	0	0
AESI			
Serious infection	5.9	5.0	3.2
Opportunistic infection	1.6	0.9	0.9
Herpes zoster	0	5.8	7.3
Malignancy (excluding NMSC)	0.8	0.5	0.9
NMSC	0	0	1.4
Renal dysfunction	0.8	0.5	0.5
Hepatic disorder	5.9	17.4	9.1
Adjudicated GI perforation	1.6	0	0
Adjudicated MACE[a,b]	0.7	0	0.5
Adjudicated VTE[a,c]	0	1.0	0.9
Anemia	13.8	6.1	4.6
Neutropenia	5.1	5.5	8.7
Lymphopenia	3.4	5.0	3.2
CPK elevation	3.9	8.1	10.1

AE, adverse event; AESI, adverse event of special interest; CPK, creatine phosphokinase; GI, gastrointestinal; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; PY, patient-years; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolic event.
All AEs were defined according to the Medical Dictionary of Regulatory Activities preferred terms. Data are study size adjusted. AESIs were pre-specified based on previous studies.[2–4]
[a]All UPA-treated patients who experienced a VTE or MACE had ≥1 known risk factor.
[b]Defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.
[c]Defined as deep vein thrombosis and pulmonary embolism (fatal and non-fatal).