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Benefit–Risk Assessment of Upadacitinib Treatment in Patients With Moderately to Severely Active Ulcerative Colitis

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OBJECTIVE

This analysis evaluated the comparative benefit–risk profile of upadacitinib (UPA) vs placebo (PBO) as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis (UC)

CONCLUSIONS

UPA as induction therapy (45 mg once daily [QD]) and maintenance therapy (15 or 30 mg QD) met the primary and all key secondary endpoints, with significantly higher efficacy vs PBO

Although induction and maintenance UPA was associated with higher risk of herpes zoster and creatine phosphokinase (CPK) elevation than PBO, and UPA 30 mg had a higher risk of NMSC than UPA 15 mg in maintenance, the safety profiles were otherwise similar

Overall, these data suggest that UPA has a favorable benefit–risk profile for induction and maintenance therapy, and fulfills an unmet need for patients with UC. Clinicians should communicate potential risks of UPA treatment to patients, especially those who have relevant risk factors

The long-term safety and efficacy of UPA will continue to be evaluated through an ongoing long-term extension study and planned pharmacoepidemiologic studies

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INTRODUCTION

- There is an unmet need for advanced therapies that provide rapid, robust, and sustained disease control and stronger benefit–risk profiles in a higher proportion of patients with UC than current standards of care[1–3]
- The efficacy and safety of UPA, an oral, selective, and reversible Janus kinase inhibitor, have been demonstrated for induction and maintenance therapy in patients with moderately to severely active UC in a Phase 3 clinical trial program[4,5]

METHODS

Study design

- The UPA UC program enrolled patients with active disease, inadequate response, loss of response, or intolerance to ≥1 oral aminosalicylate, corticosteroid, immunosuppressant, and/or biologic therapy to 3 induction trials (U-ACHIEVE [one Phase 2b and one Phase 3] and U-ACCOMPLISH [Phase 3]) and the Phase 3 U-ACHIEVE maintenance study. The study designs and eligibility criteria have been described elsewhere[4]

Assessments

- Data from the Phase 3 studies, U-ACHIEVE Induction and U-ACCOMPLISH[4], were integrated for PBO and UPA 45 mg QD
  - UPA 45 mg QD data from the U-ACHIEVE Phase 2b study were also included in this analysis
- Non-responder imputation incorporating multiple imputation was used to handle missing data due to COVID-19
- For analysis of efficacy, point estimates and 95% confidence intervals of the PBO-adjusted treatment effect were calculated across the primary and key secondary endpoints in the intent-to-treat population (see **Figure 1** for endpoints and definitions)
- For the safety risk analysis, the exposure-adjusted event rate (events/100 patient-years) was calculated for selected adverse events of special interest (AESIs) in the initial induction phase with UPA 45 mg QD, and the maintenance phase with UPA 15 mg QD and 30 mg QD (see **Figure 2** for AESIs and safety population definitions)
  - The PBO-adjusted risk was then calculated for each AESI

RESULTS

- Patients were inducted onto therapy either in the PBO group (n = 328) or 45 mg QD of UPA (n = 660)
- Overall, 681 patients progressed onto maintenance therapy and were analyzed for efficacy (PBO, n = 223; UPA 15 mg, n = 225; and UPA 30 mg, n = 233), and 746 for safety (n = 245, n = 250, and n = 251, respectively)
- Baseline demographics and clinical characteristics were well balanced across treatment groups in the intent-to-treat population[4]

Efficacy

- UPA 45 mg QD for induction and both UPA 15 mg and 30 mg QD for maintenance therapy were significantly more efficacious than PBO across the primary endpoint and all key secondary endpoints (all *P* <.001; **Figure 1**)
- The PBO-adjusted treatment effect was numerically higher with maintenance UPA 30 mg QD than UPA 15 mg QD across all endpoints analyzed **(Figure 1)**

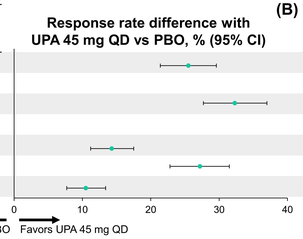
Safety

- In the induction period, 27 (7.1%) patients discontinued treatment because of an adverse event (AE) with PBO, compared with 17 (2.4%) with UPA 45 mg QD
- In the maintenance period, 25 (10.2%), 10 (4.0%), and 18 (7.2%) patients discontinued treatment due to an AE with PBO, UPA 15 mg QD, and UPA 30 mg QD, respectively
- Compared with PBO, there was an increased risk of herpes zoster and CPK elevation with UPA for induction and maintenance; there was also an increased risk of non-melanoma skin cancer (NMSC) with UPA 30 mg QD compared with UPA 15 mg QD in maintenance **(Figure 2)**
- There was no notable difference in the incidence of major adverse cardiovascular events (MACE) or venous thromboembolic events (VTE) between either UPA dose compared with PBO
  - All UPA-treated patients who experienced a VTE or MACE had ≥1 known risk factor

Figure 1. PBO-Adjusted Treatment Effects With UPA vs PBO at the End of Induction (A) and Maintenance[a] (B)

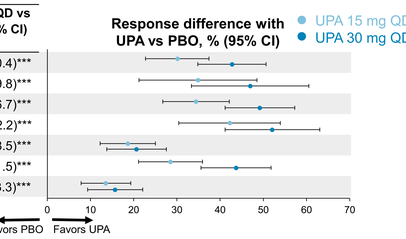
(A)

	PBO response, n (%) (n = 328)	UPA 45 mg QD response, n (%) (n = 660)	UPA 45 mg QD vs PBO, % (95% CI)
Clinical remission[b] (primary endpoint)	15 (4.4)	198 (29.9)	25.5 (21.4, 29.6)***
Maintenance of clinical remission[c]	NA	NA	NA
Endoscopic improvement[g]	26 (7.9)	266 (40.3)	32.3 (27.7, 37.0)***
Maintenance of endoscopic improvement[h]	NA	NA	NA
Endoscopic remission[i]	5 (1.6)	106 (16.0)	14.3 (11.2, 17.5)***
HEMI[m]	20 (6.2)	221 (33.5)	27.2 (22.8, 31.5)***
Mucosal healing[n]	5 (1.5)	80 (12.2)	10.5 (7.7, 13.4)***



(B)

	PBO response, % (95% CI) (n = 223)	UPA 15 mg QD response, % (95% CI) (n = 225)	UPA 30 mg QD response, % (95% CI) (n = 233)	UPA 15 mg QD vs PBO, % (95% CI)	UPA 30 mg QD vs PBO, % (95% CI)
	24 (10.8)	91 (40.4)	125 (53.6)	30.1 (22.7, 37.4)***	42.9 (35.4, 50.4)***
	16 (18.8)[d]	41 (53.6)[e]	57 (65.8)[f]	34.9 (21.2, 48.5)***	46.9 (34.0, 59.8)***
	31 (14.1)	109 (48.5)	147 (63.3)	34.4 (26.7, 42.1)***	49.0 (41.4, 56.7)***
	21 (18.3)[j]	59 (61.2)[j]	85 (71.2)[k]	42.2 (30.4, 53.9)***	51.7 (41.4, 62.2)***
	14 (6.1)	56 (24.9)	66 (28.3)	18.6 (12.2, 25.0)***	21.9 (15.4, 28.5)***
	27 (12.3)	91 (40.5)	131 (56.0)	28.5 (21.1, 35.9)***	43.8 (36.1, 51.5)***
	11 (5.1)	42 (18.8)	53 (22.6)	13.5 (7.8, 19.3)***	17.2 (11.2, 23.3)***

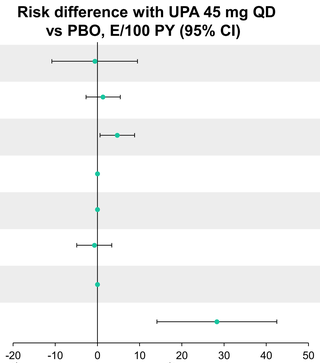


bio-IR, biologic-inadequate response; CI, confidence interval; ES, endoscopic subscore; HEMI, histologic–endoscopic mucosal improvement; NA, not applicable; PBO, placebo; QD, once daily; UPA, upadacitinib.
***P <.001. Results are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19. The point estimate and 95% CI for treatment difference are based on Cochran–Mantel–Haenszel tests adjusted for strata (induction: stratified by corticosteroid use at baseline [yes vs no]. Adapted Mayo score at baseline [≤7 vs >7], and bio-IR status [bio-IR vs non-bio-IR]; maintenance: stratified by bio-IR status [bio-IR vs non-bio-IR], corticosteroid use at week 0 of maintenance [yes vs no]). [a]Defined as all patients who achieved a clinical response after 8 weeks' induction treatment (UPA 45 mg QD) and were re-randomized to UPA 15 or 30 mg QD, or PBO, for 52 weeks. [b]Adapted Mayo score ≤2, stool frequency subscore ≤1 and not greater than baseline, rectal bleeding subscore = 0, and ES ≤1 without friability. [c]Among patients with clinical remission at the end of the induction therapy. [d]n = 85. [e]n = 76. [f]n = 87. [g]ES ≤1. [h]Among patients with endoscopic improvement at the end of the induction therapy. [i]n = 116. [j]n = 97. [k]n = 119. ES = 0. [m]ES ≤1 without friability and Geboes score ≤3.1. [n]ES = 0 and Geboes score <2.

Figure 2. PBO-Adjusted Risk Difference of Selected AESIs With UPA vs PBO at the End of Induction (A) and Maintenance[a] (B)

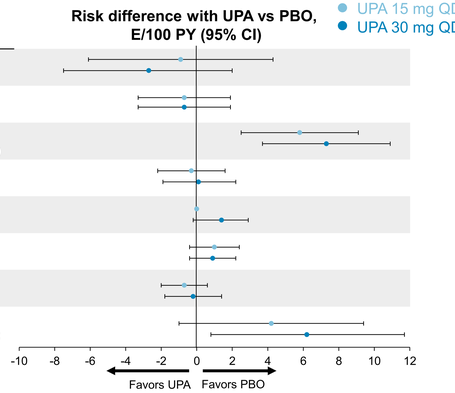
(A)

	PBO, n (%) [E/100 PY] n = 378 56 PY	UPA 45 mg QD, n (%) [E/100 PY] n = 719 110 PY	UPA 45 mg QD vs PBO, E/100 PY (95% CI)
Serious infection	5 (1.3) [10.1]	9 (1.3) [9.5]	-0.6 (-10.8, 9.5)
Opportunistic infection (excl. herpes zoster and tuberculosis)	1 (0.3) [1.3]	3 (0.4) [2.7]	1.3 (-2.7, 5.4)
Herpes zoster	0	4 (0.6) [4.7]	4.7 (0.6, 8.8)
Malignancy (excluding NMSC)	0	0	0
NMSC	0	0	0
Adjudicated VTE[b]	1 (0.3) [1.8]	1 (0.1) [1.1]	-0.7 (-4.9, 3.4)
Adjudicated MACE	0	0	0
CPK elevation	5 (1.3) [9.4]	37 (5.1) [37.7]	28.3 (14.1, 42.5)



(B)

	PBO, n (%) [E/100 PY] n = 245 135 PY	UPA 15 mg QD, n (%) [E/100 PY] n = 250 199 PY	UPA 30 mg QD, n (%) [E/100 PY] n = 251 219 PY	UPA 15 mg QD vs PBO, E/100 PY (95% CI)	UPA 30 mg QD vs PBO, E/100 PY (95% CI)
	8 (3.3) [5.9]	9 (3.6) [5.0]	7 (2.8) [3.2]	-0.9 (-6.1, 4.3)	-2.7 (-7.5, 2.0)
	2 (0.8) [1.6]	2 (0.8) [0.9]	2 (0.8) [0.9]	-0.7 (-3.3, 1.9)	-0.7 (-3.3, 1.9)
	0	12 (4.8) [5.8]	14 (5.6) [7.3]	5.8 (2.5, 9.1)	7.3 (3.7, 10.9)
	1 (0.4) [0.8]	1 (0.4) [0.5]	2 (0.8) [0.9]	-0.3 (-2.2, 1.6)	0.1 (-1.9, 2.2)
	0	0	3 (1.2) [1.4]	0	1.4 (-0.2, 2.9)
	0	2 (0.8) [1.0]	2 (0.8) [0.9]	1.0 (-0.4, 2.4)	0.9 (-0.4, 2.2)
	1 (0.4) 0.7	0	1 (0.4) [0.5]	-0.7 (-2.0, 0.6)	-0.2 (-1.8, 1.4)
	5 (2.0) [3.9]	15 (6.0) [8.1]	19 (7.6) [10.1]	4.2 (-1.0, 9.4)	6.2 (0.8, 11.7)



AESI, adverse event of special interest; CI, confidence interval; CPK, creatine phosphokinase; E, event; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; PY, patient-years; QD, once daily; UPA, upadacitinib; VTE, venous thromboembolism.
All UPA-treated patients who experienced a VTE or MACE had ≥1 known risk factor (scan QR code for further information). [a]The safety population included all patients who received ≥1 dose of study therapy (intent-to-treat population plus patients who received up to 44 weeks' maintenance therapy under earlier versions of protocol amendments). [b]The placebo event occurred in the Phase 3 study and the UPA 45 mg QD event in a Phase 2b induction study.