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Efficacy and Safety of Upadacitinib Induction Therapy in Patients With Moderately to Severely Active Crohn's Disease: Results From a Randomized Phase 3 U-EXCEL Study

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OBJECTIVE

This presentation reports the primary efficacy and safety results of U-EXCEL at week 12

CONCLUSIONS

- Upadacitinib 45 mg once daily (QD) induction treatment was superior to placebo at inducing clinical remission and endoscopic response in patients with moderate-to-severe crohn's disease with a history of conventional or biologic therapy failure
- Steroid-free clinical remission and endoscopic remission were also achieved at the end of induction treatment with upadacitinib 45 mg QD
- Rapid onset of action was observed by the achievement of clinical response as early as week 2 and clinical remission at week 4
- Upadacitinib 45 mg DQ for 12 weeks was well tolerated, with no new safety risks observed compared with the known safety profile of upadacitinib[1–3]

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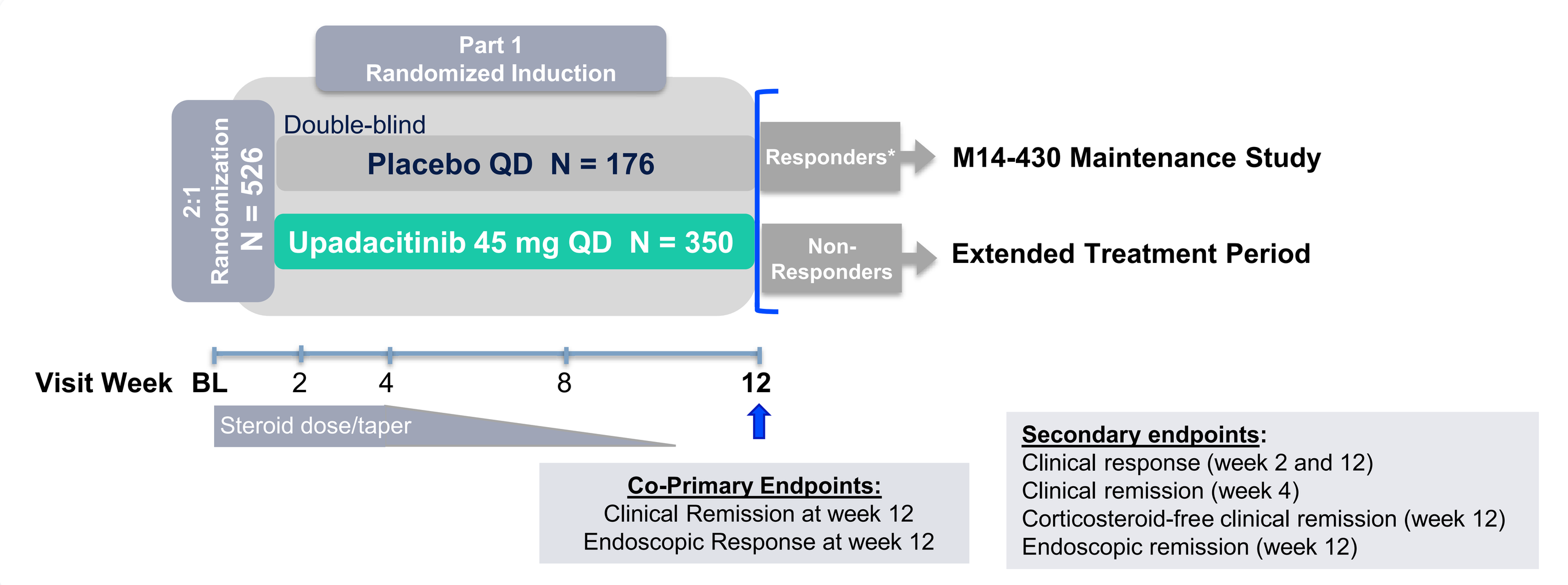
BACKGROUND

- Upadacitinib (UPA) is an oral, reversible Janus kinase (JAK) inhibitor engineered for increased selectivity for JAK1 over JAK2, JAK3, or tyrosine kinase 2
- U-EXCEL and U-EXCEED were phase 3, double-blind, placebo (PBO)-controlled trials that evaluated the efficacy and safety of UPA as induction therapy in patients with moderately to severely active Crohn's disease (CD)
  - In U-EXCEED, UPA 45 mg daily for 12 weeks was effective in inducing clinical and endoscopic improvements, with an acceptable safety profile[1]

METHODS

U-EXCEL Induction Study Design in Patients With Inadequate Response or Intolerance to Conventional or Biologic Therapy



BL, baseline, QD, once daily.

Main Inclusion Criteria:

- 18 to 75 years of age
- Moderately to severely active CD:
  - Average daily liquid/very soft stool frequency (SF) ≥4 and/or average daily abdominal pain score (APS) ≥2
  - Evidence of mucosal inflammation; Simple Endoscopic Score for CD (SES-CD ≥6) (≥4 for patients with isolated ileal disease)
- Intolerance or inadequate response to 1 or more steroid, immunosuppressant or biologic therapy
- Clinical Response per SF/APS: ≥30% decrease in average daily SF and/or in average daily APS and both not greater than baseline

RESULTS

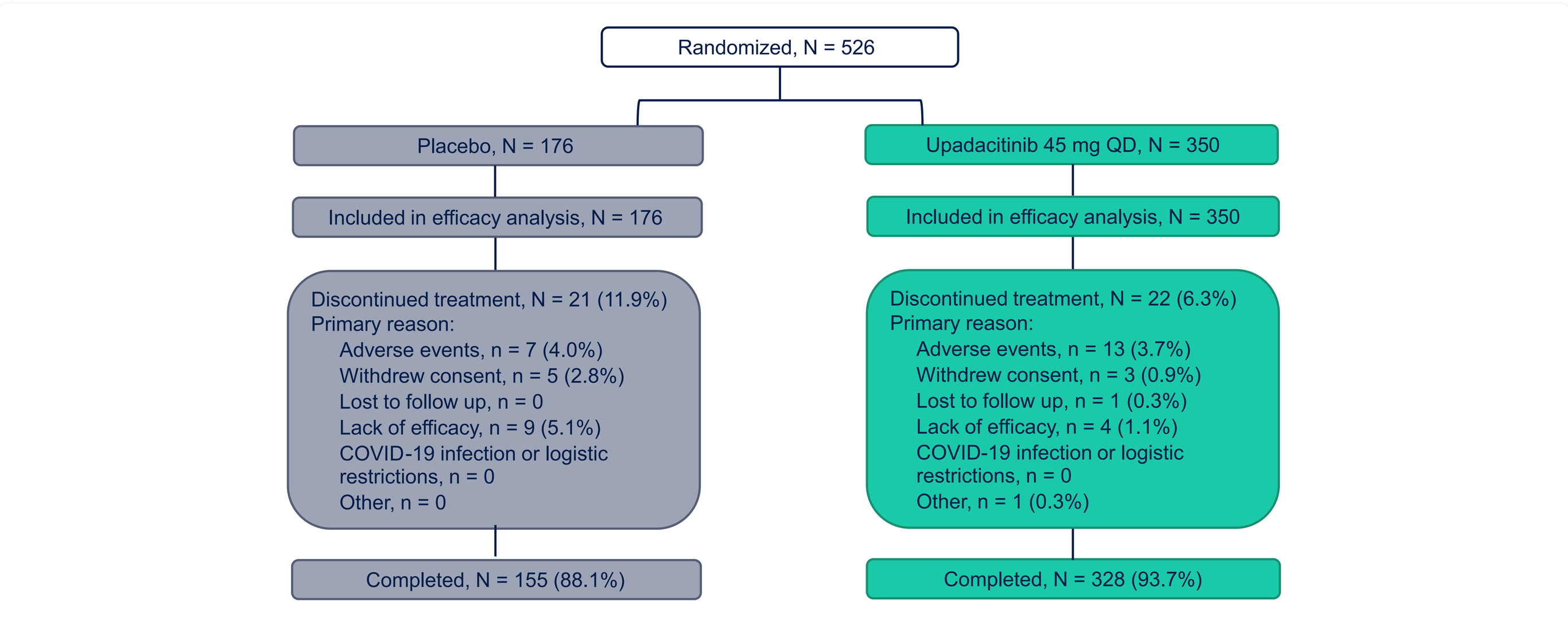
Baseline Characteristics and Demographics in U-EXCEL (ITT1 Population)

Characteristic	PBO N = 176	UPA 45 mg QD N = 350
Male sex, n (%)	94 (53.4)	189 (54.0)
Age, years, mean (SD)	39.3 (13.6)	39.7 (13.7)
Weight, kg, mean (SD)	73.9 (21.0)	70.7 (19.6)
Duration of disease, years, median (range)	5.7 (0.3, 46.3)	6.7 (0.06, 52.1)
Disease location – n (%)		
Ileal only	27 (15.3)	58 (16.6)
Colonic only	57 (32.4)	121 (34.6)
Ileal colonic	92 (52.3)	171 (48.9)
CDAI, mean (SD)[a]	293.85 (85.378)	292.42 (81.250)
SES-CD*, mean (SD)	13.6 (7.0)	13.7 (7.3)
C-reactive protein (mg/L), median (range)[b]	7.0 (0.2, 113.0)	8.2 (0.2, 120.0)
Fecal calprotectin (μg/g), median (range)[c]	949.0 (30, 24234)	904.0 (30, 28800)
Concomitant immunosuppressant use, n (%)	3 (1.7)	126 (36.0)
Concomitant aminosalicylate use, n (%)	50 (28.4)	81 (23.1)
Concomitant corticosteroid use*, n (%)	64 (36.4)	126 (36.0)
Patients with a history of conventional therapy failure only, n (%)	98 (55.7)	189 (54.0)
Patients with a history of biologic failure, n (%)*	78 (44.3)	161 (46.0)
Number of biologics: 1	28 (35.9)	58 (36.0)
2	24 (30.8)	52 (32.3)
≥3	26 (33.3)	51 (31.7)
Prior failure to TNF inhibitor[d], n (%)	75 (96.2)	157 (97.5)

CDAI, Crohn's Disease Activity Index; PBO, placebo; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor UPA, upadacitinib.
ITT1: Intent-to-treat population—randomized patients who received >1 dose of study drug in the 12-week induction period. These subjects were included in the safety analysis.
*Stratification factors for randomization: baseline corticosteroid use, endoscopic disease severity (SES <15 or ≥15), and the number of prior inadequate response or intolerance to biologics (0, 1, >1).
Patient numbers: [a]CDAI, PBO N = 176; UPA N = 349. [b]C-reactive protein, PBO N = 176; UPA N = 341. [c]Fecal calprotectin, PBO N = 161; UPA N = 319.
[d]Footnote??

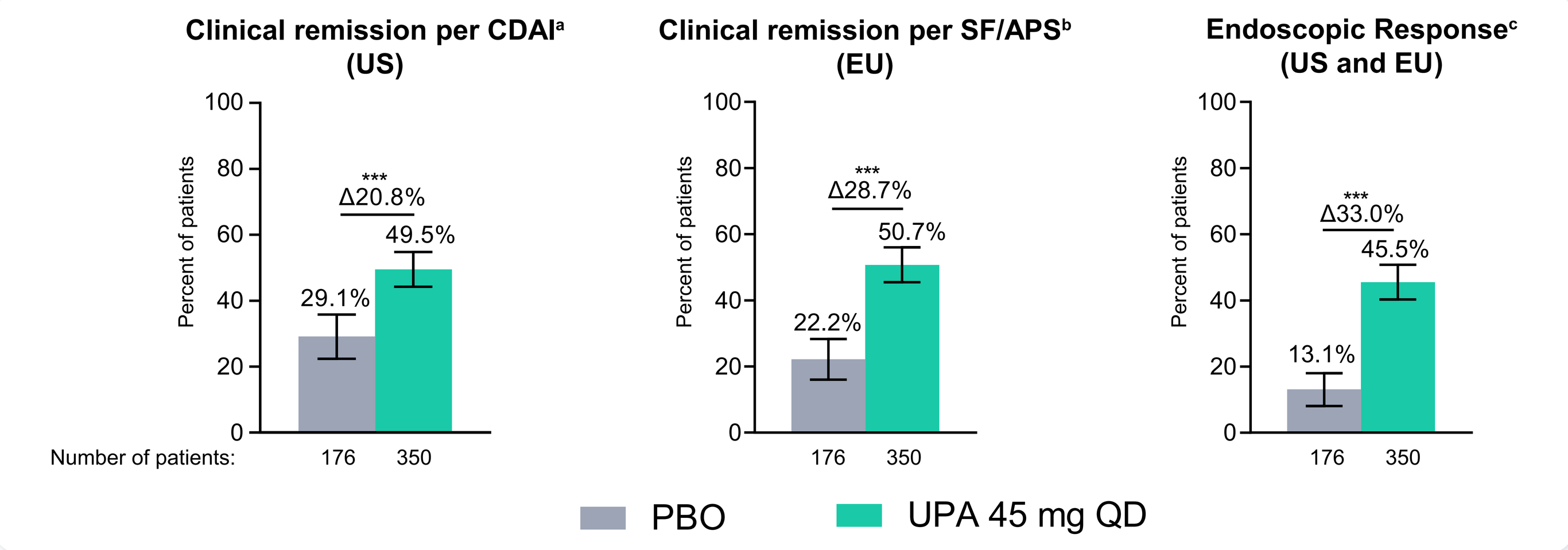
RESULTS

Patient Disposition in the 12-Week Double-Blind Induction Period (ITT1 Population)



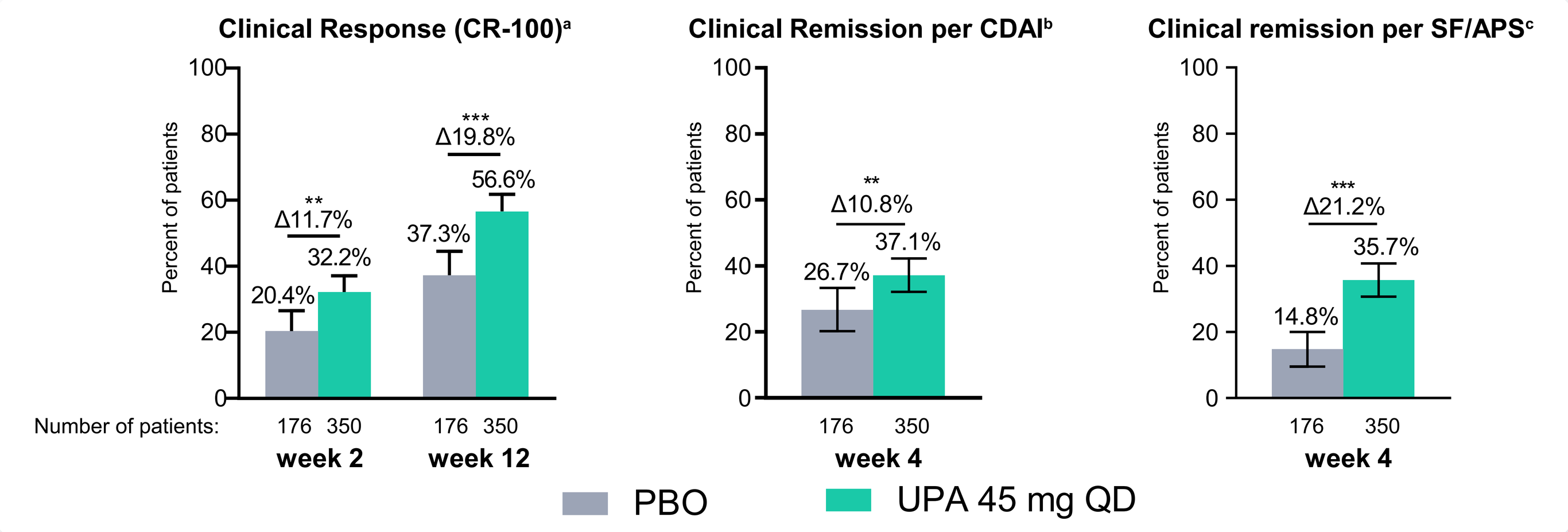
ITT1 population: includes all randomized patients who received at least 1 dose of double-blinded study drug from Part 1.
ITT1: Intention-to-treat population; QD: once daily. COVID-19: coronavirus disease 2019.

Patients Treated With UPA 45 mg QD Achieved a Significant Difference in Co-Primary Endpoints at Week 12 Compared to PBO



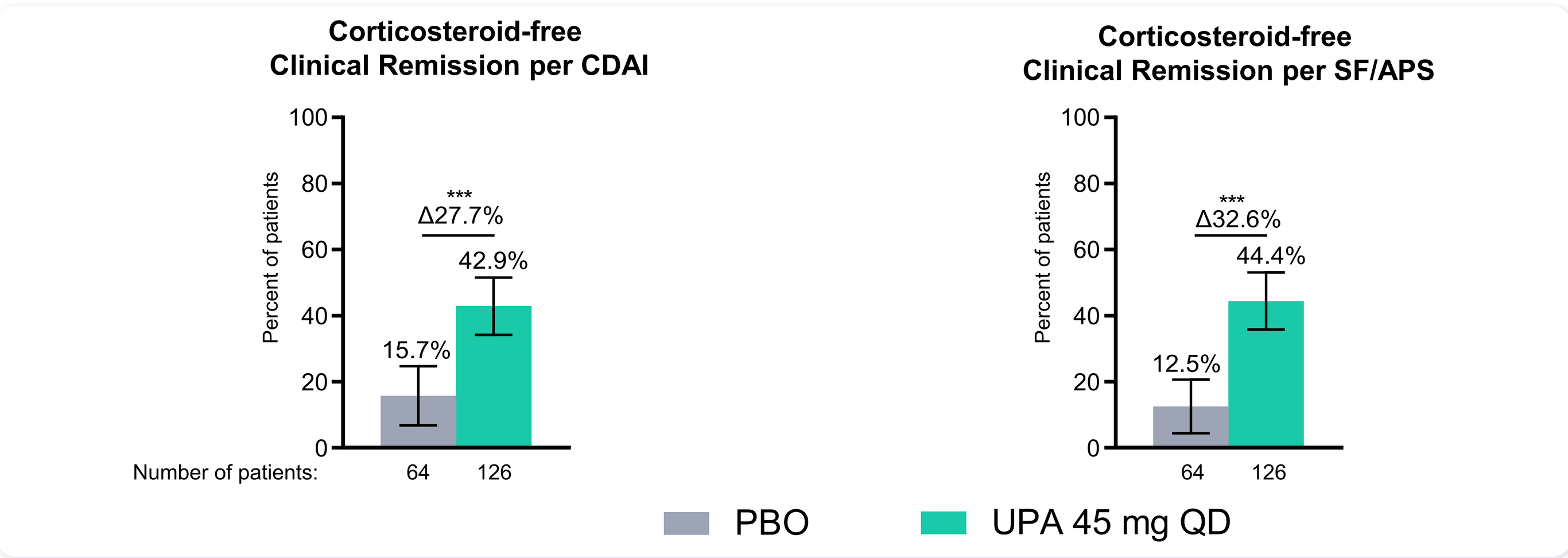
CDAI, Crohn's Disease Activity Index; EU, European Union; PBO, placebo; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF/APS, stool frequency/abdominal pain score; UPA, upadacitinib; US, United States.
[a]Clinical Remission per CDAI: CDAI <150.
[b]Clinical Remission per SF/APS: Average daily SF ≤2.8 AND average daily APS ≤1 and neither worse than baseline.
[c]Endoscopic Response: Decrease in SES-CD >50% from baseline (or SES-CD of 4), at least a 2-point reduction from baseline, scored by central reader.
95% CI for response rate is the synthetic result based on Student's *t*-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data. Point estimate and 95% CI for adjusted treatment difference are based on Cochran-Mantel-Haenszel test for adjusted strata for categorical endpoints. Non-responder imputation incorporating multiple imputation was used to handle missing data due to COVID-19; ***P <.0001 vs PBO.

A Significant Proportion of Patients Treated With UPA 45 mg QD Achieved Clinical Response as Early as Week 2 and Clinical Remission At Week 4



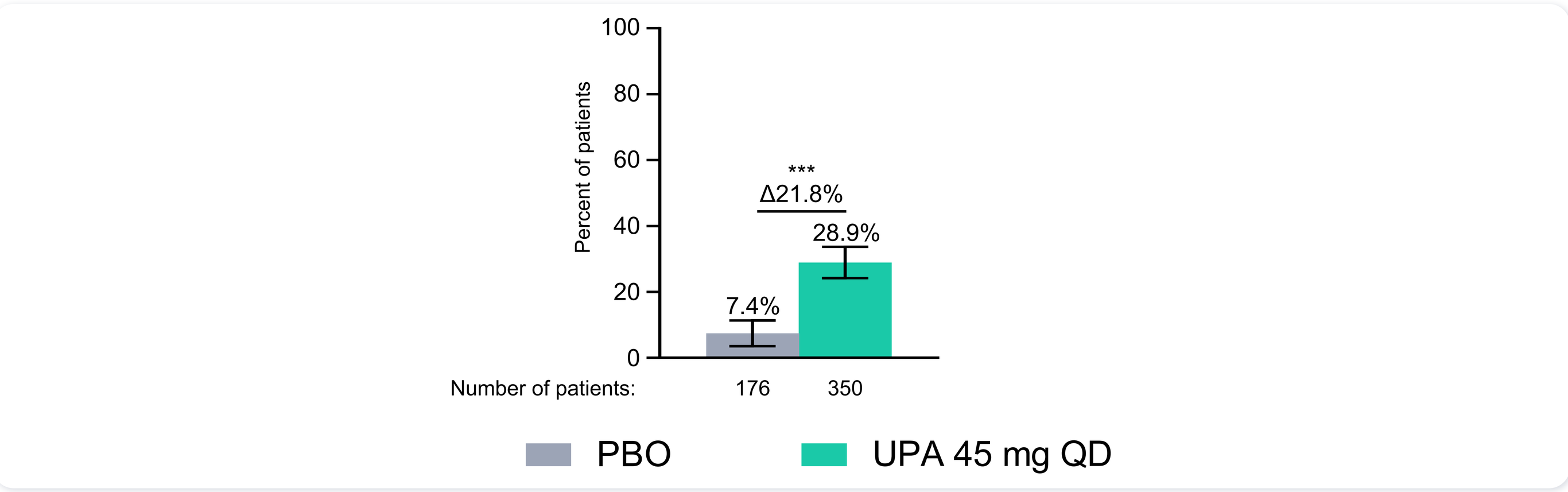
CDAI, Crohn's Disease Activity Index; PBO, placebo; SF/APS, stool frequency/abdominal pain score; UPA, upadacitinib.
[a]Clinical Response (CR-100): Decrease of ≥100 points in CDAI from baseline.
[b]Clinical Remission per CDAI: CDAI <150.
[c]Clinical Remission per SF/APS: Average daily SF ≤2.8 AND average daily APS ≤1 and neither worse than baseline.
95% CI for response rate is the synthetic result based on Student's *t*-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. Point estimate and 95% CI for adjusted treatment difference are based on Cochran-Mantel-Haenszel test for adjusted strata for categorical endpoints. Non-responder imputation incorporating multiple imputation was used to handle missing data due to COVID-19; ***P <.0001 vs PBO; **P <.01 vs PBO.

Patients on Corticosteroids at Baseline Treated With UPA 45 mg QD Achieved a Significant Difference in Corticosteroid-free Clinical Remission at Week 12



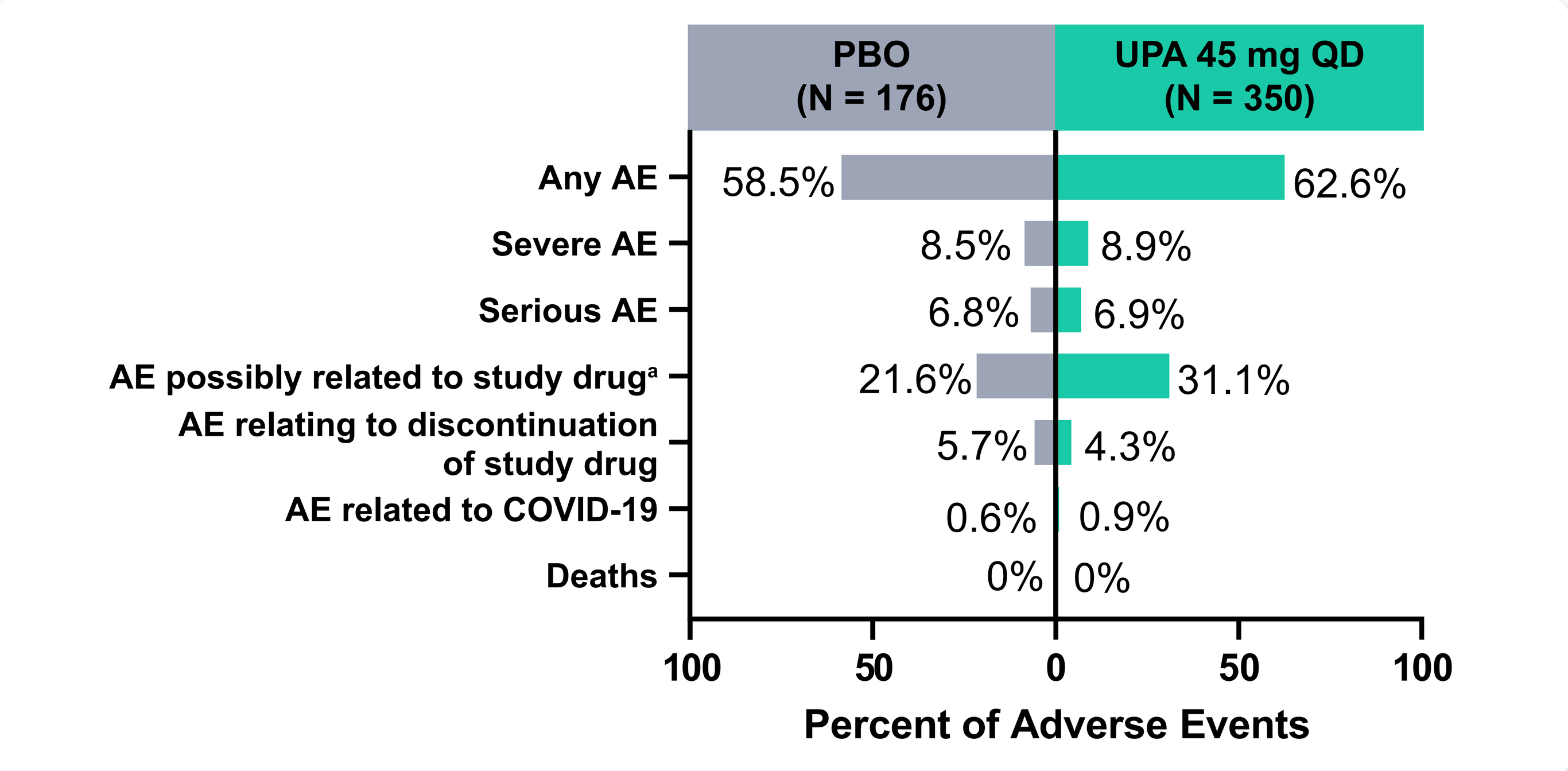
CDAI, Crohn's Disease Activity Index; PBO, placebo; SF/APS, stool frequency/abdominal pain score; UPA, upadacitinib.
Corticosteroid-free Clinical Remission per CDAI or SF/APS: Discontinuation of corticosteroid and achievement of clinical remission (per CDAI or SF/APS), among subjects on steroids at baseline.
95% CI for response rate is based on Student's *t*-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data. Point estimate and 95% CI for adjusted treatment difference are based on Cochran-Mantel-Haenszel test for adjusted strata for categorical endpoints. Non-responder imputation incorporating multiple imputation was used to handle missing data due to COVID-19; ***P <.0001 vs PBO.

Patients Treated With UPA 45 mg QD Achieved a Significant Difference in Endoscopic Remission at Week 12



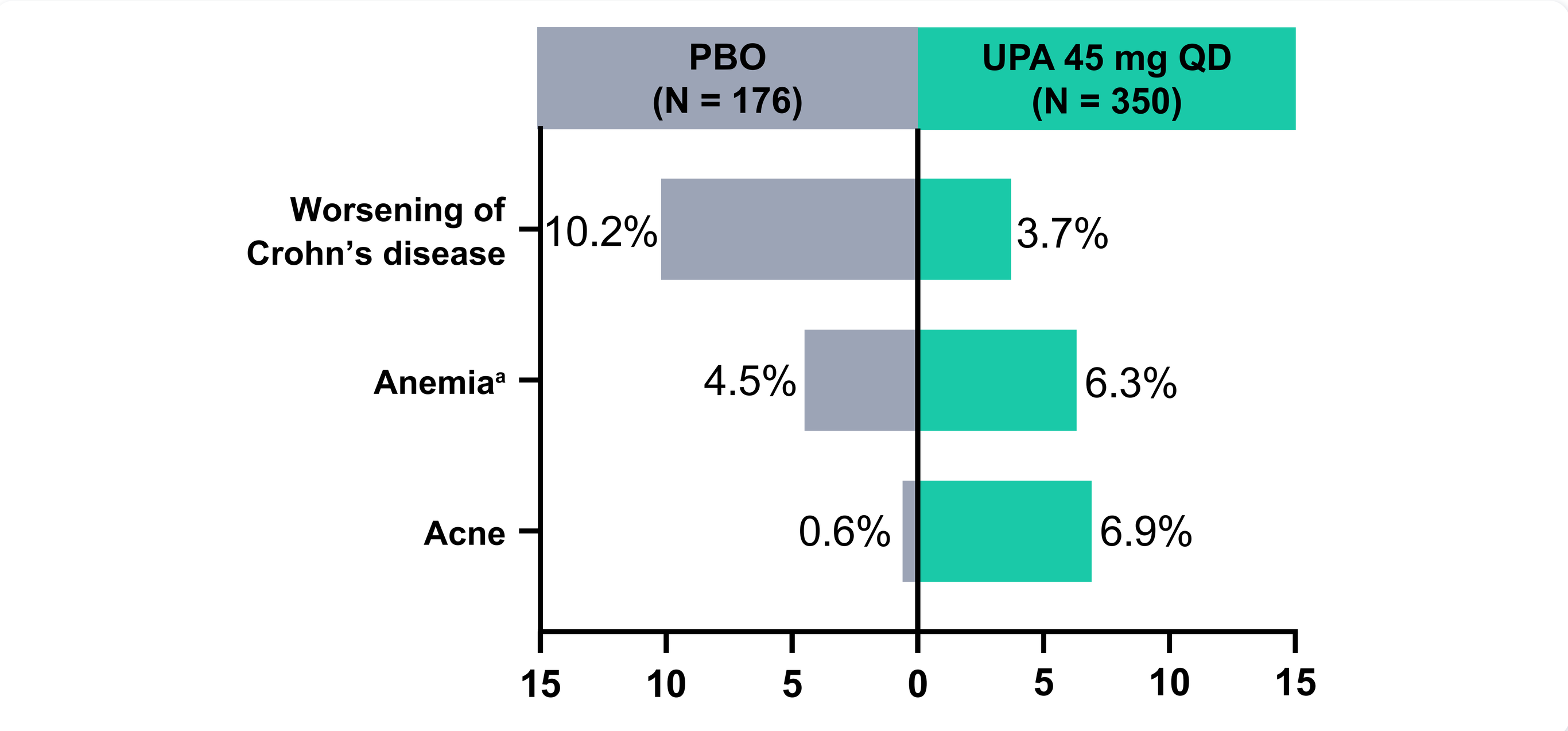
PBO, placebo; SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib.
Endoscopic remission: SES-CD ≤ 4, at least a 2-point reduction vs baseline and no subscore >1 in any individual variable, as scored by a central reviewer.
95% CI for response rate is the synthetic result based on Student's *t*-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19. Point estimate and 95% CI for adjusted treatment difference are based on Cochran-Mantel-Haenszel test for adjusted strata for categorical endpoints. Non-responder imputation incorporating multiple imputation was used to handle missing data due to COVID-19; ***P <.0001 vs PBO.

Treatment-Emergent Adverse Events (AEs)



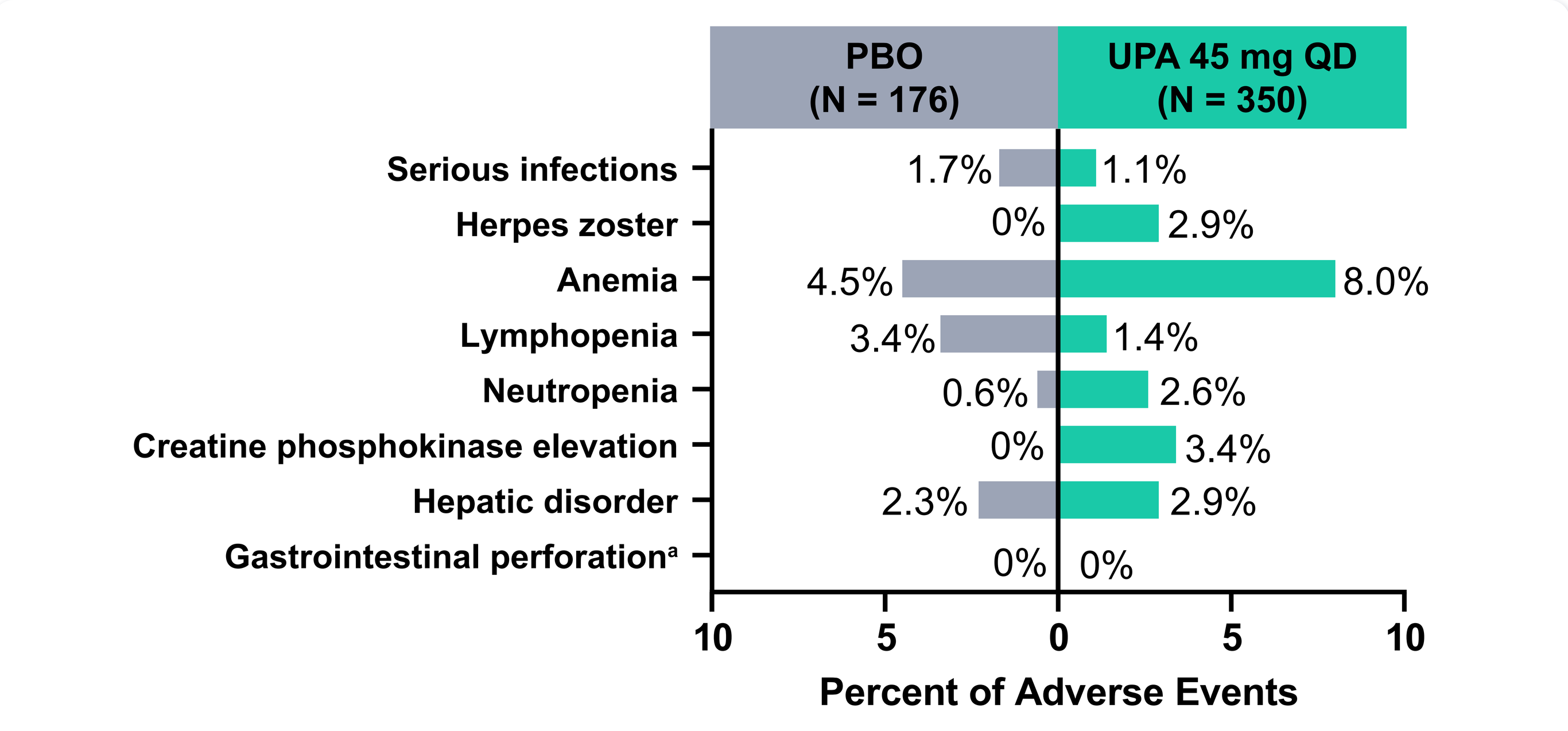
AE, adverse events; PBO, placebo; UPA, upadacitinib.
[a]As assessed by investigator

Adverse Events Reported by ≥5% in any Treatment Group



PBO, placebo; UPA, upadacitinib.
[a]As assessed by investigator.

Adverse Events of Special Interest (AESI)



PBO, placebo; UPA, upadacitinib.
No opportunistic infections (excluding tuberculosis and herpes zoster), tuberculosis, renal disorders, adjudicated cardiovascular or venous thromboembolic events, or cancer of any kind were observed in either group.
Anemia of AESI is based on CMQ search, which includes other preferred terms, in addition to the preferred term "anaemia".
[a]One event of adjudicated gastrointestinal perforation (intestinal perforation) was reported in a patient who was a clinical non-responder to PBO and was on UPA 45 mg QD in the extended treatment period.