D0380

Impact of Inflammatory Burden on Efficacy of Upadacitinib Maintenance Therapy in Ulcerative Colitis: Results From the Phase 3 U-ACHIEVE Study

Brian G. Feagan,[1] Jean-Frederic Colombel,[2] Joana Torres,[3,4] Toshimitsu Fujii,[5] Wen Zhou,[6] Xuan Yao,[6] Yuri Sanchez Gonzalez,[6] Dapo Ilo,[6] Xavier Roblin[7]

[1]Robarts Research Institute, University of Western Ontario, London, ON, Canada; [2]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]Division of Gastroenterology, Surgical Department, Hospital Beatriz Angelo, Loures, Portugal; [4]Division of Gastroenterology, Hospital da Luz, Lisbon, Portugal; [5]Departments of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Tokyo, Japan; [6]AbbVie Inc., North Chicago, IL, USA; [7]University of Lyon, Saint-Etienne, France

OBJECTIVE

To investigate whether the extent of inflammatory burden in patients with moderately to severely active ulcerative colitis (UC) affects the efficacy of maintenance doses of upadacitinib (UPA)

CONCLUSIONS

Regardless of inflammatory burden, both UPA maintenance doses were efficacious in the achievement of clinical remission and endoscopic improvement compared with placebo

There were greater differences in all efficacy endpoints between UPA 30 mg and UPA 15 mg in patients with high inflammatory burden vs patients without, except for endoscopic improvement in patients with pancolitis

Patients with a high inflammatory burden from UC may have a greater benefit from UPA 30 mg than UPA 15 mg, compared with patients without high inflammatory burden

AbbVie and the authors thank the participants, study sites, and investigators who participated in this clinical trial.

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Laura Chalmers, PhD, of 2 the Nth (Cheshire, UK) and was funded by AbbVie.

B.G. Feagan has received grants/research support from, consulted for, been a member of the speakers bureau for, and/or has been a member of the scientific advisory board for Abbott, AbbVie, AdMIRx, Akebia, Allergan, Amgen, Applied Molecular Transport, Aptevo, Asta, Atlantic, Avaxia, Avir, AZ, AZ/MedImmune, BI, Biogen Idec, BioMx Israel, BMS, Boston, Calypso, Celgene, Celltech, Centocor, Elan/Biogen, EnGene, Ferring, Galapagos, Galen/Atlantica, Genentech/Hoffmann-La Roche, GlCare, Gilead, Gossamer, GSK, Inception IBD, Intact, J&J/Janssen, Janssen, Kyowa Kakko Kirin, Lexicon, Lilly, Lycera, Merck, Mesoblast, Millennium, Nestlé, Nextbiotix, Novartis, Novo Nordisk, Parlmmune, Parvus, Pfizer, Progenity, Prometheus, Protagonist, Qu Biologics, Rebiotix, Receptos, Receptos/Celgene, Roche/Genentech, Salix, Sanofi, Santarus, Shire, Sienna, Sigmoid, Sterna, Synergy, Takeda, Teva, TiGenix, Tillotts, UCB, Vertex, VHsquared, Vivelix, and Zyngenia; and has been a Senior Scientific Officer for Robarts Clinical Trials. J.-F. Colombel has received personal fees/grant support from and/or holds stock options in AbbVie, Amgen, BI, Celgene, Celltrion, Enterome, Genentech, Genfit, Intestinal Biotech Development, J&J/Janssen, MedImmune, Merck, Pfizer, PPM Services, Protagonist, Second Genome, Seres, Shire, Takeda, and Theradiag. J. Torres has received grant funding/speaker fees from and/or has participated in advisory boards for AbbVie, Galapagos, Janssen, and Pfizer. T. Fujii has received grants/research support from and/or has been a member of the speakers bureau for AbbVie, Ajinomoto, Alfresa, BI, BMS, Celgene, Daiichi Sankyo, EA Pharma, Eisai, Gilead, Janssen, Kissei, Kyorin, Kyowa Hakko Kirin, Lilly, Mebix, Mitsubishi-Tanabe, Mochida, Nichiko, Nippon Kayaku, Taiho, Takeda, and Zeria. W. Zhou, X. Yao, Y. Sanchez Gonzalez, and D. Ilo are employees of AbbVie and may own stock and/or options. X. Roblin has received grants/research support from AbbVie, Celltrion, Galapagos, Janssen, MSD, and Takeda.

References

1. Panaccione R, et al. Presented at UEGW 2019.Abstract OP169.
2. Danese S, et al. *Lancet*. 2022;399:2113–28.

Presented at the American College of Gastroenterology (ACG 2022), October 21–26, 2022, Charlotte, NC, USA; Hybrid Meeting

INTRODUCTION

- Patients with severe disease, pancolitis, and/or extraintestinal manifestation(s) may be considered by physicians to have a high inflammatory burden
  - Evidence suggests that patients with UC who have a high inflammatory burden may respond differently to certain maintenance regimens compared with patients with a lower burden[1]
- UPA, an oral selective and reversible Janus kinase inhibitor, has demonstrated superior efficacy to placebo (PBO) and a well-characterized safety profile in patients with moderately to severely active UC in a Phase 3 program, including 2 induction trials (U-ACHIEVE Induction and U-ACCOMPLISH) and a maintenance trial (U-ACHIEVE Maintenance) in which 2 maintenance doses of UPA (30 mg and 15 mg once daily [QD]) were evaluated[2]
- There is limited evidence of the impact of inflammatory burden on the efficacy of the 2 evaluated UPA maintenance doses

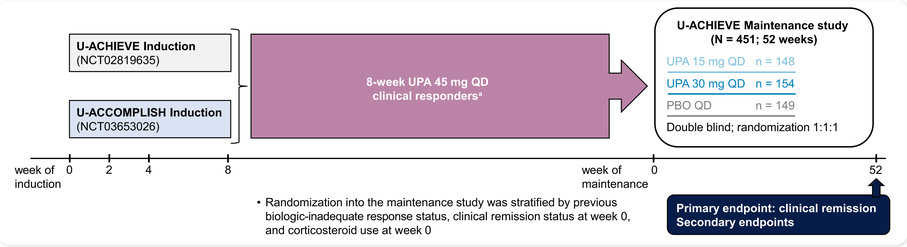
METHODS

- Patients who achieved clinical response following 8-week UPA 45 mg QD induction treatment in U-ACHIEVE Induction and U-ACCOMPLISH were re-randomized 1:1:1 to UPA 15 mg QD, UPA 30 mg QD, or PBO in U-ACHIEVE Maintenance for up to 52 weeks **(Figure 1)**

Assessments

- An extensive post hoc analysis of baseline characteristics, including (but not limited to) albumin levels, age at diagnosis, smoking status, and end of induction status, of the primary analysis population from U-ACHIEVE Maintenance[2] was performed to evaluate factors that impact achievement of treatment targets with UPA 30 mg vs UPA 15 mg
- Efficacy data for each dose were evaluated by the 3 measures of inflammatory burden identified as significant: baseline Full Mayo score >9 vs ≤9, presence of pancolitis at baseline (yes vs no), and presence of ≥1 extraintestinal manifestation at baseline (yes vs no)
- Outcomes included the proportion of patients achieving clinical remission at week 52 per Adapted Mayo score (primary endpoint; defined in **Figure 2**) and endoscopic improvement at week 52 (key secondary endpoint; defined in **Figure 3**)
- Data presented are descriptive, with no significance testing performed for differences between UPA 30 mg and UPA 15 mg

Figure 1. Study Design[1]



PBO, placebo; QD, once daily; RBS, rectal bleeding subscore; UPA, upadacitinib.
[a]Clinical responders were defined as patients who achieved clinical response per Adapted Mayo score (a decrease in Adapted Mayo score of ≥2 points and ≥30% from baseline, and a decrease in the RBS of ≥1 point or an absolute RBS of ≤1) at the end of the 8-week induction period.

RESULTS

Patient Population

- Overall, 451 patients (PBO: n = 149, UPA 15 mg: n = 148, and UPA 30 mg: n = 154) were analyzed
- Baseline demographics and clinical characteristics of patients in the U-ACHIEVE Maintenance study were generally similar across treatment groups **(Table 1)**

Table 1. Demographics and Clinical Characteristics at Baseline

Variable	PBO (n = 149)	UPA 15 mg QD (n = 148)	UPA 30 mg QD (n = 154)
Female	64 (43)	53 (36)	68 (44)
Age, years, median (range)	40 (17–75)	40 (21–75)	41 (17–76)
Disease duration, years, mean (SD)	9 (8)	9 (8)	8 (8)
Weight, kg, mean (SD)	72 (18)	74 (21)	73 (21)
Disease extent			
Left-sided	79 (53)	66 (45)	68 (44)
Extensive/pancolitis	70 (47)	82 (55)	86 (56)
Baseline Full Mayo score			
≤9	74 (50)	75 (51)	73 (47)
>9	75 (50)	73 (49)	79 (51)
Presence of ≥1 EIM at baseline			
Yes	37 (25)	36 (24)	41 (27)
No	112 (75)	112 (76)	113 (73)
Fecal calprotectin, mg/kg, median (range)	1991 (30–28,800)[a]	1718 (30–28,800)[b]	1465 (30–28,800)[c]
hsCRP, mg/L, median (range)	4 (0.2–105)	4 (0.2–83)	4 (0.2–107)
Baseline aminosalicylates use	99 (66)	99 (67)	106 (69)
Baseline CS use	60 (40)	55 (37)	57 (37)
Prior anti-TNF use	72 (48)	68 (46)	69 (45)
Biologic-IR	81 (54)	71 (48)	73 (47)
Number of biologics ≤1	24 (30)	26 (37)	26 (36)
Number of biologics >1	57 (70)	45 (63)	47 (64)

CS, corticosteroids; EIM, extraintestinal manifestation; hsCRP, high-sensitivity C-reactive protein; IR, inadequate responder; PBO, placebo; QD, once daily; SD, standard deviation; TNF, tumor necrosis factor; UPA, upadacitinib.
Data are n (%) unless otherwise specified.
[a]n = 127, [b]n = 130, [c]n = 129.

RESULTS CONTINUED

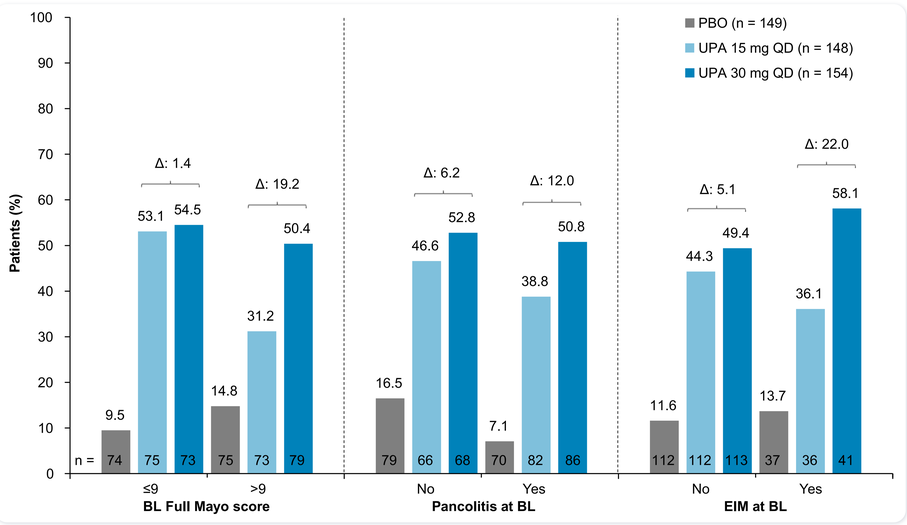
Efficacy

- Differences in the proportions of responders who achieved clinical remission (per Adapted Mayo score) at week 52 with UPA 30 mg vs UPA 15 mg were greater in patients with a high inflammatory burden (difference range: 12.0–22.0%) vs patients without a high inflammatory burden (difference range: 1.4–6.2%) **(Figure 2)**
- A similar pattern was seen for the proportion of patients achieving endoscopic improvement at week 52 (high inflammatory burden [difference range: 12.0–26.1%] vs patients without a high inflammatory burden [difference range: 0.2–14.1%]) **(Figure 3)**
  - However, there were similar differences between UPA 30 mg and UPA 15 mg in patients with (12.0%) or without (14.1%) high burden of pancolitis achieving endoscopic improvement at week 52

Limitations

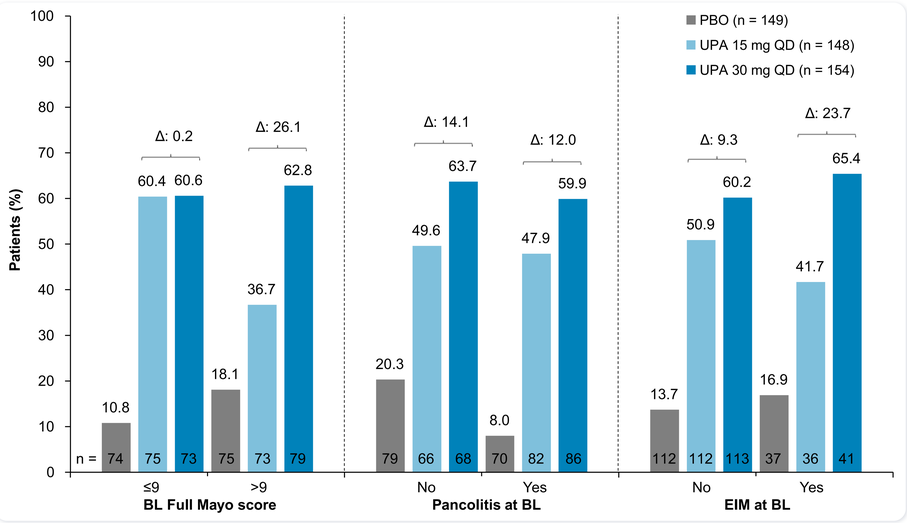
- These results should be interpreted with respect to the following limitations:
  - Results are descriptive in nature only
  - The sample size is small in some subgroups

Figure 2. Clinical Remission[a] at Week 52 per Adapted Mayo Score



Δ, difference; BL, baseline; EIM, extraintestinal manifestation; ITT, intent-to-treat; PBO, placebo; QD, once daily; UPA, upadacitinib.
Data are from the ITT population, defined as the first 450 randomized and treated patients with 8-week UPA 45 mg QD induction treatment who were enrolled in Cohort 1 under the protocol for the 52-week maintenance treatment period. The actual number of patients in the analysis was 451 due to the same enrollment date of the 450th and 451st patients.
Non-responder imputation incorporating multiple imputations was performed to handle missing data due to COVID-19. The difference between UPA 30 mg and UPA 15 mg was not part of the predefined statistical analyses.
[a]Adapted Mayo score ≤2, with stool frequency subscore ≤1 (and not greater than induction baseline), rectal bleeding subscore = 0, and endoscopic subscore ≤1 without friability.

Figure 3. Endoscopic Improvement[a] at Week 52



Δ, difference; BL, baseline; EIM, extraintestinal manifestation; ITT, intent-to-treat; PBO, placebo; QD, once daily; UPA, upadacitinib.
Data are from the ITT population, defined as the first 450 randomized and treated patients with 8-week UPA 45 mg QD induction treatment who were enrolled in Cohort 1 under the protocol for the 52-week maintenance treatment period. The actual number of patients in the analysis was 451 due to the same enrollment date of the 450th and 451st patients.
Non-responder imputation incorporating multiple imputations was performed to handle missing data due to COVID-19. The difference between UPA 30 mg and UPA 15 mg was not part of the predefined statistical analyses.
[a]Endoscopic subscore ≤1 without friability.