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Efficacy of Upadacitinib Dose Escalation in a Phase 3 Long-Term Extension Ulcerative Colitis Study

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OBJECTIVE

This presentation reports an evaluation of the efficacy of dose escalation to upadacitinib (UPA) 30 mg once daily (QD), in patients who failed to respond to, or experienced an inadequate response to, UPA 15 mg QD, from the UPA clinical trials program who entered the Phase 3, open-label, Long-Term Extension (LTE) U-ACTIVATE study

CONCLUSIONS

In the LTE U-ACTIVATE study, dose escalation to UPA 30 mg QD improved key clinical and endoscopic efficacy outcomes in patients with an inadequate response or loss of response to UPA 15 mg QD

Although both UPA doses demonstrated superior efficacy to placebo in U-ACHIEVE Maintenance,[1] the findings of U-ACTIVATE suggest that dose escalation to UPA 30 mg QD may be beneficial in patients who do not achieve or maintain therapeutic benefits with UPA 15 mg QD

The availability of 2 UPA doses that have demonstrated efficacy as maintenance therapy for ulcerative colitis allows clinicians the flexibility to tailor treatment to patients' individual needs by escalating UPA dose from 15 mg QD to 30 mg QD when needed

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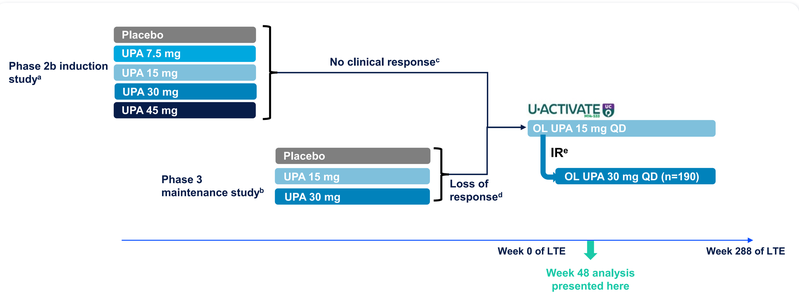
BACKGROUND

- UPA, an oral, selective, Janus kinase (JAK) inhibitor, has recently gained approval in Europe for the treatment of moderate to severe UC[2]
  - The approval of UPA was based on the demonstration of significant clinical efficacy and an acceptable safety profile in a clinical trials program comprising 2 induction trials (the Phase 2b/3 U-ACHIEVE [NCT02819635] and Phase 3 U-ACCOMPLISH [NCT03653026] trials), and a Phase 3 maintenance trial (U-ACHIEVE Maintenance [NCT02819635])[1]
- Given the loss of response in some patients receiving advanced therapies for UC,[3] optimal disease management requires multiple therapeutic and dosing options

METHODS

U-ACTIVATE Eligibility



OL, open-label; RBS, rectal bleeding subscore; SFS, stool frequency subscore.
[a]n = 3 patients entered from the Phase 3 induction studies owing to missing endoscopic data at week 8/16; [b]Patients were also eligible to enter U-Activate from the Phase 3 maintenance study if they received 44 weeks' treatment only or had no week 52 endoscopic data owing to COVID-19; [c]Decrease from baseline in the Adapted Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1; [d]Loss of response is defined as an SFS and RBS score each ≥1 point greater than end of induction on 2 consecutive visits ≥14 days apart, or either an SFS or RBS ≥1 point greater than end of induction value on 2 consecutive visits ≥14 days apart, associated with the presence of signs or symptoms of UC progression; [e]IR is defined as an SFS + RBS value that remains unchanged or has increased on 2 consecutive visits ≥7 days apart, SFS and RBS ≥1 point greater than the week 0 value on 2 consecutive visits ≥7 days apart, or for patients with SFS or RBS ≥2.1 at week 0, an increase in SFS or RBS of ≥1 point greater than the week 0 value on 2 consecutive visits ≥7 days apart and presence of signs/symptoms of UC progression.

Efficacy Endpoints and Statistical Methods

Efficacy Endpoints Evaluated at Week 48

Endpoint	Definition
Clinical remission per Adapted Mayo score	SFS ≤1 and not greater than induction baseline, RBS = 0, and ES ≤1 with no friability
CS-free clinical remission	Clinical remission per Adapted Mayo score without use of CS
Clinical remission per Adapted Mayo score at week 48 and CS-free clinical remission for ≥90 days prior to week 48	Clinical remission per Adapted Mayo score at week 48 and without CS use for ≥90 days prior to week 48
Endoscopic improvement	ES ≤1 with no friability
Endoscopic remission	ES = 0

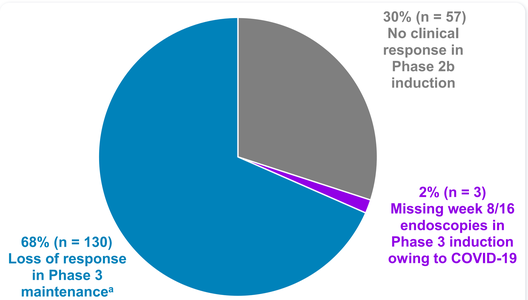
CI, confidence interval; CS, corticosteroid; ES, endoscopic subscore; ITT, intention to treat; NRI, non-responder imputation.

Statistical methods

- Efficacy was analyzed in a subset of the ITT population: all subjects who received at least 1 dose of UPA in the LTE study, had the potential to complete week 48, and had their dose escalated to UPA 30 mg QD prior to week 48
- Results were based on NRI with 95% CIs calculated by normal approximation to binomial distribution

RESULTS

Patients Disposition and Exposure (N = 190)



- Most patients in U-ACTIVATE had prematurely discontinued from U-ACHIEVE Maintenance
- At the time of dose escalation, patients had been receiving UPA 15 mg QD for a median of 70 days
- At week 48, patients had received UPA 30 mg QD for a median of 468 days since dose escalation

[a]Includes patients who received 44 weeks' treatment only or had no week 52 endoscopic data owing to COVID-19.

Baseline Demographics and Clinical Characteristics

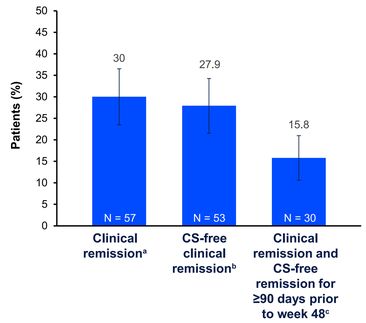
Characteristic	N = 190
Female sex, n (%)	67 (35.3)
Age, years	41.3 (13.6)
Weight, kg	75.2 (19.6)
Disease extent, n (%)	
Left-sided	87 (45.8)
Extensive/pancolitis	103 (54.2)
Disease duration, years	7.4 (6.7)
Baseline Full Mayo Score, n (%)	
≤9	84 (44.2)
>9	106 (55.8)
Presence of ≥1 EIM, n (%)	46 (24.2)
FCP, mg/kg	3018.0 (3884.6)
hs-CRP, mg/L	11.1 (16.5)

Characteristic	N = 190
Aminosalicylate use, n (%)	98 (51.6)
CS use, n (%)	113 (59.5)
Prior TNF inhibitor exposure, n (%)	139 (73.2)
Bio-IR status, n (%)	
Bio-IR	139 (73.2)
Non-bio-IR	51 (26.8)
Number of prior biologic treatments, n (%)	
≤1	27 (19.4)
>1	112 (80.6)

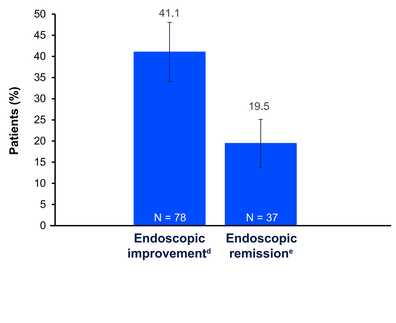
EIM, extraintestinal manifestation; FCP, fecal calprotectin; hs-CRP, high sensitivity C-reactive protein; TNF, tumor necrosis factorData are mean (SD) unless otherwise specified.
[a]A small number of patients entered from this study due to missing endoscopic data at week 8/16 due to COVID-19.

Dose Escalation to UPA 30 mg QD Improved Clinical and Endoscopic Outcomes in Patients With an IR to UPA 15 mg QD at Week 48

Clinical Outcomes at Week 48 (N = 190)



Endoscopic Outcomes at Week 48 (N = 190)



CS, corticosteroids.
[a]Clinical remission per Adapted Mayo score: SFS ≤1 and not greater than induction baseline, RBS = 0, and ES ≤1 with no friability; [b]Clinical remission per Adapted Mayo score without use of CS; [c]Clinical remission per Adapted Mayo score at week 48 without use of CS for ≥90 days prior to week 48; [d]ES ≤1 with no friability; [e]ES = 0.