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Matching-Adjusted Indirect Comparison of Upadacitinib vs Vedolizumab as Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis

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OBJECTIVE

To conduct a placebo (PBO)-anchored matching-adjusted indirect comparison (MAIC) of efficacy and safety outcomes between upadacitinib (UPA) and vedolizumab (VEDO) in patients with moderately to severely active ulcerative colitis (UC)

CONCLUSIONS

In this indirect treatment comparison, UPA demonstrated better efficacy during induction treatment compared with VEDO in patients with moderately to severely active UC

Risk differences of safety outcomes were generally similar between UPA and PBO; UPA had a numerically higher proportion of adverse events, but not statistically different from VEDO during induction treatment in patients with moderately to severely active UC

Analysis of number needed to treat/harm (NNT/NNH) suggest UPA has a favorable benefit-risk profile vs VEDO as induction therapy

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INTRODUCTION

- In recent years, several treatments have been investigated for management of moderate to severe UC
- UPA is an oral, reversible, selective Janus kinase inhibitor approved to treat patients with moderately to severely active UC, with efficacy and safety studied in phase 3 trials U-ACHIEVE (NCT02819635) and U-ACCOMPLISH (NCT03653026)[1,2]
- VEDO is a humanized α4β7 integrin monoclonal antibody approved for the treatment of patients with moderately to severely active UC, based on studies including the phase 3 GEMINI 1 trial (NCT00783718)[3]
- The comparative efficacy and safety of UPA vs VEDO adjusting for differences in trial characteristics has not previously been assessed

METHODS

Study Design and Patients

- This is an indirect comparison of efficacy and safety outcomes based on a PBO-anchored MAIC of phase 3 induction studies U-ACHIEVE Induction, U-ACCOMPLISH, and GEMINI 1
- Patients received UPA 45 mg oral, once daily for 8 weeks with disease evaluation at 8 weeks; VEDO 300 mg intravenously at weeks 0 and 2 with disease evaluation at 6 weeks; or corresponding PBO
- Active UC was defined as:
  - A diagnosis of UC for ≥90 days prior to baseline with an Adapted Mayo score (centrally read endoscopic subscore) of 5 to 9 points in UPA trials
  - A diagnosis of UC for at least 6 months prior to enrollment with a Full Mayo score of 6 to 12 in VEDO trial

Outcomes

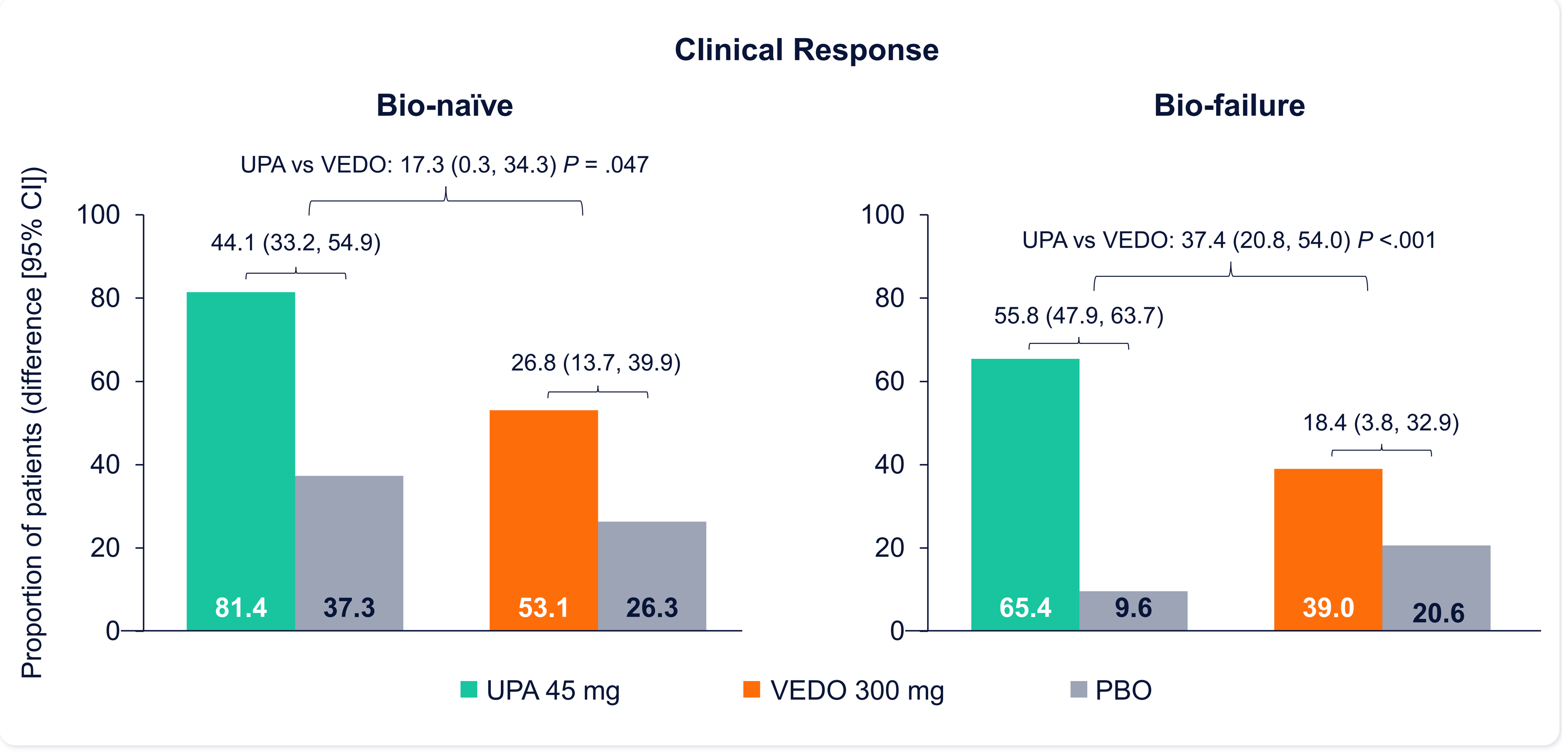
- Efficacy outcomes evaluated at Week 6 (VEDO)/week 8 (UPA) were:
  - Clinical remission per full Mayo score (FMS; FMS ≤2 with no subscore >1)
  - Clinical response per FMS (decrease from baseline in FMS ≥3 points and ≥30%, accompanied by a decrease in rectal bleeding score [RBS] of ≥1 or an absolute RBS of 0 or 1)
  - Endoscopic improvement (endoscopic subscore 0 or 1)
- Safety outcomes evaluated at week 6 (VEDO)/week 8 (UPA) were: all adverse events (AEs), serious AEs (SAEs), any infection, and serious infections
- NNT/NNH based on efficacy/safety differences between UPA and VEDO

Statistical analysis

- MAIC is a methodology designed to reduce confounding of treatment effects in order to compare clinical outcomes between UPA and VEDO using individual patient data from the phase 3 trials of UPA and summary data (baseline characteristics and outcomes) from the phase 3 trial of VEDO
- In the MAIC analysis, baseline characteristics for age, gender, duration of disease, total Mayo score, corticosteroid use, and fecal calprotectin levels from the UPA trials were weighted to match those reported in GEMINI for the efficacy analysis plus previous anti-tumor necrosis factor/biologic therapy use/failure, Inflammatory Bowel Disease Questionnaire score, hemoglobin concentration, and white-cell count for the safety analysis
- MAIC was performed on efficacy outcomes in bio-naïve (no exposure to any biologic at baseline) and bio-failure (inadequate response, loss of response, or intolerance to biologic treatment at baseline) patients; safety outcomes were assessed in the overall population
- Proportions for efficacy and risk differences for safety were compared using weighted scores and reported with *P*-values and 95% confidence intervals (CI)
- NNT/NNH were calculated as the inverse of the PBO-adjusted difference in proportions achieving efficacy/safety outcomes between UPA and VEDO

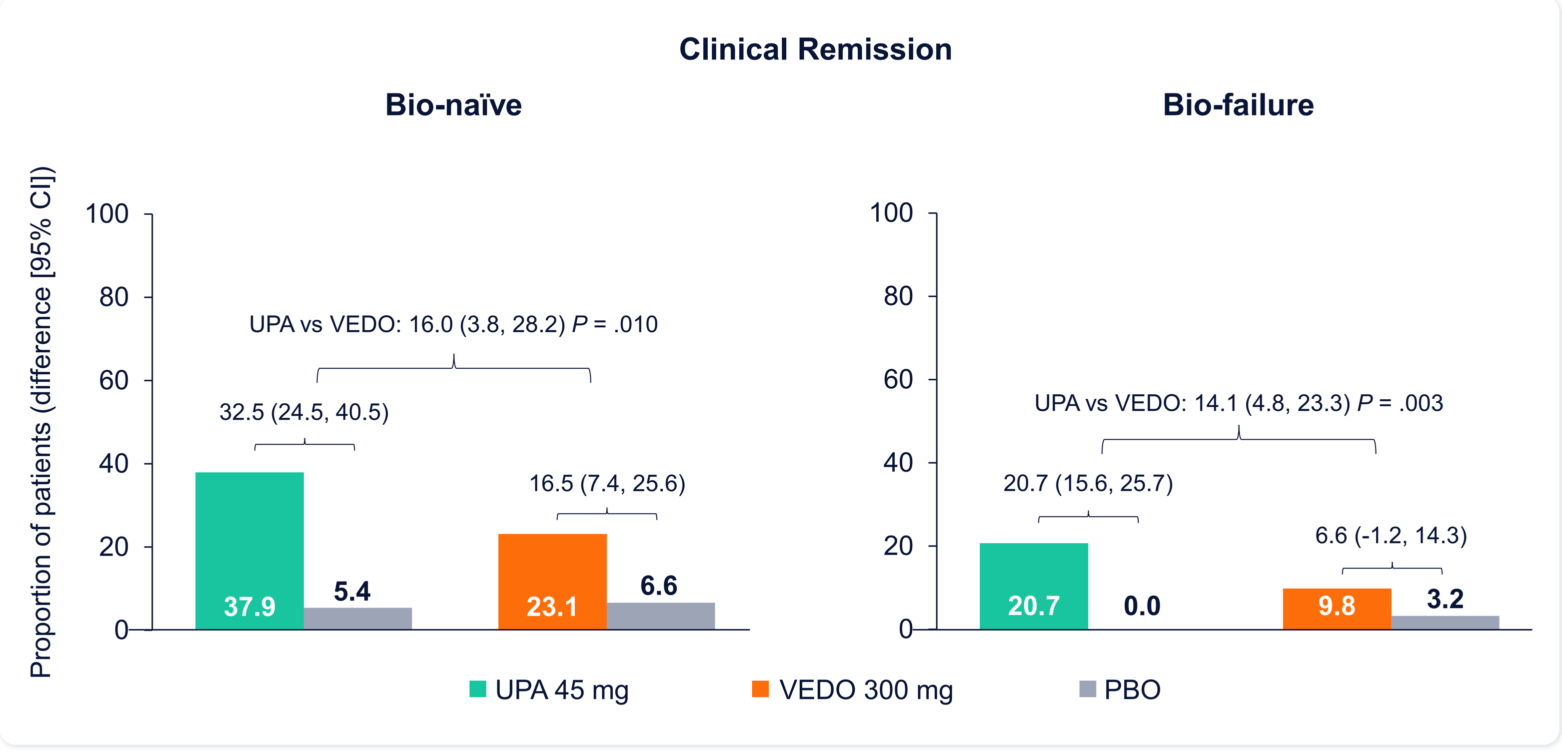
RESULTS

Figure 1. In Both Bio-Naïve and Bio-Failure Groups, a Significantly Greater Proportion of Patients Receiving UPA (Week 8) vs VEDO (Week 6) Achieved Clinical Response at Induction



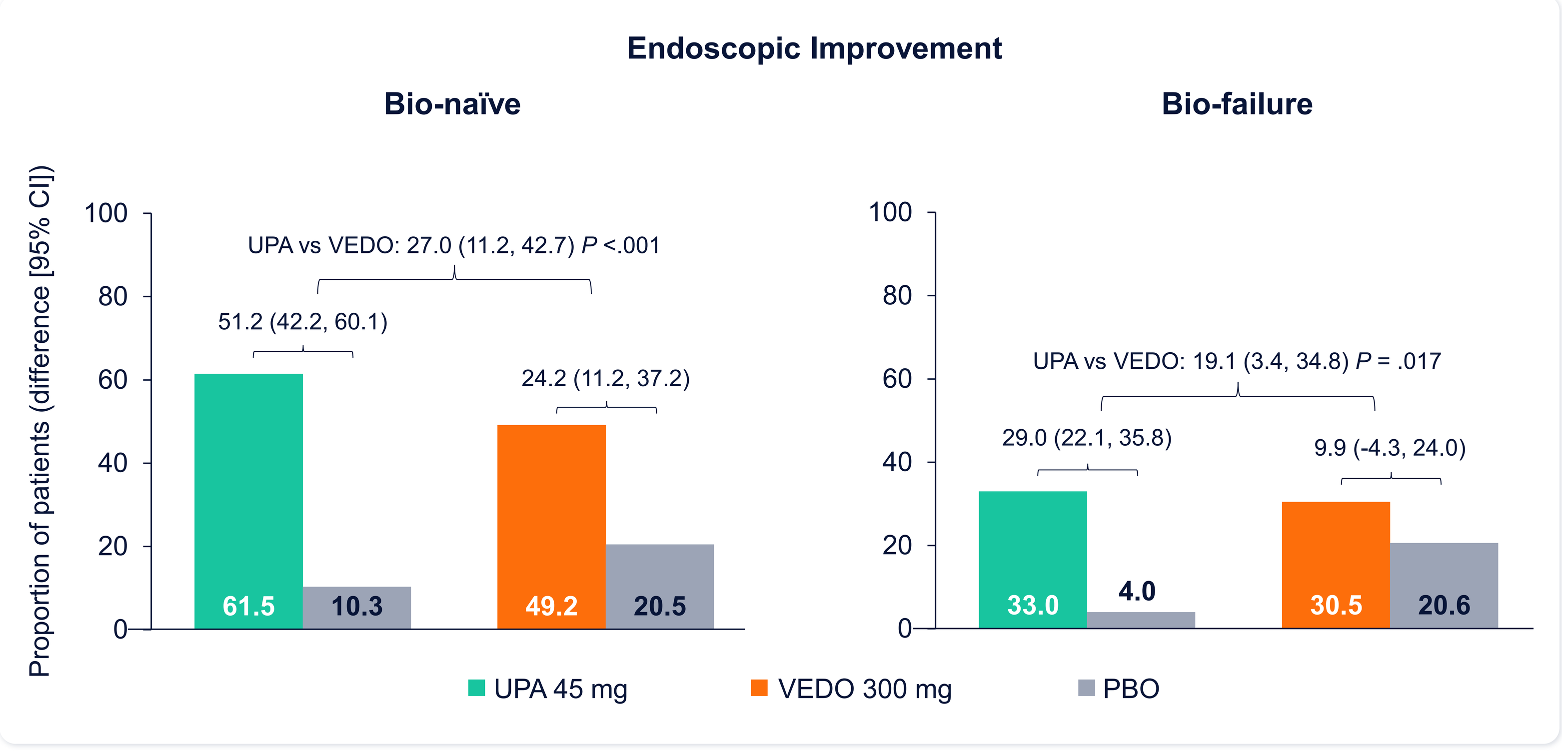
CI, confidence interval; PBO, placebo; UPA, upadacitinib; VEDO, vedolizumab.
Patient number (bio-naïve/bio-failed): UPA 45 mg (262/292), placebo-UPA (132/147), VEDO (130/82), placebo-VEDO (76/63).

Figure 2. In Both Bio-Naïve and Bio-Failure Groups, a Significantly Greater Proportion of Patients Receiving UPA (Week 8) vs VEDO (Week 6) Achieved Clinical Remission at Induction



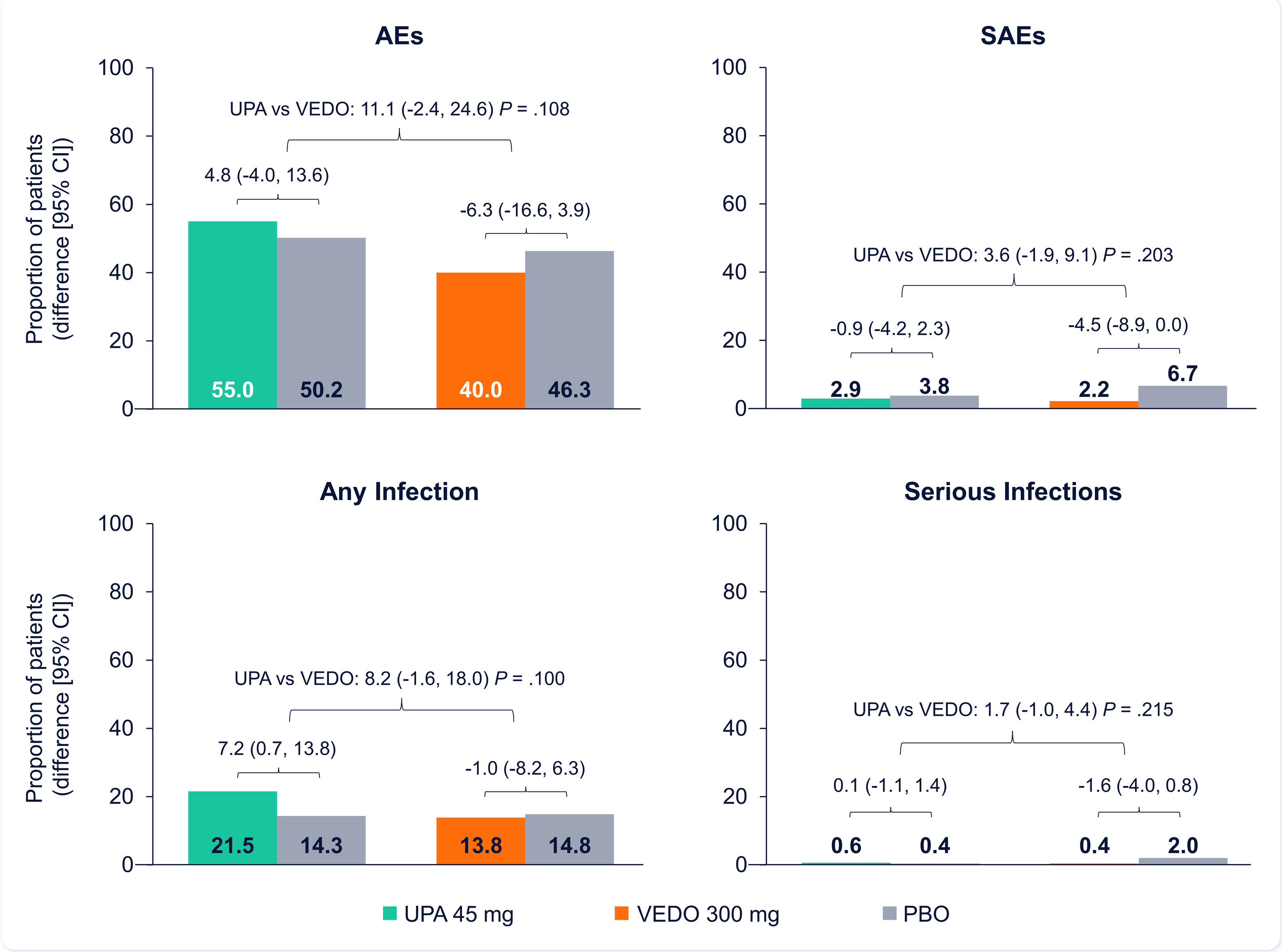
CI, confidence interval; PBO, placebo; UPA, upadacitinib; VEDO, vedolizumab.
Patient number (bio-naïve/bio-failed): UPA 45 mg (262/292), placebo-UPA (132/147), VEDO (130/82), placebo-VEDO (76/63).

Figure 3. A Significantly Greater Proportion of Patients Receiving UPA (Week 8) vs VEDO (Week 6) Achieved Endoscopic Improvement at Induction in Both Bio-Naïve and Bio-Failure Groups



CI, confidence interval; PBO, placebo; UPA, upadacitinib; VEDO, vedolizumab.
Patient number (bio-naïve/bio-failed): UPA 45 mg (262/292), placebo-UPA (132/147), VEDO (130/82), placebo-VEDO (76/63).

Figure 4. PBO-Adjusted Risk Differences of AEs, SAEs, Any Infection, and Serious Infections Were Not Significantly Different Between Patients Receiving UPA (Week 8) vs VEDO (Week 6) at Induction



AE, adverse events; CI, confidence interval; PBO, placebo; SAE, serious adverse events; UPA, upadacitinib; VEDO, vedolizumab.
Patient number: UPA 45 mg (562), placebo-UPA (286), VEDO (225), placebo-VEDO (149).

Table 1. NNT Demonstrate Greater Efficacy of UPA vs VEDO

Efficacy outcome	UPA vs VEDO proportion difference	NNT
Clinical response		
Bio-naïve	17.3*	5.8
Bio-failure	37.4***	2.7
Clinical remission		
Bio-naïve	16.0**	6.3
Bio-failure	14.1**	7.2
Endoscopic improvement		
Bio-naïve	27.0***	3.8
Bio-failure	19.1*	5.3

NNT, number needed to treat; UPA, upadacitinib; VEDO, vedolizumab. **P* <.05; ***P* <.01; ****P* <.001.

Table 2. NNH Demonstrate Greater but Small Safety Risk Differences of UPA vs VEDO

Safety outcome in overall population	UPA vs VEDO proportion difference	NNH
Any adverse event	11.1	9.0
Serious adverse event	3.6	27.9
Any infection	8.2	12.1
Serious infection	1.7	58.5

NNH, number needed to harm; UPA, upadacitinib; VEDO, vedolizumab. **P* <.05; ***P* <.01; ****P* <.001.

LIMITATIONS

- The generalizability of these results may be limited, as the patient population enrolled in a clinical trial may differ from the general population
- There may be potential bias due to unobserved confounders, as only known baseline factors which were consistently reported in UPA and VEDO trials were matched and adjusted in the analysis
- Differences between trials, such as the timing of outcome collection (8 weeks for UPA and 6 weeks for VEDO), the use of central reading of endoscopic subscore, and the onset of action may impact results