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Background: Upadacitinib (UPA) is a selective and reversible Janus kinase inhibitor.U-ACCOMPLISH is one of two phase 3 induction trials that evaluated the safety and efficacy of UPA 45 mg once daily (QD) in adults with ulcerative colitis (UC).

Methods: U-ACCOMPLISH was a multicentre, randomized, double-blind, placebo-controlled trial (NCT03653026) that enrolled patients with moderate-to-severe UC (defined as adapted Mayo score 5–9 with centrally read endoscopic score 2–3) who had inadequate response, loss of response, or intolerance to aminosalicylates, immunosuppressants, corticosteroids and/or biologics. Patients were randomized 2:1 to UPA 45 mg QD or placebo (PBO) for 8 weeks. At week 8, responders entered the maintenance phase and non-responders entered the extended treatment period to receive open-label UPA 45 mg QD for additional 8 weeks.The primary endpoint (clinical remission per adapted Mayo Score) and ranked secondary endpoints including symptomatic, endoscopic– histologic evaluations from the 8-week PBO-controlled period are reported here. Non-responder imputation incorporating multiple imputation for missing data due to COVID-19 are reported.

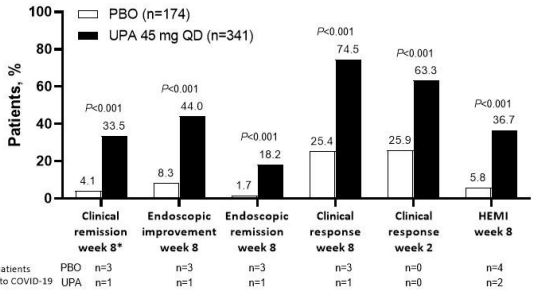
Results: 522 patients were randomized (UPA, n=345; PBO, n=177); the intent-to-treat population included 341 patients in UPA and 174 patients in PBO group. Baseline demographics and disease characteristics were similar between groups; 50.7% and 51.1% were biologic inadequate responders in UPA and PBO groups, respectively (Table 1). A significantly higher proportion of patients receiving UPA 45 mg QD (33.5%) versus PBO (4.1%) achieved the primary endpoint (adjusted treatment difference: 29.0% [23.2, 34.7]; $P<0.001$). A significantly higher proportion of patients receiving UPA versus PBO also achieved all ranked secondary endpoints (all $P<0.001$; Figure 1).Serious adverse events were reported by 3.2% and 4.5% of patients in UPA and PBO groups, respectively (Table 2). Similar rates of serious infection were observed in both groups (0.6%); 2 events each of herpes zoster and opportunistic infection were reported in UPA group. No active tuberculosis, malignancy, adjudicated major adverse cardiovascular events, or deaths were reported in the study. One patient with venous thromboembolism (deep vein thrombosis and pulmonary embolism) and 1 patient with gastrointestinal perforation were reported in the placebo group.

Table 1. Baseline Demographics and Characteristics

Variable	PBO (n=174)*	UPA 45 mg QD (n=341)*
Female, n (%)	67 (38.5)	127 (37.2)
Race, white, n (%)	124 (71.3)	234 (68.6)
Age, median (range), y	42.0 (17, 75)	40.0 (17, 74)
Disease duration, mean (SD), y	7.4 (7.2)	7.3 (6.4)
Weight, mean (SD), kg	73.7 (20.1)	74.0 (18.6)
Faecal calprotectin, median (range), mg/kg	1552.5 (84, 28,800)	1654.5 (46, 28,800)
hsCRP, median (range), mg/L	4.7 (0.2, 166)	3.8 (0.2, 107)
Baseline aminosalicylates use, n (%)	120 (69.0)	233 (68.3)
Baseline corticosteroid use†, n (%)	72 (41.4)	118 (34.6)
Baseline Biologic-IR Status,† n (%)	89 (51.1)	173 (50.7)
Baseline Adapted Mayo Score,† n (%)		
≤7	103 (59.2)	205 (60.3)
>7	71 (40.8)	135 (39.7)
Endoscopic subscore, mean (SD)	2.7 (0.5)	2.7 (0.5)

*ITT population: 3 patients each in the PBO and UPA 45 mg QD groups were excluded from the efficacy analysis because of significant site non-compliance; these patients were included in the safety analysis. †Stratification factors for randomization. hsCRP, high-sensitivity C reactive protein; IR, inadequate responder; ITT, intent-to-treat; PBO, placebo; QD, once daily; UPA, upadacitinib.

Figure 1. Primary and ranked secondary endpoints.



HEMI, Histologic Endoscopic Mucosal Improvement; IR, inadequate responder; PBO, placebo; QD, once daily; UPA, upadacitinib.

*Primary endpoint per adapted Mayo score, defined as stool frequency subscore ≤1 and not greater than baseline, rectal bleeding subscore of 0, and Mayo endoscopic subscore ≤1 at week 8. Evidence of friability during endoscopy in patients with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2.

Endoscopic improvement defined as Mayo endoscopic subscore ≤1.

Endoscopic remission defined as Mayo endoscopic subscore 0.

Clinical response at week 8 based on adapted Mayo score (defined as decrease in adapted Mayo score ≥2 points and ≥30% from baseline and a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding scroe ≤1).

Clinical response at week 2 based on partial adapted Mayo score (defined as decrease in adapted Mayo score ≥1 points and ≥30% from baseline and a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding scroe ≤1).

HEMI defined as endoscopic subscore of 0 or 1 and Geboes score ≤3.1; more patients had missing data because of COVID related travel restrictions that prevented biopsy.

The randomization was stratified by biologic-IR status (biologic-IR vs non-biologic-IR), corticosteroid use (yes or no) and adapted Mayo score (≤7 or > 7) at baseline.

Table 2. Treatment-emergent adverse events throughout 8 weeks

AEs, n (%)	Placebo (n=177)	UPA 45 mg QD (n=344)
Any AE	70 (39.5)	182 (52.9)
AE possibly related to study drug	12 (6.8)	81 (23.5)
Severe AE	7 (4.0)	9 (2.6)
Serious AE	8 (4.5)	11 (3.2)
AE leading to discontinuation of study drug	9 (5.1)	6 (1.7)
AEs reported by ≥4% of patients in any treatment group		
Acne	3 (1.7)	24 (7.0)
Blood creatine phosphokinase increased	2 (1.1)	16 (4.7)
Anaemia	4 (2.3)	14 (4.1)
Headache	9 (5.1)	8 (2.3)
Ulcerative colitis	8 (4.5)	6 (1.7)
AEs of special interest		
Creatine phosphokinase elevation*	2 (1.1)	16 (4.7)
Anaemia†	4 (2.3)	15 (4.4)
Neutropenia*	0	15 (4.4)
Hepatic disorder*	1 (0.6)	10 (2.9)
Lymphopenia‡	1 (0.6)	6 (1.7)
Serious infection	1 (0.6)	2 (0.6)
Opportunistic infection excluding TB or HZ	0	2 (0.6)
HZ	0	2 (0.6)
Adjudicated gastrointestinal perforation	1 (0.6)	0
Adjudicated venous thromboembolic event§	1 (0.6)	0

AE, adverse event, AESI, AE of special interest, CMQ, Customized MedDRA Query; HZ, herpes zoster; TB, tuberculosis; PT, preferred term. *None of the hepatic disorder events were serious or led to study drug discontinuation. †One serious event each in the UPA and PBO groups; anaemia of AESI is based on CMQ search, which includes other PTs in addition to PT of "anaemia." ‡One moderate, nonserious event led to treatment discontinuation. §Venous thromboembolic events included deep vein thrombosis and pulmonary embolism.

Conclusion: In U-ACCOMPLISH, 8-week UPA 45 mg QD induction treatment led to statistically significant improvements in clinical, endoscopic, and combined endoscopic-histologic endpoints. The treatment was well tolerated, and the safety profile and AE prevalence was comparable with previous studies of UPA with no new safety signals identified.

OP24

Efficacy and safety of upadacitinib induction therapy in patients with Moderately to Severely Active Ulcerative Colitis: Results from the phase 3 U-ACHIEVE study

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Background: An unmet therapeutic need remains in patients with ulcerative colitis (UC). U-ACHIEVE is one of two phase 3 induction trials evaluating the safety and efficacy of the selective Janus kinase–1 inhibitor upadacitinib (UPA) 45 mg once daily (QD) in adults with UC.

Methods: U-ACHIEVE is a multicentre, double-blind, placebo (PBO)–controlled trial (NCT02819635) that randomized patients with moderately to severely active UC 2:1 to UPA 45 mg QD or PBO for 8 weeks. Patients were stratified by response to biologic therapy (inadequate vs non–inadequate responder), baseline corticosteroid use (yes or no), and baseline adapted Mayo score (≤7 or >7). The primary endpoint was proportion of patients achieving clinical remission (per adapted Mayo Score) at week 8.Ranked secondary endpoints included endoscopic improvement, endoscopic remission, and clinical response per adapted Mayo Score at week 8; clinical response per partial adapted Mayo Score at week 2; and histologic-endoscopic mucosal improvement at week 8. Non-responder imputation incorporating multiple imputations for missing data due to COVID-19 are reported. Safety was assessed through week 8.

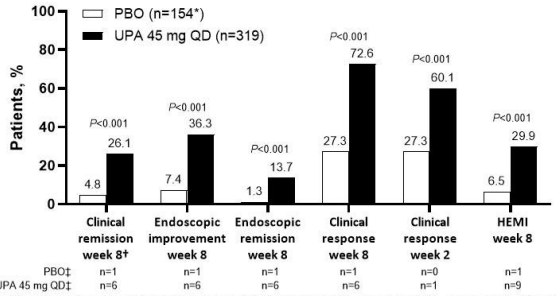
Results: 474 patients were randomized (UPA, n=319; PBO, n=155). Baseline characteristics were well balanced between groups (Table 1). A significantly higher proportion of patients receiving UPA (26.1%) vs PBO (4.8%) achieved clinical remission at week 8 (adjusted treatment difference [95% CI], 21.6% [15.8, 27.4]; *P*<0.001; Figure 1). For all ranked secondary endpoints, UPA was superior to PBO (*P*<0.001; Figure 1). A significant difference in clinical response favouring UPA vs PBO was seen as early as week 2 (60.1% vs 27.3%) and was sustained over 8 weeks (79.0% vs 41.6%; Figure 2). There were more serious adverse events (AEs), severe AEs, and AEs leading to study drug discontinuation with PBO (Table 2). The most common AEs were acne, creatine phosphokinase elevation, and nasopharyngitis with UPA and worsening of UC and anaemia with PBO. Incidence of serious infection was similar between UPA and PBO. Neutropenia and lymphopenia were reported more frequently with UPA vs PBO (Table 2).No adjudicated gastrointestinal perforation, major cardiovascular AEs, or thrombotic events and no active tuberculosis, malignancy, or deaths were reported.

Table 1. Baseline Demographics and Characteristics

Variable	PBO (n=154)*	UPA 45 mg QD (n=319)
Female, n (%)	57 (37.0)	121 (37.9)
Race, white, n (%)	100 (64.9)	206 (64.6)
Age, median (range), y	44.5 (18, 76)	43.0 (19, 76)
Disease duration, mean (SD), y	9.1 (8.8)	8.6 (7.2)
Weight, mean (SD), kg	74.0 (19.2)	71.3 (17.4)
Faecal calprotectin, median (range), mg/kg	1902 (30, 28,800)	1780 (30, 28,800)
hsCRP, median (range), mg/L	4.7 (0.2, 179)	4.1 (0.2, 105)
Baseline aminosalicylates use, n (%)	102 (66.2)	220 (69.0)
Baseline corticosteroid use†, n (%)	61 (39.6)	124 (38.9)
Baseline biologic-IR Status†		
Biologic-IR, n (%)	78 (50.6)	168 (52.7)
Non–biologic-IR, n (%)	76 (49.4)	151 (47.3)
Baseline adapted Mayo score,† n (%)		
≤7	94 (61.0)	195 (61.3)
>7	60 (39.0)	123 (38.7)

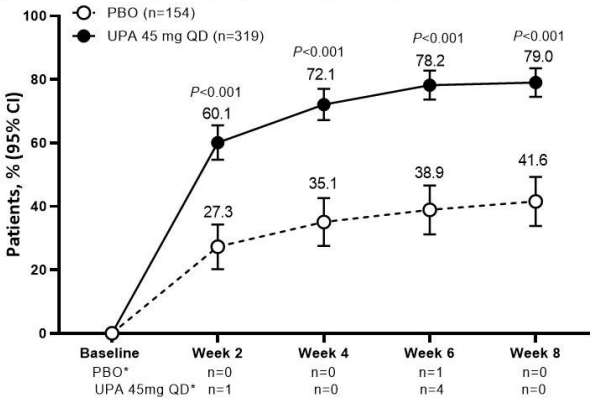
hsCRP, high-sensitivity C reactive protein; IR, inadequate responder; PBO, placebo; QD, once daily; UPA, upadacitinib.
*One PBO patient was excluded from efficacy analyses because of site non-compliance
†Stratification factors for randomization.

Figure 1. Primary and ranked secondary endpoints



HEMI, histologic endoscopic mucosal improvement; PBO, placebo; QD, once daily; UPA, upadacitinib. *One PBO patient was excluded from efficacy analyses because of site non-compliance. †Primary endpoint per adapted Mayo score, defined as stool frequency subscore ≤1 and not greater than baseline, rectal bleeding subscore of 0, and Mayo endoscopic subscore ≤1 at week 8. Evidence of friability during endoscopy in patients with otherwise "mild" endoscopic activity will confer an endoscopic subscore of 2. ‡Missing because of COVID-19. Endoscopic improvement defined as Mayo endoscopic subscore ≤1. Endoscopic remission defined as Mayo endoscopic subscore 0. Clinical response at week 8 based on adapted Mayo score (defined as decrease in adapted Mayo score ≥2 points and ≥30% from baseline and a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding score ≤1). Clinical response at week 2 based on partial adapted Mayo score (defined as decrease in adapted Mayo score ≥1 points and ≥30% from baseline and a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding score ≤1). HEMI defined as endoscopic subscore of 0 or 1 and Geboes score ≤3.1.

Figure 2. Clinical response per partial adapted Mayo score



PBO, placebo; QD, once daily; UPA, upadacitinib. *Missing because of COVID-19

Table 2. Treatment-emergent adverse events throughout 8 weeks

AEs, n (%)	Placebo (n=155)	UPA 45 mg QD (n=319)
Any AE	93 (60.0)	180 (56.4)
AE possibly related to study drug	36 (23.2)	87 (27.3)
Severe AE	14 (9.0)	9 (2.8)
Serious AE	9 (5.8)	8 (2.5)
Serious AE possibly related to study drug*	3 (1.9)	4 (1.3)
AE leading to discontinuation of study drug	14 (9.0)	6 (1.9)
Death	0	0
AEs reported by ≥4% of patients in any treatment group		
Acne	1 (0.6)	15 (4.7)
Blood creatine phosphokinase increased	3 (1.9)	15 (4.7)
Nasopharyngitis	6 (3.9)	15 (4.7)
Headache	4 (2.6)	13 (4.1)
Anaemia	9 (5.8)	7 (2.2)
Colitis ulcerative	21 (13.5)	3 (0.9)
AEs of special interest		
Serious infection	2 (1.3)	5 (1.6)
Hepatic disorder*	6 (3.9)	9 (2.8)
Anaemia†	14 (9.0)	9 (2.8)
Neutropenia‡	1 (0.6)	16 (5.0)
Lymphopenia‡	1 (0.6)	10 (3.1)
Creatine phosphokinase elevation‡	3 (1.9)	15 (4.7)
Opportunistic infection (excluding TB and herpes zoster)	0	1 (0.3)
Herpes zoster	0	1 (0.3)

AE, adverse event, AESI, AE of special interest, CMQ, Customized MedDRA Query; PT, preferred term; TB, tuberculosis.*Most events were reported as transaminase increase; none of the hepatic disorder events were serious or led to study drug discontinuation. †Anaemia of AESI is based on CMQ search, which includes other PTs in addition to PT of "anaemia." ‡None of the neutropenia, lymphopenia and creatine phosphokinase elevation events were serious or led to study drug discontinuation.

Conclusion: In patients with moderately to severely active UC, UPA 45 mg QD induction therapy was superior to PBO in inducing clinical remission/response, and endoscopic remission/response over 8 weeks; responses were significant and rapid. UPA 45 mg QD was well tolerated; safety was comparable with the known safety profile of UPA, and no new safety signals were identified.

OP25

Efficacy of filgotinib in patients with Ulcerative Colitis by line of therapy in the phase ²b/3 SELECTION trial

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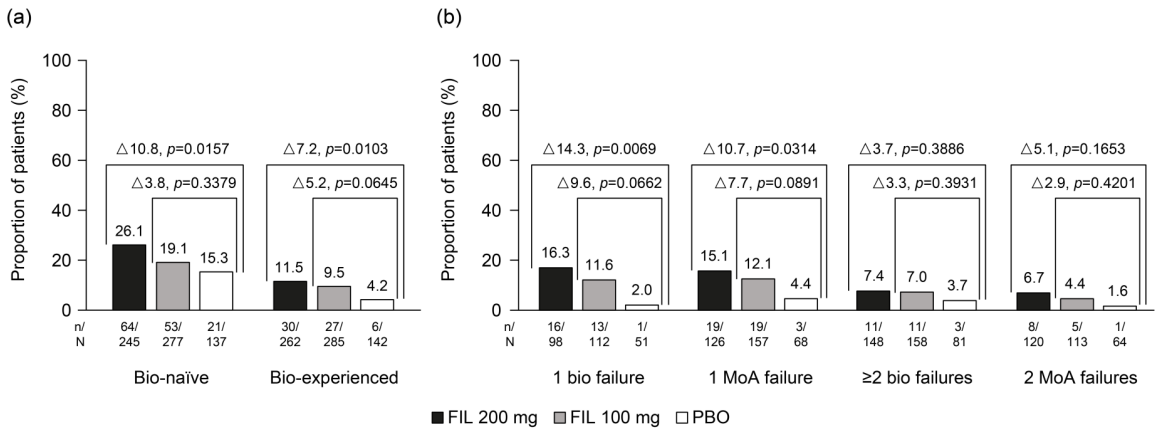
Background: Patients with ulcerative colitis (UC) often do not respond to treatment or lose response over time, and thus switch between therapies with various mechanisms of action (MoAs).[1] Filgotinib (FIL) is a once-daily, oral, Janus kinase 1 preferential inhibitor in development as a UC treatment. We assessed the efficacy of FIL in biologic (bio)-naïve and bio-experienced patients with UC, and in bio-experienced patients with failure of 1 or ≥2 biologics or 1 or 2 MoAs.

Methods: SELECTION (NCT02914522) was a phase ²b/3 double-blind, randomised, placebo-controlled trial comprising two induction studies and a maintenance study. Adults (18–75 years) with moderately to severely active UC were randomised 2:2:1 to FIL 200 mg, FIL 100 mg or placebo (PBO) once daily for 11 weeks in Induction Study A (bio-naïve) and B (bio-experienced). Patients in either clinical remission or Mayo Clinic Score (MCS) response at week 10 (responders) could enter the Maintenance Study. Responders who received induction FIL were re-randomised 2:1 to continue their induction regimen or PBO through week 58. Responders who received induction PBO continued PBO. We assessed clinical remission and MCS response at weeks 10 and 58 in bio-naïve patients and bio-experienced patients with failure of 1 or ≥2 biologics and 1 or 2 MoAs (TNF antagonists and vedolizumab). All *p* values for subgroup analyses are nominal.

Results: At week 10, clinical remission was achieved by a significantly higher proportion of bio-naïve and -experienced patients treated with FIL 200 mg than PBO (Figure [1]a). A higher proportion of bio-experienced patients with 1 biologic or MoA failure treated with FIL 200 mg than PBO achieved clinical remission at week 10 ($p<0.05$); a smaller treatment effect was seen in patients with ≥2 biologic or 2 MoA failures (Figure [1]b). None of these comparisons reached $p<0.05$

Figure 1. Proportions of (a) bio-naïve and bio-experienced patients, and (b) bio-experienced patients with failure of 1 or ≥2 biologics and 1 or 2 MoAs, who achieved clinical remission at week 10.



Clinical remission is defined as a Mayo endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1-point decrease in stool frequency subscore from induction baseline to achieve a subscore of 0 or 1.

Patients may be included in both the biologic failure and MoA failure subgroups.

p values in (a) were determined using the Cochran–Mantel–Haenszel test; *p* values in (b) were determined using Fisher's Exact test.

Bio, biologic; FIL, filgotinib; MoA, mechanism of action; PBO, placebo.