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Efficacy of Upadacitinib in a Randomized Trial of Patients With Active Ulcerative Colitis

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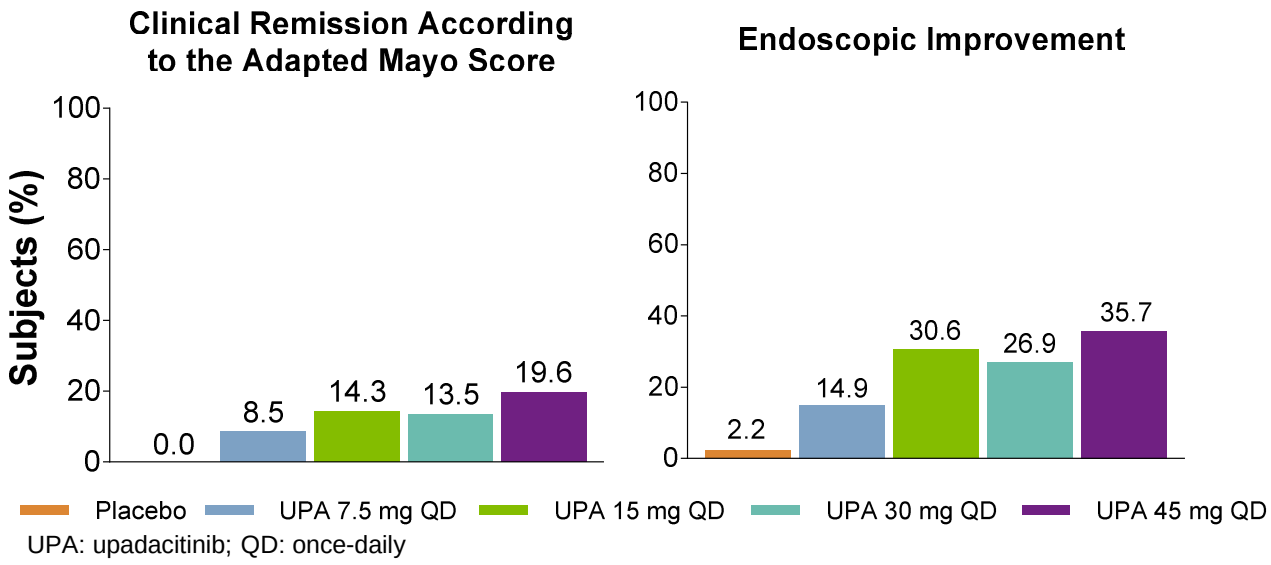
250 adults with median disease duration of 5.92 years: 54% of the patients had pancolitis and 36.1% of the patients had Adapted Mayo score > 7, and 73.2% of patients had been previously exposed to a TNF antagonist.

Upadacitinib was more effective than placebo as an induction therapy in patients with ulcerative colitis at Week 8



Upadacitinib was well tolerated. The frequency of adverse events of special interest was generally low (<5%) in the upadacitinib groups with the exception of anemia, hepatic disorder and creatine phosphokinase elevation.

Gastroenterology

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Abbreviations used in this manuscript: AE, adverse event; CMH, Cochran-Mantel-Haenszel; CPK, creatine phosphokinase; DVT, deep venous thrombosis; ES, endoscopic subscore; ICH, International Conference on Harmonization; ITT, intention-to-treat; JAK, Janus kinase; MCP-Mod, multiple comparison procedure and modelling; PE, pulmonary embolism; QD, once daily; RBS, rectal bleeding subscore; SFS, stool frequency subscore; STATs, signal transducers and activators of transcription; TK, tyrosine kinase;

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Authors' contributions to the manuscript

W. J. Sandborn, S. Ghosh, J. Panes, S. Schreiber, G. D'Haens, S. Tanida, J. Siffledeen, J. Enejosa, W. Zhou, A. A. Othman, B. Huang, and P. D. R. Higgins contributed to the study concept and design, acquisition of data, and analysis and interpretation of the data. W. J. Sandborn, S. Ghosh, J. Panes, S. Schreiber, G. D'Haens, S. Tanida, J. Siffledeen, J. Enejosa, W. Zhou, A. A. Othman, B. Huang, and P. D. R. Higgins provided critical revision of the manuscript for important intellectual content. Statistical analysis was provided by B. Huang. Administrative,

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ABSTRACT

Background & Aims: We evaluated the efficacy and safety of upadacitinib, an oral selective inhibitor of Janus kinase 1, as induction therapy for ulcerative colitis (UC).

Methods: We performed a multicenter, double-blind, phase 2b study of 250 adults with moderately to severely active UC and an inadequate response, loss of response, or intolerance to corticosteroids, immunosuppressive agents, and/or biologic therapies. Patients were randomly assigned to groups that received placebo or induction therapy with upadacitinib (7.5 mg, 15 mg, 30 mg, or 45 mg, extended release), once daily for 8 weeks. The primary endpoint was the proportion of subjects who achieve clinical remission according to the Adapted Mayo score at week 8. No multiplicity adjustments were applied.

Results: At week 8, 8.5%, 14.3%, 13.5%, and 19.6% of patients receiving 7.5 mg, 15 mg, 30 mg, or 45 mg upadacitinib, respectively, achieved clinical remission compared with none of the patients receiving placebo ($P = .052$, $P = .013$, $P = .011$, and $P = .002$, compared with placebo, respectively). Endoscopic improvement at week 8, defined as endoscopic subscore ≤ 1, was achieved in 14.9%, 30.6%, 26.9%, and 35.7% of patients receiving upadacitinib 7.5 mg, 15 mg, 30 mg, or 45 mg, respectively compared with 2.2% receiving placebo ($P = .033$, $P < .001$, $P < .001$, $P < .001$, compared with placebo, respectively). One event of herpes zoster and 1 subject with pulmonary embolism and deep venous thrombosis (diagnosed 26 days after treatment discontinuation) were reported in the group that received upadacitinib 45 mg once daily. Increases in serum lipid levels and creatine phosphokinase with upadacitinib were observed.

Conclusion: In a phase 2b trial, 8 weeks treatment with upadacitinib was more effective than placebo for inducing remission in patients with moderately to severely active UC.

ClinicalTrials.gov no: NCT02819635

Keywords: U-ACHIEVE, inflammatory bowel disease; IBD treatment; selective JAK1 inhibitor

Introduction

Ulcerative colitis is a chronic, relapsing inflammatory disease of the colon, leading to a significant burden and disability for patients.(1-4) Current therapeutic options include mesalamine, glucocorticoids, immunosuppressives, and biologics. However, these available treatments are not effective in more than one third of patients and can be associated with side effects that limit their use.(5-8) New treatments are needed to provide sustained improvements in symptomatic and endoscopic outcomes in a higher proportion of patients with ulcerative colitis.(9)

Janus kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2) are intracellular tyrosine kinases (TK). They are activated by binding of a cytokine ligand, leading to recruitment, phosphorylation, and activation of signal transducers and activators of transcription (STATs).(10, 11) STATs control many functions of innate and adaptive immunity, haematopoiesis, and cellular processes, including cell growth, survival, differentiation, and migration.(11) Increasingly, JAK inhibition has been evaluated as a target for management of many immune-mediated diseases, including ulcerative colitis. Tofacitinib, a pan-JAK inhibitor, has demonstrated efficacy in three phase 3 placebo-controlled studies in patients with moderately to severely ulcerative colitis and has been approved for the treatment of ulcerative colitis.(12) Upadacitinib is a once daily, oral, small-molecule therapy that was engineered to have increased selectivity for JAK1 over JAK2, JAK3 and TK2.(13) We report the results of a phase 2b trial, investigating the dose-response, efficacy, and safety of upadacitinib, in patients with moderately-to-severely active ulcerative colitis.

Methods

Trial design and oversight

The overarching U-ACHIEVE program comprises 3 studies: a phase 2b dose-ranging induction study (study 1), a phase 3 dose-confirming induction study (study 2), and a phase 3 maintenance study (study 3). Here we report the results of the primary and secondary efficacy endpoints and safety from study 1. This was a multicenter, randomized, double-blind, placebo-controlled trial, conducted from October 2016 through April 2018, at 142 sites in 28 countries. A total of 250 patients were randomized in study 1 part 1; after the enrollment in this study part was completed, an additional 132 patients were enrolled in study 1 part 2 and randomized into upadacitinib groups 30 mg and 45 mg once daily (QD) to avoid interrupting the study activities and to provide a sufficient number of clinical responders for the maintenance portion of the study. An exploratory analysis for the combined results of study 1 part 1 and part 2 is provided in the **Supplementary Appendix (Table S8-Table S11)**. The complete study design of study 1 is shown in **Figure S1**.

This study was conducted per the International Conference on Harmonization (ICH) guidelines, applicable regulations, and the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (NCT02819635). The protocol was approved by institutional ethics committees and is available with the full text of this article at gastrojournal.org. Safety data were regularly assessed by an independent data monitoring committee. Cardiovascular and embolic and thrombotic events were reviewed and adjudicated by an independent Cardiovascular Adjudication Committee in a blinded manner. Written informed consent was provided by all subjects. AbbVie sponsored the study and the academic authors collaborated with AbbVie on the study design, data analysis, interpretation of results, and the preparation, review, and approval of the final version of the manuscript. AbbVie provided writing support. The first and last authors wrote the first draft of the manuscript, and all the authors contributed to subsequent drafts. All

the authors had access to the data, reviewed and approved the final manuscript, and vouch for its accuracy.

Patients

Eligible patients were aged 18-75 years, with a confirmed diagnosis of ulcerative colitis for at least 90 days. Patients had moderately-to-severely active disease, defined as an Adapted Mayo score (Mayo score excluding physician's global assessment) of 5 to 9 points with a centrally read endoscopy subscore of 2 or 3. The Mayo score is a composite of the stool frequency subscore, rectal bleeding subscore, endoscopy subscore, and Physician's Global Assessment subscore, which ranges from 0 to 12, with each of the four subscores ranging from 0 to 3. Exclusion criteria were a diagnosis of Crohn's disease or indeterminate colitis, ulcerative colitis limited to the rectum, clinical signs of fulminant colitis, toxic megacolon, or patients with a history of colectomy. Patients were required to have had an inadequate response, loss of response or intolerance to corticosteroids, immunosuppressives, and/or biologics. Permitted concomitant medications for ulcerative colitis included oral aminosalicylates, methotrexate, and oral corticosteroids (≤ 30 mg/day of prednisone or equivalent) at stable doses and kept unchanged during the study. Prohibited concomitant therapies included biologics, cyclosporine, tacrolimus, live vaccines, intravenous corticosteroids, azathioprine, and 6-mercaptopurine.

Randomization and masking

In part 1 of study 1, eligible patients were randomized at baseline to receive double-blind 8-week induction therapy with placebo or upadacitinib at 7.5 mg, 15 mg, 30 mg, 45 mg extended-release QD in a 1:1:1:1:1 ratio. In part 2 of study 1, eligible patients were randomized to receive double-blind 8-week induction therapy with upadacitinib 30 mg or 45 mg extended-release QD in a 1:1 ratio. Randomization was performed centrally using a web based Interactive Response

Technology and was stratified by previous biologic use, baseline corticosteroid use, and baseline Adapted Mayo score (≤ 7 and > 7). Patients, investigators, and the sponsor were masked to treatment assignment.

Efficacy, safety and pharmacokinetic evaluations

The Adapted Mayo score and the Mayo score were determined at weeks 0 and 8. The Partial Mayo score (Mayo score excluding the endoscopic subscore) was determined at weeks 0, 2, 4, and 8. Adapted Mayo scores were calculated based on the data collected from the patient diaries and centrally read endoscopic score. Endoscopy and biopsy for histologic assessment were performed at screening and week 8. Endoscopies were reviewed by a primary central reader who was blinded to the subject's clinical data, the site's endoscopy assessment and the subject's therapy. Biopsies for evaluation of the histologic endpoints were obtained from the area of most severe inflammation in rectosigmoid colon. The samples were then sent for histologic evaluation to central readers who are board certified gastrointestinal pathologists with expertise in inflammatory bowel diseases (IBD). One of the central readers performed the reading and determined the histologic score. The patient reported outcomes were measured at baseline and weeks 2, 4, 6 and 8. Treatment emergent adverse events were monitored in all patients from the time of study drug administration until 30 days following discontinuation of study drug. Adverse events were tabulated by system organ class and preferred term using the Medical Dictionary for Regulatory Activities. Blood samples for pharmacokinetic analysis were collected at weeks 2, 4, 6, and 8 to determine upadacitinib plasma concentrations.

Endpoints

The primary efficacy endpoint of study 1 part 1 was clinical remission according to the Adapted Mayo score, defined as stool frequency subscore (SFS) ≤ 1, rectal bleeding subscore (RBS) = 0,

and endoscopic subscore (ES) ≤ 1 by central reading at week 8. Ranked secondary endpoints were endoscopic improvement (defined as ES ≤ 1) at week 8; clinical remission according to the Mayo score (defined as a Mayo score ≤ 2 with no subscore > 1) at week 8; clinical response according to the Adapted Mayo score (defined as 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) at week 8; clinical response according to the Partial Mayo score (defined as decrease from baseline in the Partial Mayo score ≥ 2 points and ≥ 30% from baseline, plus a decrease in RBS ≥ 1 or an absolute RBS ≤ 1) at week 2; endoscopic remission (defined as ES of 0) at week 8; histologic improvement (defined as any decrease from baseline in Geboes score) at week 8; and change in the Mayo score from Baseline to week 8. A complete list of additional secondary efficacy endpoints is provided in **Table S3** of the **Supplementary Appendix**.

Statistical analysis

The sample size was based on the expected proportion of subjects who would achieve clinical remission according to the Adapted Mayo score at week 8. A total sample size of 250 subjects (50 subjects per treatment group) was deemed sufficient to test for the presence of a dose-response signal, to select the best dose-response model for the observed data out of a pre-specified set of candidate models, and to estimate target doses of interest via modeling using the Multiple comparison procedure and modelling (MCP-Mod) approach. This approach provides an average power of 68% to detect a dose effect at 5% level of significance (two-sided) with the log linear, E_{max}, exponential, logistic, and $sigE_{max}$ models pre-specified as likely candidates to characterize the dose-response for upadacitinib for the primary endpoint of clinical remission. Efficacy endpoints were analysed in the intention-to-treat (ITT) population, defined as all randomly assigned patients who received at least one dose of study drug. For selected endpoints

(clinical remission according to the Adapted Mayo score and endoscopic improvement), the overall dose-response relationships between multiple upadacitinib doses and placebo were modelled using the MCP-Mod approach (**Supplementary Appendix, Table S2**).

The pairwise comparisons for the difference in proportions of subjects between the treatment groups and placebo group were performed using the Cochran-Mantel-Haenszel (CMH) test. The CMH-based two-sided 95% CIs for the difference in proportions between groups were calculated. All statistical tests were two-sided with the significance level of .05.

The non-responder imputation method was used to impute missing values at week 8. The last observation carried forward method was used in sensitivity analyses of all the efficacy endpoints.

A closed testing procedure was not used, and no multiplicity adjustments were applied for the pairwise comparisons, so reported *P* values should be considered nominal.

The safety analysis set consists of all subjects who received at least one dose of study medication in the study. For the safety analysis, subjects were assigned to a treatment group based on the treatment actually received, regardless of the randomly selected treatment group. Safety analyses were summarized by study group and presented as proportions of patients. Comparisons of the percent of subjects experiencing an adverse event between treatment groups and placebo were performed using Fisher's exact tests.

Results

Patient characteristics

In study 1 part 1, 250 subjects were randomly allocated to placebo (n = 46), and upadacitinib 7.5 mg (n = 47), 15 mg (n = 49), 30 mg (n = 52), and 45 mg QD (n = 56; **Figure 1**). The number of patients in the 30 and 45mg groups is slightly larger due to a randomization error in which 12 subjects were randomized with only two options, the upadacitinib 30 mg or 45 mg QD doses.

Overall, 227 subjects (90.8%) completed the study; the most common reasons for discontinuation of study drug were adverse events (14/250; 5.6%) and lack of efficacy (7/250; 2.8%).

Patient demographics and baseline clinical characteristics were similar between the placebo and upadacitinib groups (**Table 1**). The median disease duration was 5.92 years, 54% of the patients had pancolitis, 36.1% of the patients had Adapted Mayo score > 7; the median fecal calprotectin at baseline was 1703.0 mcg/gram of stool. Of the 250 randomized patients, 77.6% (194/250) of patients have been previously exposed to biologic treatment (19.2% to one biologic, 30.8% to 2 biologics, and 23.2% to 3 biologics); 73.2% (183/250) of patients had been previously exposed to a TNF antagonist, 46.8% (117/250) of patients have been previously exposed to vedolizumab, 44.0% (110/250) have been exposed to both a TNF antagonist and vedolizumab, and none were exposed to tofacitinib or other JAK inhibitors.

Efficacy

Primary endpoint

An overall positive dose-response relationship between multiple upadacitinib doses and placebo was detected by MCP-Mod for clinical remission according to the Adapted Mayo score in the log-linear and E_{max} pre-specified candidate models (**Table S2**). Clinical remission was reported in 8.5% (*P* = .052), 14.3% (*P* = .013), 13.5% (*P* = .011), and 19.6% (*P* = .002) of patients receiving upadacitinib 7.5 mg, 15 mg, 30 mg, and 45 mg QD, respectively compared with 0% of patients receiving placebo (**Figure 2A and Table 2**). After adjustment for prior biologic use, baseline corticosteroid use, and baseline Adapted Mayo score, CMH-adjusted risk differences (95% CI) for the upadacitinib 7.5 mg, 15 mg, 30 mg, and 45 mg QD groups versus placebo were 8.1 (-0.1 to 16.3), 12.7 (2.7 to 22.6), 12.7 (3.0 to 22.5), and 19.4 (7.4 to 31.4) percent,

respectively. Subgroup analyses are shown in **Figure S2** in the **Supplementary Appendix**. In general, the treatment effect of all upadacitinib doses was lower in patients who had received previous treatment with biologics compared with those who had not. The efficacy results excluding the 12 patients who were only randomized to upadacitinib 30 mg or 45 mg in part 1 are reported in the **Supplementary Appendix Table S7**. The results of this sensitivity analysis were consistent with the ITT analysis. Combined results for the study 1 part 1 and part 2 are shown in **Table S10** in the **Supplementary Appendix.**

Secondary endpoints

The key secondary endpoint, endoscopic improvement at week 8, occurred in more patients receiving upadacitinib 7.5 mg (14.9%; $P = .033$), 15 mg (30.6; $P < .001$), 30 mg (26.9%; $P < .001$), and 45 mg QD (35.7%; $P < .001$) compared with placebo (2.2%; **Figure 2C and Table 2**). The overall dose-response relationship across the range of upadacitinib doses was confirmed by MCP-Mod in four of the five pre-specified candidate models (except for the less pharmacologically plausible exponential model; **Supplementary Appendix, Table S2**). Clinical remission according to the full Mayo score at week 8 occurred in a higher proportion of patients receiving upadacitinib 15 mg (10.2%; $P = .027$), 30 mg (11.5%; $P = .016$), and 45 mg QD (19.6%; $P = .001$) compared with 0% of patients receiving placebo. More patients achieved clinical response according to the Adapted Mayo score at week 8 with upadacitinib 7.5 mg (29.8%; $P = .046$), 15 mg (44.9%; $P < .001$), 30 mg (44.2%; $P < .001$), and 45 mg QD (50.0%; $P < .001$) compared with placebo (13.0%; **Figure 2B and Table 2**). At week 8, histologic improvement was reported more in patients receiving upadacitinib 7.5 mg (31.9%; $P = .003$), 15 mg (51.0%; $P < .001$), 30 mg (44.2%; $P < .001$), and 45 mg QD (48.2%; $P < .001$) compared with placebo (6.5%; **Figure 2D and Table 2).** Endoscopic remission at week 8 occurred in a

higher proportion of patients receiving upadacitinib 30 mg (9.6%; *P* = .015) and 45 mg QD (17.9%; *P* = .004; **Table 2)**. Other ranked secondary endpoints also showed consistent efficacy (results provided in **Table 2)**.

The change from baseline in high-sensitivity C-reactive protein (hs-CRP) to week 2, 4, and 8 was greater for all upadacitinib groups compared with placebo (**Figure 3A and Table S5**). At week 8, the changes from baseline in fecal calprotectin were numerically greater in all upadacitinib groups than in the placebo group (**Figure 3B and Table S6**).

Safety

Incidences of adverse events (AEs) and AEs leading to discontinuation were similar across upadacitinib groups, and numerically higher in the placebo group **(Table 3).** Rates of serious AEs were 10.9%, 0%, 4.1%, 5.8%, and 5.4%, for placebo, upadacitinib 7.5 mg, 15 mg, 30 mg, and 45 mg QD, respectively. Serious infections occurred in patients receiving placebo (4.3%, n = 2), 15 mg QD (2.0%, n = 1), and 45 mg QD (3.6%, n = 2). Adverse events of special interest were generally low (<5%) except for hepatic disorders and creatine phosphokinase (CPK) elevation in the upadacitinib 45 mg QD group and anemia in upadacitinib 15 mg QD and placebo treatment groups. The hepatic disorders were mainly due to transaminase elevations and were mostly transient. One event of herpes zoster with 45 mg QD was reported, the case was disseminated and cutaneous only, moderate in severity. The study drug was not discontinued. No malignancy was reported in study 1; one case of change in appearance of a mole was reported in the upadacitinib 7.5 mg QD treatment group; the case was later diagnosed as melanoma after the patient entered the maintenance study 3. One subject with adjudicated severe AE of pulmonary embolism (PE) and mild AE of deep venous thrombosis (DVT) was reported with upadacitinib 45 mg QD. These concurrent events were reported 26 days after the study drug discontinuation

due to ulcerative colitis worsening. The risk factors include age of 65 years old, former smoker, hospitalization, fluid loss and bed rest during ulcerative colitis worsening, with concomitant use of corticosteroids. There were no reports of lymphoma, death, gastrointestinal perforation, active/latent tuberculosis, or renal dysfunction.

Rates of AE Grade 3 or 4 laboratory values were generally less than 5% in the upadacitinib groups. At week 8, significant increases from baseline in average cholesterol, high-density lipoprotein, and low-density lipoprotein were observed in all upadacitinib treatment groups. Grade 3 or higher of increased CPK level was reported more frequently in upadacitinib treatment groups.

Pharmacokinetics

Upadacitinib exposures were approximately dose-proportional over the evaluated 7.5 mg to 45 mg QD dose range, consistent with previous pharmacokinetic evaluations of upadacitinib.(14, 15) Within 24 hours of dosing, upadacitinib mean plasma concentrations ranged (around peak time to around trough time) from 13 ng/mL to 1.6 ng/mL for the 7.5 mg dose, from 33 ng/mL to 3.6 ng/mL for 15 mg, from 59 ng/mL to 8.1 ng/mL for 30 mg, and from 75 ng/mL to 11 ng/mL for the 45 mg.

Discussion

Upadacitinib is a selective JAK1 inhibitor engineered to address the hypothesis that JAK1 selectivity will have a more favorable benefit-risk profile over the pan-JAK inhibitors. Studies in cellular assays demonstrated that upadacitinib is up to 60-fold selective for JAK1 over JAK2, and > 100 fold selective over JAK3.(16) The efficacy and safety of selective JAK1 inhibitors filgotinib and upadacitinib have been studied in phase 2 trials in Crohn’s disease with positive

results.(17, 18) This is the first phase 2 study evaluating the efficacy and safety of a selective JAK1 inhibitor in ulcerative colitis patients.

The U-ACHIEVE study 1 evaluated the safety and efficacy of multiple doses of upadacitinib extended-release formulation in patients with moderately-to-severely active ulcerative colitis, with most patients having pancolitis and being refractory to biologic therapy. The study evaluated a broad range of upadacitinib doses as an induction treatment for ulcerative colitis and showed efficacy with doses of 7.5 mg QD to 45mg QD. The study incorporated a new definition for the primary endpoint of clinical remission using the Adapted Mayo score with a more stringent criteria than previous studies. A consistent dose-response relationship with upadacitinib for this primary endpoint was observed. The definition of endoscopic improvement (ES = 0 or 1) in this study was used to define the mucosal healing in previous studies.(12) A stringent definition for endoscopic remission (ES = 0) was used in the study and was achieved at 30 mg QD and 45 mg QD treatment groups. Histologic change was evaluated using Geboes score by central reading.(19) Histologic improvement was demonstrated in all treatment arms. Geboes score generates a score between 0 and 5.4, with higher scores indicating greater level of inflammation and has been wildly used in ulcerative colitis trials.(20) The onset of action was rapid, demonstrated by improvement in the Partial Mayo score at week 2. Treatment effect was greater with all upadacitinib doses compared with placebo for the primary and all secondary endpoints.

The type of AEs reported in this study were similar to those previously observed in clinical trials with JAK inhibitors in patients with moderately-to-severely active IBD (12, 21, 22) and rheumatoid arthritis (RA).(23-29) Serious infections were observed in patients receiving upadacitinib or placebo.

One subject who received upadacitinib 45 mg QD had adjudicated cardiovascular events of DVT and PE. These events were reported 26 days after treatment discontinuation, risk factors including former smoker, hospitalization, fluid loss and bed rest during ulcerative colitis worsening, with concomitant use of corticosteroids. No other cardiovascular events were reported. In this study, the reports of embolic and thrombotic events and cardiovascular events were adjudicated by an independent adjudication committee. Patients with IBD have an increased risk of thrombosis, which has been reported to be 2- to 3-fold higher than that of patients without IBD and is exacerbated during times of disease flare.(30-32) In upadacitinib studies for RA, venous thromboembolism events (VTEs) were reported in all treatment groups, including placebo, upadacitinib and active comparator (e.g. methotrexate and adalimumab).(33) With long-term exposure, the rates of VTEs occurred at comparable frequency on upadacitinib versus active comparators. The rate of VTEs in subjects with upadacitinib was not dose related. All subjects with VTE had at least one risk factor present at baseline of the studies.

One non-serious event of herpes zoster was reported with upadacitinib 45 mg QD treatment. An increased risk of herpes zoster infection has been reported with the use of tofacitinib and baricitinib in RA.(34, 35) Data from the upadacitinib clinical trials in RA also showed that the rates of herpes zoster were higher with upadacitinib versus placebo.(33). In tofacitinib phase 2/3 UC program, an increased risk of herpes zoster was also identified.(36) Overall, 5.6% of the patients developed herpes zoster. The data suggests that herpes zoster may be a risk for the JAK inhibitor class.

A rigorous estimation of the risk and incidence of herpes zoster and pulmonary embolus with upadacitinib exposure is warranted and requires additional evaluation in larger and long-term studies.

This study has some limitations. The study was a phase 2 dose ranging study with limited sample size and exposure time and not sufficient to fully characterize the safety of upadacitinib in the treatment of ulcerative colitis. These limitations will be addressed with the phase 3 program. There was no adjustment for multiple testing or secondary endpoints.

In conclusion, upadacitinib was more effective than placebo for inducing remission in patients with moderately to severely active ulcerative colitis. The benefit-risk profile supports further development of upadacitinib as a novel treatment for ulcerative colitis.

Role of authors and sponsor

The authors and AbbVie scientists designed the study and analyzed and interpreted the data. AbbVie funded the research and provided writing support. All authors contributed to the development of the content. The authors and AbbVie reviewed and approved the manuscript; the authors maintained control over the final content.

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Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g. protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-

trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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Table Legend

Table 1: Patient demographics and baseline disease characteristics. QD=once daily; UC=ulcerative colitis; hs-CRP=high sensitivity C-reactive protein; TNF=tumor necrosis factor.

Table 2: Efficacy Outcomes in the U-ACHIEVE Study 1 part 1 trial. QD=once daily; CI=confidence interval.

Table 3: Safety Outcomes at week 8 in the U-ACHIEVE Study 1 part 1 trial. AE=adverse event; QD=once daily.

Figure Legend

Figure 1: CONSORT flow chart Study 1 Part 1. QD: once daily

Figure 2. Proportion of patients with clinical remission according to the Adapted Mayo score (A), clinical response according to the Adapted Mayo score (B), endoscopic improvement (C), and histologic improvement (D). UPA: upadacitinib; QD: once daily

Figure 3. Change from baseline in hs-CRP (A) and FC (B) in the U-ACHIEVE Study 1 part 1. QD: once daily; hs-CRP: high sensitivity C-reactive protein; FC: fecal calprotectin.

***, **, * statistically significant versus placebo at 0.001, 0.01, and 0.05 levels, respectively.

p-value is for comparing the mean change from baseline.

Table 1:

Characteristic	Placebo n=46	Upadacitinib 7.5 mg QD n=47	Upadacitinib 15 mg QD n=49	Upadacitinib 30 mg QD n=52	Upadacitinib 45 mg QD n=56
Female, n (%)	17 (37.0)	24 (51.1)	19 (38.8)	21 (40.4)	19 (33.9)
Age, years, median (range)	40 (21-67)	41 (18-75)	47 (22-71)	42 (20-72)	37 (19-74)
UC duration, years, median (range)	5.19 (0.4-30.8)	6.59 (0.8-43.7)	4.58 (0.2-43.0)	6.06 (0.3-27.5)	6.46 (0.4-23.9)
Disease extent, n (%)					
Rectosigmoid	0	1 (2.1)	0	0	0
Left-sided colitis	19 (41.3)	21 (44.7)	25 (51.0)	23 (44.2)	26 (46.4)
Extensive colitis or pancolitis	27 (58.7)	25 (53.2)	24 (49.0)	29 (55.8)	30 (53.6)
Mayo score, median (range)	9.3 (7-12)	9.0 (7-12)	9.7 (7-12)	9.0 (6-12)	9.0 (7-12)
Adapted Mayo score					
≤ 7	27 (58.7)	30 (63.8)	31 (63.3)	33 (63.5)	38 (67.9)
7 - 9	19 (41.3)	17 (36.2)	18 (36.7)	19 (36.5)	17 (30.4)
Median (range)	6.9 (5-9)	7.0 (5-9)	7.0 (4-9)	7.0 (4-9)	6.7 (5-9)
hs-CRP, mg/L, median (range)	5.4	4.9	8.7	6.7	6.3

	(0.35-41.2)	(0.2-29.1)	(1.27-117)	(0.2-82.9)	(0.2-67)
Fecal calprotectin, μg/g, median (range)	2100.5 (93-28800)	1576.0 (91-17690)	1843.0 (48-18865)	1648.0 (30-18053)	1666.0 (30-17259)
Baseline corticosteroid use, n (%)	25 (54.3)	25 (53.2)	27 (55.1)	25 (48.1)	28 (50.0)
Prior immunosuppressant use, n (%)	36 (78.3)	31 (66.0)	38 (77.6)	39 (75.0)	41 (73.2)
Prior all biologics use, n (%)	35 (76.1)	36 (76.6)	38 (77.6)	42 (80.8)	43 (76.8)
Prior TNF antagonist use	33 (71.7)	33 (70.2)	37 (75.5)	41 (78.8)	39 (69.6)
Prior vedolizumab use	23 (50.0)	25 (53.2)	24 (50.0)	22 (42.3)	23 (41.1)
Prior TNF antagonist and vedolizumab use	22 (47.8)	23 (48.9)	23 (46.9)	22 (42.3)	20 (35.7)
Previous inadequate response/loss of response, n (%)					
Corticosteroid	30 (65.2)	29 (61.7)	22 (44.9)	29 (55.8)	29 (51.8)
Immunosuppressant	22 (47.8)	24 (51.1)	27 (49.0)	22 (42.3)	20 (35.7)
TNF antagonist	30 (65.2)	26 (55.3)	34 (69.4)	38 (73.1)	34 (60.7)
Biologics other than TNF antagonist	24 (52.2)	23 (48.9)	22 (44.9)	24 (46.2)	24 (42.9)

Table 2:

		Upadacitinib			
	Placebo	**7.5 mg QD**	**15 mg QD**	**30 mg QD**	**45 mg QD**
End Point	**N=46**	**N=47**	**N=49**	**N=52**	**N=56**
Clinical remission according to the Adapted Mayo score at week 8					
n (%)	0	4 (8.5)	7 (14.3)	7 (13.5)	11 (19.6)
Adjusted risk difference (95% CI)		8.1 (-0.1 to 16.3)	12.7 (2.7 to 22.6)	12.7 (3.0 to 22.5)	19.4 (7.4 to 31.4)
P value		.052	.013	.011	.002
Endoscopic improvement at week 8					
n (%)	1 (2.2)	7 (14.9)	15 (30.6)	14 (26.9)	20 (35.7)
Adjusted risk difference (95% CI)		12.9 (1.1 to 24.7)	26.9 (12.6 to 41.2)	26.5 (12.2 to 40.7)	36.0 (19.6 to 52.3)
P value		.033	< .001	< .001	< .001
Clinical remission according to the full Mayo score at week 8					
n (%)	0	4 (8.5)	5 (10.2)	6 (11.5)	11 (19.6)
Adjusted risk difference (95% CI)		8.1 (-0.1 to 16.3)	9.0 (1.0 to 17.0)	12.0 (2.2 to 21.7)	20.3 (8.2 to 32.4)
P value		.052	.027	.016	.001

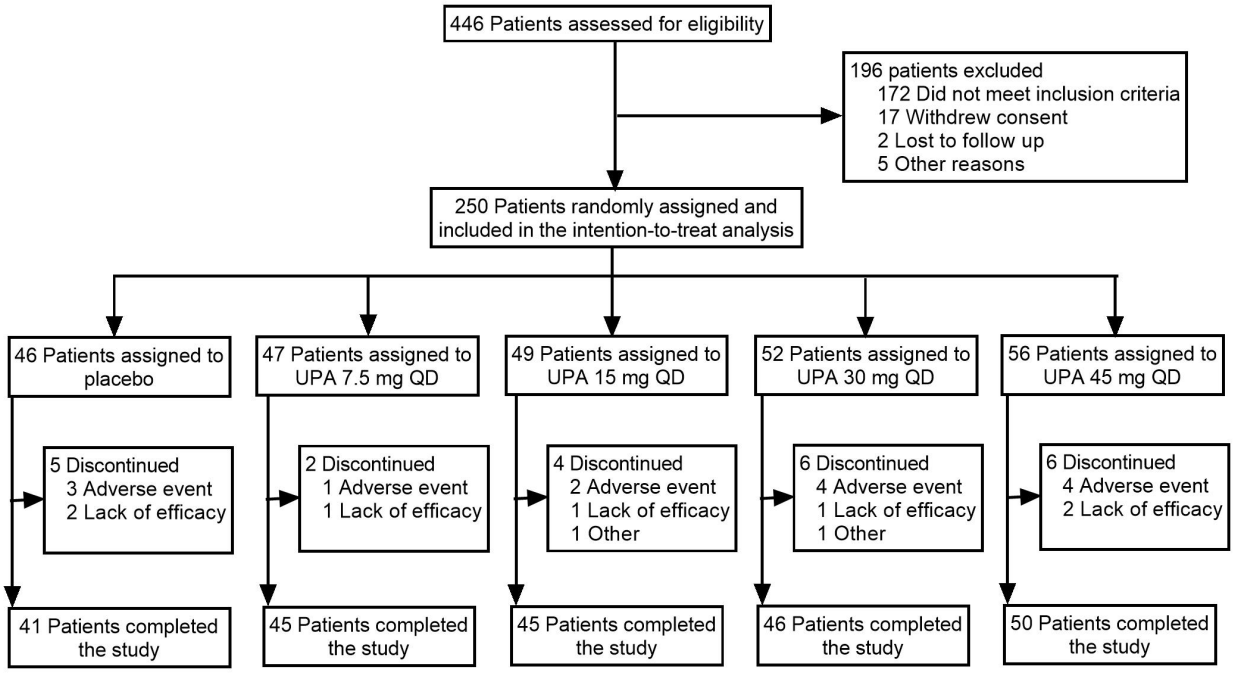
Clinical response according to the Adapted Mayo score at week 8					
n (%)	6 (13.0)	14 (29.8)	22 (44.9)	23 (44.2)	28 (50.0)
Adjusted risk difference (95% CI)		16.0 (0.3 to 31.7)	30.2 (12.5 to 47.8)	31.2 (13.9 to 48.6)	38.4 (20.1 to 56.8)
P value		.046	< .001	< .001	< .001
Clinical response according to the Partial Mayo score at week 2					
n (%)	7 (15.2)	11 (23.4)	18 (36.7)	19 (36.5)	31 (55.4)
Adjusted risk difference (95% CI)		8.8 (-8.0 to 25.6)	20.2 (2.4 to 38.1)	22.0 (4.4 to 39.6)	43.0 (23.8 to 62.1)
P value		.305	.027	.014	< .001
Change in Mayo score from Baseline to week 8, median (range)	-0.350 (-5.30, 4.00)	-2.000 (-10.70, 3.30)	-3.300 (-8.70, 1.30)	-3.700 (-11.00, 2.00)	-5.000 (-10.00, 3.00)
P value		< .001	< .001	< .001	< .001
Endoscopic remission at week 8					
n (%)	0	3 (6.4)	2 (4.1)	5 (9.6)	10 (17.9)
Adjusted risk difference (95% CI)		5.9 (-1.2 to 13.0)	3.5 (-2.0 to 9.0)	10.9 (2.1 to 19.7)	17.8 (5.8 to 29.8)
P value		.101	.212	.015	.004
Histologic improvement at week 8					

n (%)	3 (6.5)	15 (31.9)	25 (51.0)	23 (44.2)	27 (48.2)
Adjusted risk difference (95% CI)		24.8 (8.2 to 41.5)	43.0 (24.9 to 61.2)	39.4 (21.3 to 57.6)	43.4 (24.6 to 62.2)
P value		.003	< .001	< .001	< .001

Table 3:

Adverse event	Placebo n=46	Upadacitinib 7.5 mg QD n=47	Upadacitinib 15 mg QD n=49	Upadacitinib 30 mg QD n=52	Upadacitinib 45 mg QD n=56
Any AE, n (%)	33 (71.7)	30 (63.8)	30 (61.2)	36 (69.2)	35 (62.5)
Colitis ulcerative, n (%)	6 (13.0)	1 (2.1)	3 (6.1)	6 (11.5)	4 (7.1)
Any serious AE, n (%)	5 (10.9)	0	2 (4.1)	3 (5.8)	3 (5.4)
Any AE leading to discontinuation, n (%)	4 (8.7)	1 (2.1)	2 (4.1)	4 (7.7)	4 (7.1)
Infections and infestations, n (%)	16 (34.8)	9 (19.1)	10 (20.4)	6 (11.5)	13 (23.2)
Serious infections	2 (4.3)	0	1 (2.0)	0	2 (3.6)
Opportunistic infection	1 (2.2)	0	0	0	1 (1.8)
Herpes zoster	0	0	0	0	1 (1.8)
Any hepatic disorder, n (%)	1 (2.2)	2 (4.3)	0	0	6 (10.7)
Anemia, n (%)	3 (6.5)	1 (2.1)	4 (8.2)	2 (3.8)	0
Any creatine phosphokinase elevation, n (%)	0	0	3 (6.1)	2 (3.8)	5 (8.9)
Adjudicated cardiovascular events, n (%)	0	0	0	0	1 (1.8)
Abnormal laboratory test results					
Hemoglobin (g/L)					
Grade 3 (< 80)	1/46 (2.2)	2/47 (4.3)	2/49 (4.1)	2/50 (4.0)	0/56
Lymphocytes ($x10^9$/L)					
Grade 3 (0.5-0.2)	0/46	2/47 (4.3)	1/49 (2.0)	2/50 (4.0)	2/56 (3.6)
Grade 4 (< 0.2)	0 /46	0/47	0/49	0/50	0/56
Neutrophils ($x10^9$/L)					

Grade 3 (0.5 - < 1.0)	0/46	0/47	1/49 (2.0)	0/50	2/56 (3.6)
Grade 4 (< 0.5)	0/46	0/47	0/49	0/50	0/56
Alanine Aminotransferase (U/L)					
Grade 3 (5.0 - < 20.0*ULN)	0/46	0/47	0/49	0/52	0/56
Grade 4 (> 20.0*ULN)	0/46	0/47	0/49	0/52	0/56
Aspartate Aminotransferase (U/L)					
Grade 3 (5.0 - < 20.0*ULN)	0/46	0/47	0/49	0/52	1/56 (1.8)
Grade 4 (> 20.0*ULN)	0/46	0/47	0/49	0/52	0/56
Creatine phosphokinase (U/L)					
Grade 3 (> 5.0 - 10.0 x ULN)	0/46	0/47	1/49 (2.0)	1/52 (1.9)	2/55 (3.6)
Grade 4 (> 10.0 x ULN)	0/46	0/47	1/49 (2.0)	0/52	2/55 (3.6)


446 Patients assessed for eligibility
196 patients excluded
172 Did not meet inclusion criteria
17 Withdrew consent
2 Lost to follow up
5 Other reasons
250 Patients randomly assigned and included in the intention-to-treat analysis
46 Patients assigned to placebo
47 Patients assigned to UPA 7.5 mg QD
49 Patients assigned to UPA 15 mg QD
52 Patients assigned to UPA 30 mg QD
56 Patients assigned to UPA 45 mg QD
5 Discontinued
3 Adverse event
2 Lack of efficacy
2 Discontinued
1 Adverse event
1 Lack of efficacy
4 Discontinued
2 Adverse event
1 Lack of efficacy
1 Other
6 Discontinued
4 Adverse event
1 Lack of efficacy
1 Other
6 Discontinued
4 Adverse event
2 Lack of efficacy
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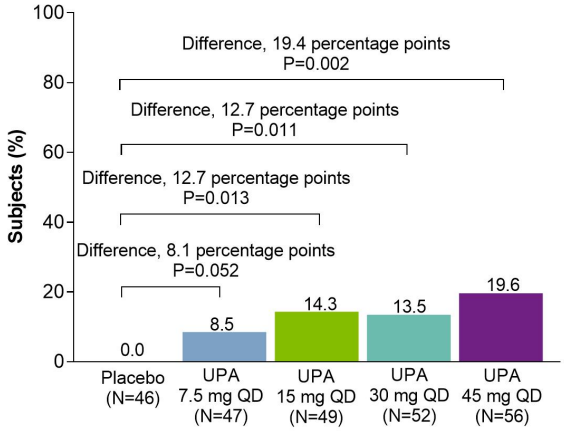
45 Patients completed the study
45 Patients completed the study
46 Patients completed the study
50 Patients completed the study

A.


Subjects (%)
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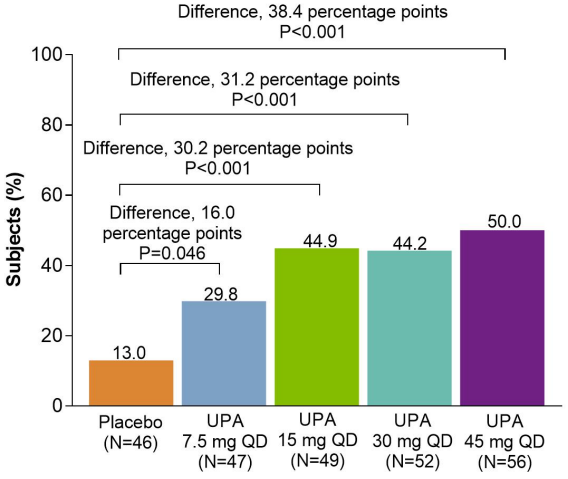
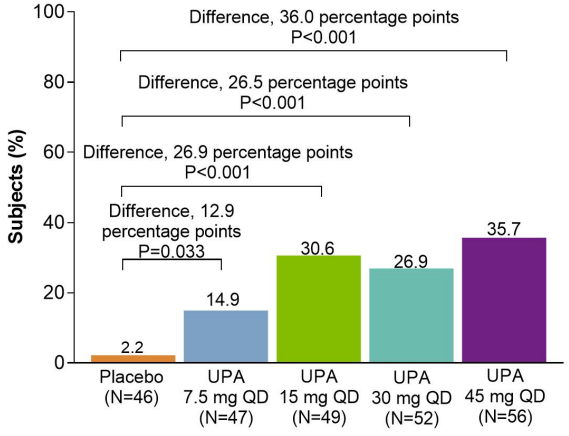
80
60
40
20
0
Difference, 19.4 percentage points
P=0.002
Difference, 12.7 percentage points
P=0.011
Difference, 12.7 percentage points
P=0.013
Difference, 8.1 percentage points
P=0.052
0.0
8.5
14.3
13.5
19.6
Placebo (N=46)
UPA 7.5 mg QD (N=47)
UPA 15 mg QD (N=49)
UPA 30 mg QD (N=52)
UPA 45 mg QD (N=56)

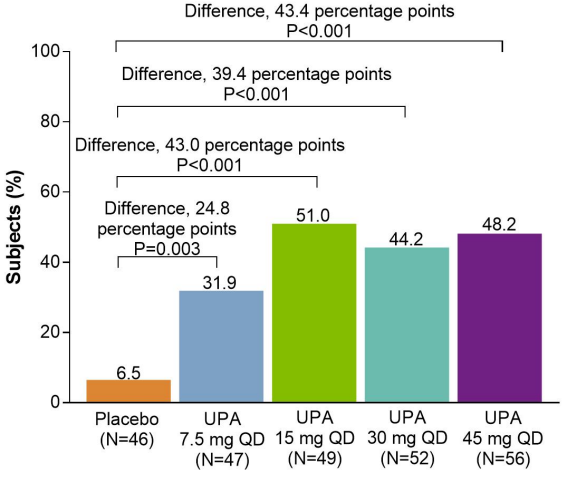
B.


Subjects (%)
100
80
60
40
20
0
Difference, 38.4 percentage points
P<0.001
Difference, 31.2 percentage points
P<0.001
Difference, 30.2 percentage points
P<0.001
Difference, 16.0 percentage points
P=0.046
13.0
29.8
44.9
44.2
50.0
Placebo (N=46)
UPA 7.5 mg QD (N=47)
UPA 15 mg QD (N=49)
UPA 30 mg QD (N=52)
UPA 45 mg QD (N=56)

C.


Subjects (%)
100
80
60
40
20
0
Difference, 36.0 percentage points
P<0.001
Difference, 26.5 percentage points
P<0.001
Difference, 26.9 percentage points
P<0.001
Difference, 12.9 percentage points
P=0.033
2.2
14.9
30.6
26.9
35.7
Placebo (N=46)
UPA 7.5 mg QD (N=47)
UPA 15 mg QD (N=49)
UPA 30 mg QD (N=52)
UPA 45 mg QD (N=56)

D.


Subjects (%)
100
80
60
40
20
0
Difference, 43.4 percentage points
P<0.001
Difference, 39.4 percentage points
P<0.001
Difference, 43.0 percentage points
P<0.001
Difference, 24.8 percentage points
P=0.003
6.5
31.9
51.0
44.2
48.2
Placebo (N=46)
UPA 7.5 mg QD (N=47)
UPA 15 mg QD (N=49)
UPA 30 mg QD (N=52)
UPA 45 mg QD (N=56)

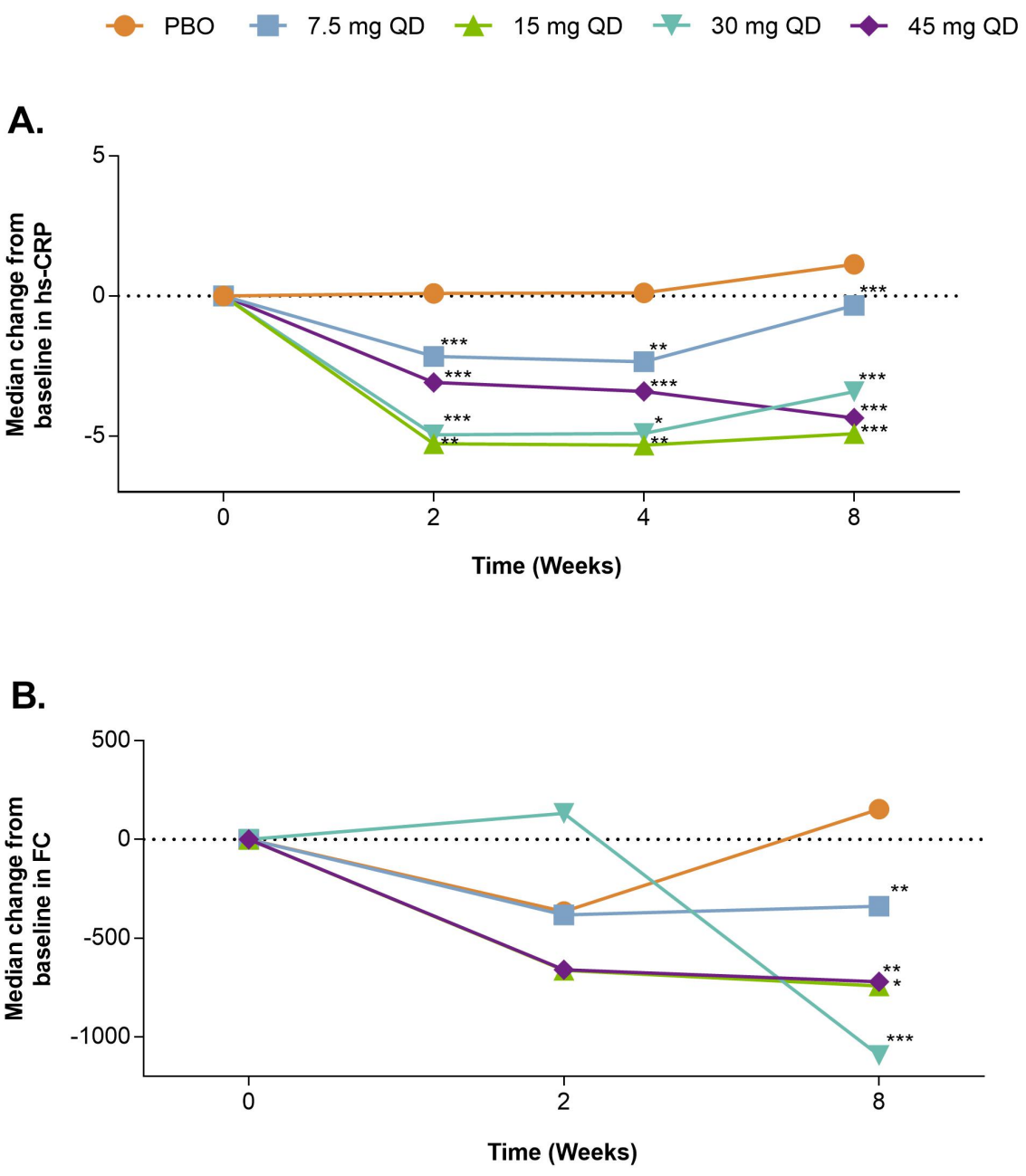

PBO
7.5 mg QD
15 mg QD
30 mg QD
45 mg QD
A.
Median change from baseline in hs-CRP
5
0
-5
0
2
4
8
Time (Weeks)
B.
Median change from baseline in FC
500
0
-500
-1000
0
2
8
Time (Weeks)

Table of Contents

Section 1. Study investigators and sites

The Principal Investigators at each of the study sites that randomized patients in U-ACHIEVE Substudy 1 are listed below.

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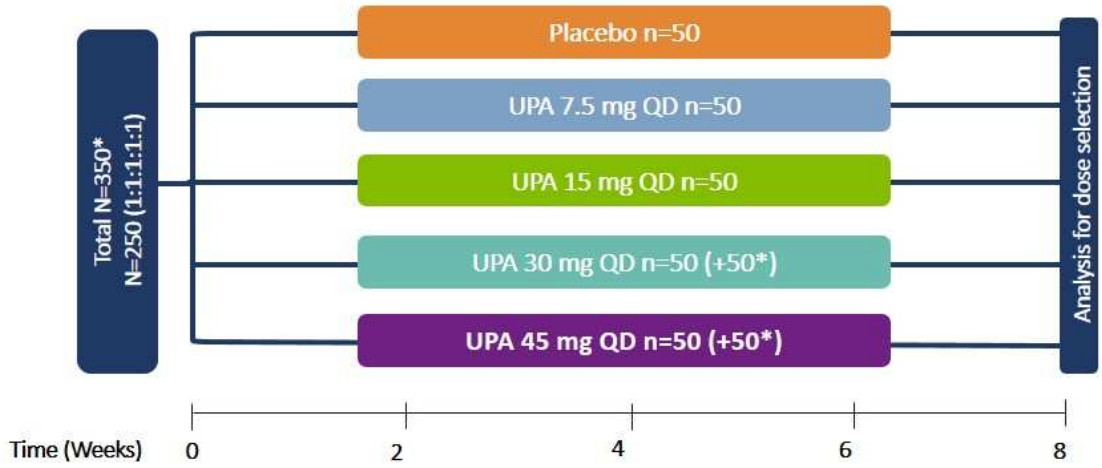
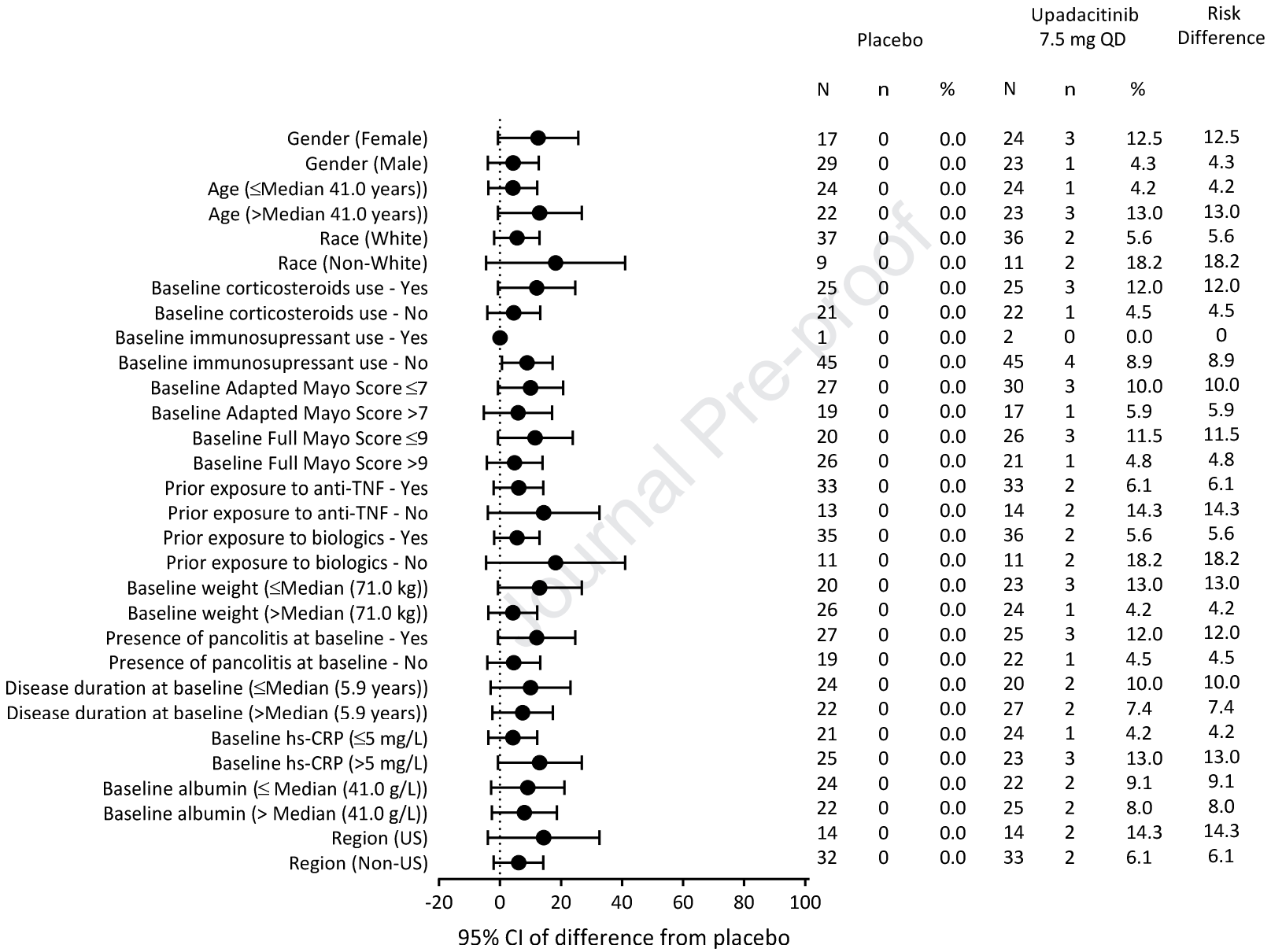
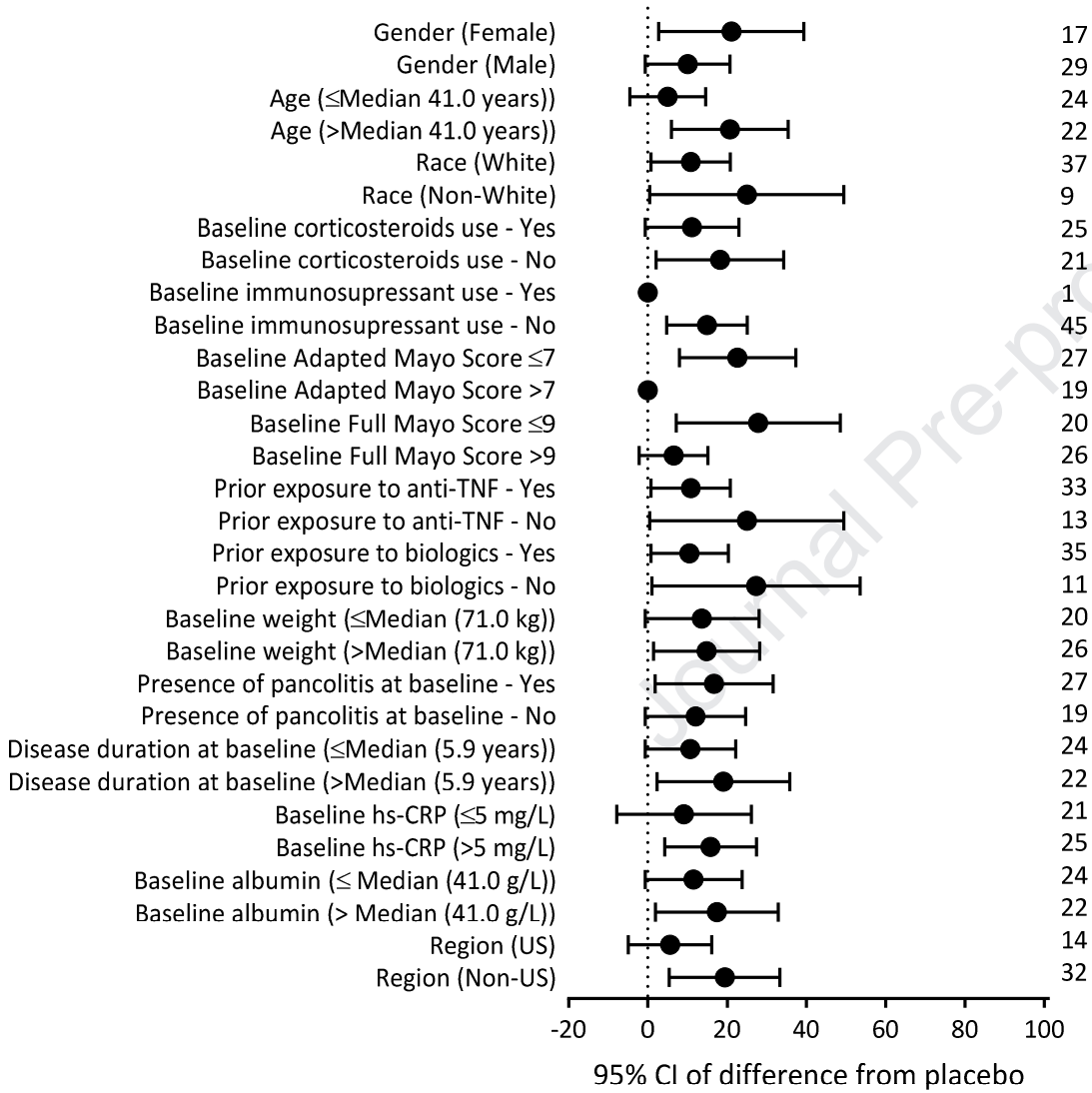
Figure S1. U-ACHIEVE study 1 design. QD=once daily; UPA=upadacitinib



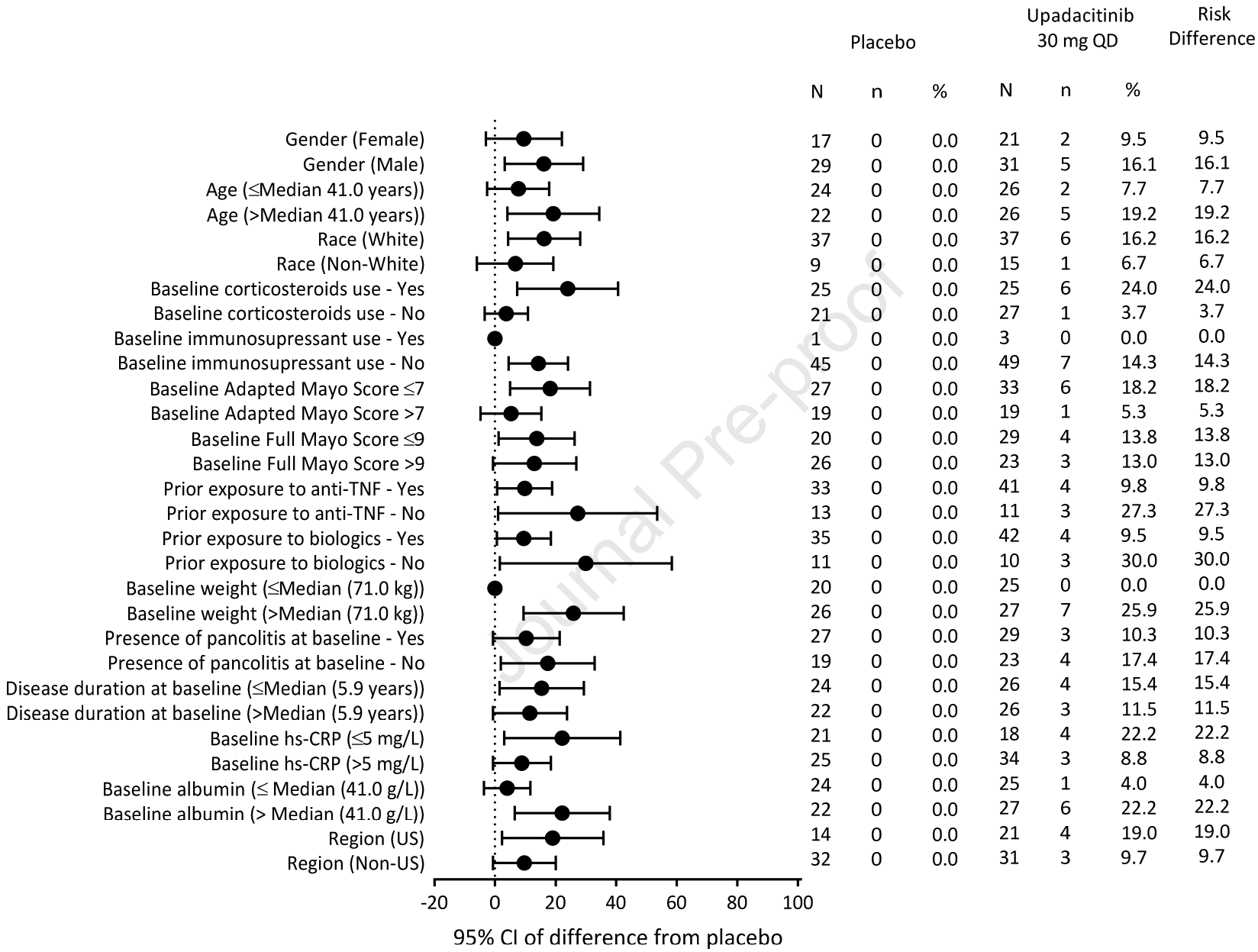
* During the analysis period for part 1, 132 additional subjects were enrolled in the 30 mg QD and 45 mg QD treatment groups.

Figure S2. Proportion of patients with clinical remission according to the Adapted Mayo score at Week 8 in the pre-specified subgroup analyses in the U-ACHIEVE study 1 part 1





	Placebo			Upadacitinib 15 mg QD			Risk Difference
	N	n	%	N	n	%	
Gender (Female)	17	0	0.0	19	4	21.1	21.1
Gender (Male)	29	0	0.0	30	3	10.0	10.0
Age (≤Median 41.0 years))	24	0	0.0	20	1	5.0	5.0
Age (>Median 41.0 years))	22	0	0.0	29	6	20.7	20.7
Race (White)	37	0	0.0	37	4	10.8	10.8
Race (Non-White)	9	0	0.0	12	3	25.0	25.0
Baseline corticosteroids use - Yes	25	0	0.0	27	3	11.1	11.1
Baseline corticosteroids use - No	21	0	0.0	22	4	18.2	18.2
Baseline immunosupressant use - Yes	1	0	0.0	2	0	0.0	0.0
Baseline immunosupressant use - No	45	0	0.0	47	7	14.9	14.9
Baseline Adapted Mayo Score ≤7	27	0	0.0	31	7	22.6	22.6
Baseline Adapted Mayo Score >7	19	0	0.0	0	0	0.0	0.0
Baseline Full Mayo Score ≤9	20	0	0.0	18	5	27.8	27.8
Baseline Full Mayo Score >9	26	0	0.0	31	2	6.5	6.5
Prior exposure to anti-TNF - Yes	33	0	0.0	37	4	10.8	10.8
Prior exposure to anti-TNF - No	13	0	0.0	12	3	25.0	25.0
Prior exposure to biologics - Yes	35	0	0.0	38	4	10.5	10.5
Prior exposure to biologics - No	11	0	0.0	11	3	27.3	27.3
Baseline weight (≤Median (71.0 kg))	20	0	0.0	22	3	13.6	13.6
Baseline weight (>Median (71.0 kg))	26	0	0.0	27	4	14.8	14.8
Presence of pancolitis at baseline - Yes	27	0	0.0	24	4	16.7	16.7
Presence of pancolitis at baseline - No	19	0	0.0	25	3	12.0	12.0
Disease duration at baseline (≤Median (5.9 years))	24	0	0.0	28	3	10.7	10.7
Disease duration at baseline (>Median (5.9 years))	22	0	0.0	21	4	19.0	19.0
Baseline hs-CRP (≤5 mg/L)	21	0	0.0	11	1	9.1	9.1
Baseline hs-CRP (>5 mg/L)	25	0	0.0	38	6	15.8	15.8
Baseline albumin (≤ Median (41.0 g/L))	24	0	0.0	26	3	11.5	11.5
Baseline albumin (> Median (41.0 g/L))	22	0	0.0	23	4	17.4	17.4
Region (US)	14	0	0.0	18	1	5.6	5.6
Region (Non-US)	32	0	0.0	31	6	19.4	19.4



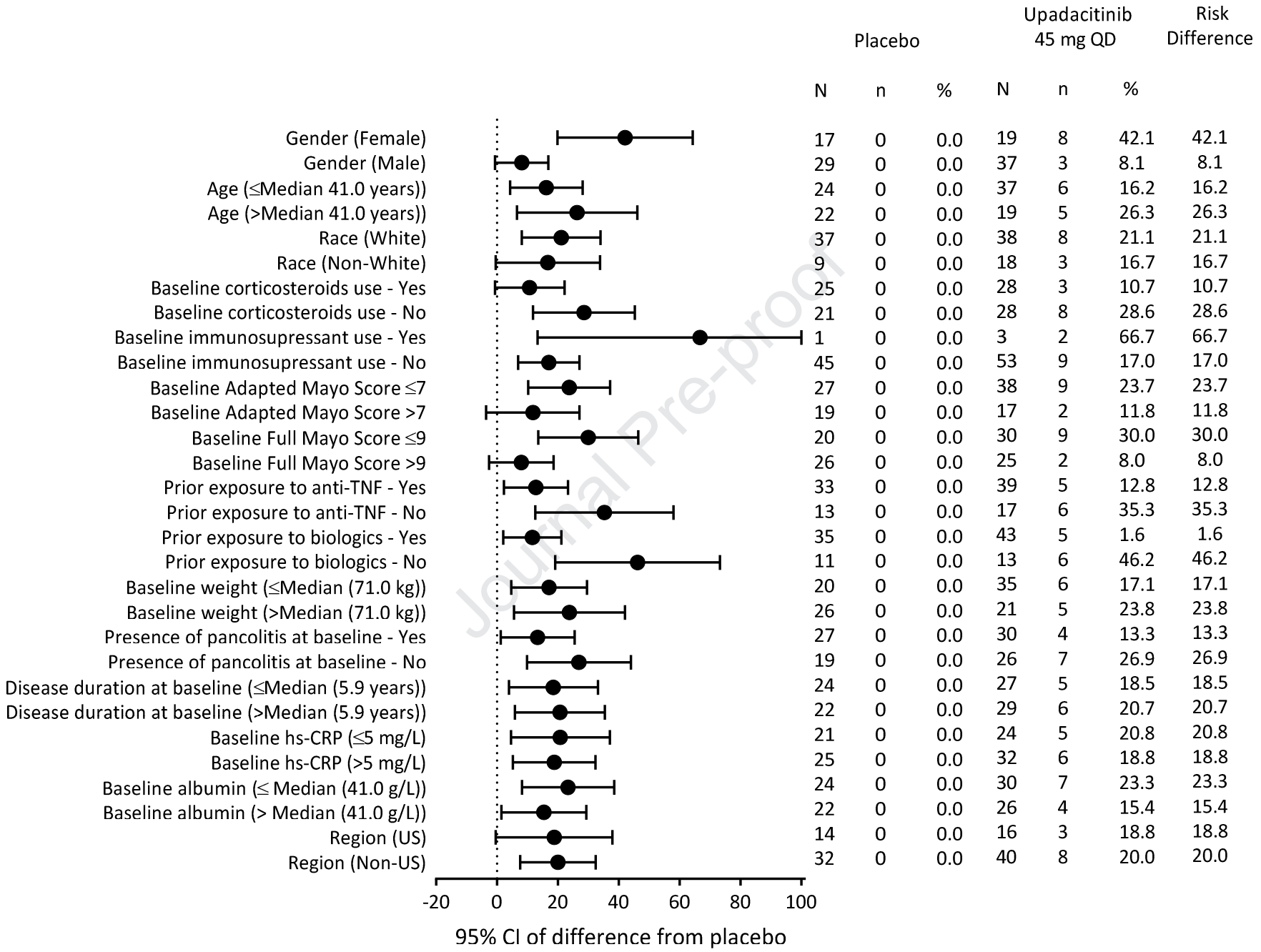


Table S1. Stool frequency subscore and Rectal bleeding subscore at Week 8 in the U-ACHIEVE study 1 part 1

		Upadacitinib			
	Placebo	**7.5 mg QD**	**15 mg QD**	**30 mg QD**	**45 mg QD**
Adapted Mayo Score Component at week 8, n (%)	**N=46**	**N=47**	**N=49**	**N=52**	**N=56**
Stool Frequency Subscore ≤1	6 (13.0)	16 (34.0)	13 (26.5)	19 (36.5)	26 (46.4)
Rectal Bleeding Subscore =0	12 (26.1)	17 (36.2)	20 (40.8)	27 (51.9)	33 (58.9)

Table S2. MCP-Mod dose-response modeling in the U-ACHIEVE study 1 part 1

Outcome	Rate	Models, p-value
Clinical remission according to the Adapted Mayo score	Placebo: 0% 7.5 mg QD: 8.5% 15 mg QD: 14.3% 30 mg QD: 13.5% 45 mg QD: 19.6%	Exponential: 0.147 E_{max}: 0.0404 $SigE_{max}$: 0.0642 Log-Linear: 0.0328 Logistic: 0.107
Endoscopic improvement	Placebo: 2.2% 7.5 mg QD: 14.9% 15 mg QD: 30.6% 30 mg QD: 26.9% 45 mg QD: 35.7%	Exponential: 0.0765 $E_{max:}$ 0.0037 $SigE_{max}$: 0.0094 Log-Linear: 0.0023 Logistic: 0.0222

QD= once daily. MCP-Mod= Multiple Comparison Procedure and Modeling.

In addition to estimating the relative treatment effect of upadacitinib to placebo, an important goal of this phase 2b study was to establish dose-response relationships to facilitate the dose selection for future phase 3 trials. Multiple Comparison Procedure and dose-response Modeling (MCP-Mod) with a pre-defined group of candidate dose-response curves will be tested against flat dose-response curve to best characterize the dose-response relationship.

Steps of MCP-Mod:
1.Choose a candidate set of S models.
2.Compute the optimum contrast for each model.
3.Use contrast test to find the significant Tmodels while preserving FWER.
4.Use AIC criteria to find the most significant model from the significant Tmodels found from Step 3.
5.Use the model found from Step 4 to fit observed data from the study and make inference (e.g., to find Minimum Effective Dose (MED) or the dose achieving certain amount of maximum effect), or use all significant models to make inference about the weighted target dose of interest.

ADDPLAN or R will be used to evaluate different dose-response models and to make dose recommendation.

Table S3. Additional efficacy endpoints in the U-ACHIEVE Study 1 part 1 Protocol

Efficacy endpoints	**Reported in this manuscript or supplement**	**Nor reported in this manuscript or supplement**
Proportion of subjects who are taking corticosteroids at Baseline and are steroid-free over time		**X**
Proportion of subjects who achieve clinical remission according to the Adapted Mayo score over time		**X**
Proportion of subjects achieving clinical remission according to the Partial Mayo score over time		**X**
Proportion of subjects achieving clinical remission defined as stool frequency subscore ≤ 1, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1 with absence of friability over time		**X**
Proportion of subjects achieving clinical remission defined as stool frequency subscore of 0, rectal bleeding subscore of 0, and endoscopic subscore of 0 over time		**X**
Proportion of subjects achieving clinical response according to the Partial Mayo score over time		**X**
Proportion of subjects with stool frequency subscore ≤ 1 over time		**X**
Proportion of subjects with rectal bleeding subscore of 0 over time		**X**
Proportion of subjects with fecal calprotectin below 150 mg/kg over time		**X**
Proportion of subjects with IBDQ response (increase of IBDQ ≥ 16 from Baseline) over time		**X**
Change from Baseline in hs-CRP over time	**X**	

Change from Baseline in fecal calprotectin over time	**X**	
Change from Baseline in corticosteroid dose over time		**X**
Change from Baseline in Adapted Mayo score, Mayo score, Partial Mayo score and Mayo subscores over time		**X**
Change from Baseline in UCEIS score over time		**X**
Change from Baseline in histologic score over time		**X**
Change from Baseline in laboratory and nutritional parameters (e.g. hemoglobin, hematocrit, albumin, total protein concentration, and weight)		**X**
Change from Baseline in subject-reported stool frequency (absolute values)		**X**
Change from Baseline in IBDQ score over time		**X**
Change from Baseline in EQ-5D-5L score over time		**X**
Change from Baseline in WPAI scores over time		**X**
Change from Baseline in SF-36 PCS, MCS components and domain scores over time		**X**
Change in PGIC score over time		**X**
Change from Baseline in FACIT-F score over time		**X**
Change from Baseline in UC-SQ score over time		**X**
Health care resource utilization (UC-related hospitalizations and surgeries) during the study		**X**

Table S4. Efficacy outcomes by prior biologic exposure in the U-ACHIEVE study 1 part 1

		Upadacitinib			
	Placebo	**7.5 mg QD**	**15 mg QD**	**30 mg QD**	**45 mg QD**
End Point	**N=46**	**N=47**	**N=49**	**N=52**	**N=56**
Clinical remission according to the Adapted Mayo score at week 8					
Bio-IR, N	34	34	36	40	42
n (%)	0	2 (5.9)	3 (8.3)	4 (10.0)	5 (11.9)
Risk difference (95% CI)		5.9 (-2.0 to 13.8)	8.3 (-0.7 to 17.4)	10.0 (0.7 to 19.3)	11.9 (2.1 to 21.7)
P value		0.493	0.120	0.120	0.061
Non Bio-IR, N	12	13	13	12	14
n (%)	0	2 (15.4)	4 (30.8)	3 (25.0)	6 (42.9)
Risk difference (95% CI)		15.4 (-4.2 to 35.0)	30.8 (5.7 to 55.9)	25.0 (0.5 to 49.5)	42.9 (16.9 to 68.8)
P value		0.480	0.096	0.217	0.017
Endoscopic improvement at week 8					
Bio-IR, N	34	34	36	40	42
n (%)	0	3 (8.8)	9 (25.0)	8 (20.0)	11 (26.2)
Risk difference (95% CI)		8.8 (-0.7 to 18.4)	25.0 (10.9 to 39.1)	20.0 (7.6 to 32.4)	26.2 (12.9 to 39.5)

P value		0.239	0.002	0.006	<0.001
Non Bio-IR	12	13	13	12	14
n (%)	1 (8.3)	4 (30.8)	6 (46.2)	6 (50.0)	9 (64.3)
Risk difference (95% CI)		22.4 (-7.1 to 52.0)	37.8 (6.5 to 69.1)	41.7 (9.3 to 74.0)	56.0 (26.4 to 85.5)
P value		0.322	0.073	0.069	0.005
Clinical remission according to the full Mayo score at week 8					
Bio-IR, N	34	34	36	40	42
n (%)	0	2 (5.9)	1 (2.8)	3 (7.5)	4 (9.5)
Risk difference (95% CI)		5.9 (-2.0 to 13.8)	2.8 (-2.6 to 8.1)	7.5 (-0.7 to 15.7)	9.5 (0.6 to 18.4)
P value		0.493	1.000	0.245	0.123
Non Bio-IR, N	12	13	13	12	14
n (%)	0	2 (15.4)	4 (30.8)	3 (25.0)	7 (50.0)
Risk difference (95% CI)		15.4 (-4.2 to 35.0)	30.8 (5.7 to 55.9)	25.0 (0.5 to 49.5)	50.0 (23.8 to 76.2)
P value		0.480	0.096	0.217	0.006
Clinical response according to the Adapted Mayo score at week 8					
Bio-IR, N	34	34	36	40	42

n (%)	2 (5.9)	8 (23.5)	13 (36.1)	13 (32.5)	17 (40.5)
Risk difference (95% CI)		17.6 (1.3 to 34.0)	30.2 (12.7 to 47.8)	26.6 (10.1 to 43.1)	34.6 (17.8 to 51.4)
P value		0.040	0.002	0.005	<0.001
Non Bio-IR, N	12	13	13	12	14
n (%)	4 (33.3)	6 (46.2)	9 (69.2)	10 (83.3)	11 (78.6)
Risk difference (95% CI)		12.8 (-25.2 to 50.8)	35.9 (-0.7 to 72.5)	50.0 (16.0 to 84.0)	45.2 (11.0 to 79.5)
P value		0.688	0.073	0.013	0.020
Clinical response according to the Partial Mayo score at week 2					
Bio-IR, N	34	34	36	40	42
n (%)	5 (14.7)	6 (17.6)	11 (30.6)	14 (35.0)20.3 (1.3	22 (52.4)
Risk difference (95% CI)		2.9 (-14.5 to 20.4)	15.8 (-3.3 to 35.0)	to 39.3)	37.7 (18.4 to 56.9)
P value		0.742	0.114	0.046	<0.001
Non Bio-IR, N	12	13	13	12	14
n (%)	2 (16.7)	5 (38.5)	7 (53.8)	5 (41.7)	9 (64.3)
Risk difference (95% CI)		21.8 (-12.0 to 55.6)	37.2 (2.8 to 71.5)	25.0 (-10.0 to 60.0)	47.6 (14.8 to 80.4)
P value		0.378	0.097	0.371	0.014
Change in the full Mayo score from Baseline to week					

8, median (range)					
Bio-IR, N	30	33	34	36	37
	-0.300	-2.000	-2.500	-2.550	-4.300
	(-5.30 to 4.00)	(-8.00 to 1.00)	(-8.30 to 1.30)	(-8.70 to 2.00)	(-10.00 to 3.00)
Non Bio-IR, N	12	13	13	11	14
	-2.150	-3.700	-5.400	-6.300	-5.850
	(-5.30 to 1.60)	(-10.70 to 3.30)	(-8.70 to 1.30)	(-11.00 to -2.70)	(-9.00 to 1.00)
Endoscopic remission at week 8					
Bio-IR, N	34	34	36	40	42
n (%)	0	1 (2.9)	0	1 (2.5)	5 (11.9)
Risk difference (95% CI)		2.9 (-2.7 to 8.6)		2.5 (-2.3 to 7.3)	11.9 (2.1 to 21.7)
P value		1.000		1.000	0.061
Non Bio-IR, N	12	13	13	12	14
n (%)	0	2 (15.4)	2 (15.4)	4 (33.3)	5 (35.7)
Risk difference (95% CI)		15.4 (-4.2 to 35.0)	15.4 (-4.2 to 35.0)	33.3 (6.7 to 60.0)	35.7 (10.6 to 60.8)
P value		0.480	0.480	0.093	0.042
Histologic improvement at week 8					
Bio-IR, N	34	34	36	40	42

n (%)	3 (8.8)	7 (20.6)	15 (41.7)	15 (37.5)	20 (47.6)
Risk difference (95% CI)		11.8 (-4.8 to 28.4)	32.8 (14.1 to 51.6)	28.7 (10.9 to 46.5)	38.8 (20.9 to 56.7)
P value		0.171	0.002	0.004	<0.001
Non Bio-IR, N	12	13	13		
n (%)	0	8 (61.5)	10 (76.9)	8 (66.7)	7 (50.0)
Risk difference (95% CI)		61.5 (35.1 to 88.0)	76.9 (54.0 to 99.8)	66.7 (40.0 to 93.3)	50.0 (23.8 to 76.2)
P value		0.002	<0.001	0.001	0.006

Biologic inadequate response (Bio-IR)=patients who had inadequate response, loss of response or intolerance to an TNF antagonist or other biologic agent; Non biologic inadequate response (Non Bio-IR)= patients who had no inadequate response, loss of response or intolerance to an TNF antagonist or other biologic agent

Table S5. Change from baseline in hs-CRP in the U-ACHIEVE study 1 part 1

		Upadacitinib			
Visit Treatment,	**Placebo**	**7.5 mg QD**	**15 mg QD**	**30 mg QD**	**45 mg QD**
Median (range)	**N=46**	**N=47**	**N=49**	**N=52**	**N=56**
Week 2	0.095 (-15.98, 30.10)	-2.150 (-20.58, 4.30)	-5.275 (-115.37, 36.84)	-4.950 (-45.00, 2.93)	-3.090 (-61.73, 19.69)
Week 4	0.115 (-20.70, 86.43)	-2.350 (-20.44, 18.86)	-5.330 (-115.27, 32.53)	-4.900 (-49.38, 115.59)	-3.405 (-60.69, 28.50)
Week 8	1.135 (-21.27, 168.76)	-0.340 (-16.20, 10.00)	-4.920 (-115,34, 20.94)	-3.420 (-45.00, 24.12)	-4.355 (-64.81, 41.00)

QD=once daily

Table S6. Change from baseline in fecal calprotectin in the U-ACHIEVE study 1 part 1

		Upadacitinib			
Visit Treatment,	**Placebo**	**7.5 mg QD**	**15 mg QD**	**30 mg QD**	**45 mg QD**
Median (range)	**N=46**	**N=47**	**N=49**	**N=52**	**N=56**
Week 2	-365.0 (-11820, 8522)	-382.5 (-6593, 13402)	-662.0 (-15174, 25639)	132.0 (-17838, 5341)	-659.0 (-16528, 11610)
Week 8	154.0 (-5896, 16680)	-338.0 (-17313, 3521)	-742.0 (-18475, 18063)	-1093.0 (-18018, 4059)	-720.0 (-16830, 24916)

QD=once daily

Table S7: Efficacy outcomes in the U-ACHIEVE Study 1 part 1 trial excluding the 12 patients with randomization error

		Upadacitinib			
	Placebo	**7.5 mg QD**	**15 mg QD**	**30 mg QD**	**45 mg QD**
End Point	**N=46**	**N=47**	**N=49**	**N=46**	**N=50**
Clinical remission according to the Adapted Mayo score at Week 8					
Overall					
n (%)	0	4 (8.5)	7 (14.3)	7 (15.2)	9 (18.0)
Adjusted risk difference (95% CI)		8.1 (-0.1 to 16.3)	12.7 (2.7 to 22.6)	13.5 (3.1 to 23.8)	17.7 (5.9 to 29.5)
P value		0.052	0.013	0.011	0.003
Bio-IR					
n (%)	0	2 (5.9)	3 (8.3)	4 (11.4)	4 (10.5)
Risk difference (95% CI)		5.9 (-2.0 to 13.8)	8.3 (-0.7 to 17.4)	11.4 (0.9 to 22.0)	10.5 (0.8 to 20.3)
P value		0.493	0.240	0.114	0.117
Non Bio-IR					
n (%)	0	2 (15.4)	4 (30.8)	3 (27.3)	5 (41.7)
Risk difference (95% CI)		15.4 (-4.2 to 35.0)	30.8 (5.7 to 55.9)	27.3 (1.0 to 53.6)	41.7 (13.8 to 69.6)
P value		0.480	0.096	0.093	0.037

Endoscopic improvement at Week 8					
Overall					
n (%)	1 (2.2)	7 (14.9)	15 (30.6)	13 (28.3)	18 (36.0)
Adjusted risk difference (95% CI)		12.9 (1.1 to 24.7)	26.9 (12.6 to 41.2)	26.1 (11.7 to 40.6)	36.3 (19.6 to 52.9)
P value		0.033	<0.001	<0.001	<0.001
Bio-IR					
n (%)	0	3 (8.8)	9 (25.0)	7 (20.0)	10 (26.3)
Risk difference (95% CI)		8.8 (-0.7 to 18.4)	25.0 (10.9 to 39.1)	20.0 (6.7 to 33.3)	26.3 (12.3 to 40.3)
P value		0.239	0.002	0.011	0.001
Non Bio-IR					
n (%)	1 (8.3)	4 (30.8)	6 (46.2)	6 (54.5)	8 (66.7)
Risk difference (95% CI)		22.4 (-7.1 to 52.0)	37.8 (6.5 to 69.1)	46.2 (12.9 to 79.5)	58.3 (27.4 to 89.3)
P value		0.322	0.073	0.027	0.009
Clinical remission according to the full Mayo score at Week 8					
Overall					
n (%)	0	4 (8.5)	5 (10.2)	6 (13.0)	9 (18.0)
Adjusted risk difference (95% CI)		8.1 (-0.1 to 16.3)	9.0 (1.0 to 17.0)	12.7 (2.4 to 23.0)	18.6 (6.8 to 30.5)

P value		0.052	0.027	0.016	0.002
Bio-IR					
n (%)	0	2 (5.9)	1 (2.8)	3 (8.6)	3 (7.9)
Risk difference (95% CI)		5.9 (-2.0 to 13.8)	2.8 (-2.6 to 8.1)	8.6 (-0.7 to 17.8)	7.9 (-0.7 to 16.5)
P value		0.493	1.000	0.239	0.242
Non Bio-IR					
n (%)	0	2 (15.4)	4 (30.8)	3 (27.3)	6 (50.0)
Risk difference (95% CI)		15.4 (-4.2 to 35.0)	30.8 (5.7 to 55.9)	27.3 (1.0 to 53.6)	50.0 (21.7 to 78.3)
P value		0.480	0.096	0.093	0.014
Clinical response according to the Adapted Mayo score at Week 8					
Overall					
n (%)	6 (13.0)	14 (29.8)	22 (44.9)	21 (45.7)	22 (44.0)
Adjusted risk difference (95% CI)		16.0 (0.3 to 31.7)	30.2 (12.5 to 47.8)	31.7 (13.9 to 49.5)	33.6 (15.2 to 52.0)
P value		0.046	<0.001	<0.001	<0.001
Bio-IR					
n (%)	2 (5.9)	8 (23.5)	13 (36.1)	12 (34.3)	13 (34.2)
Risk difference (95% CI)		17.6 (1.3 to 34.0)	30.2 (12.7 to 47.8)	28.4 (10.8 to 46.0)	28.3 (11.3 to 45.4)

P value		0.040	0.002	0.003	0.003
Non Bio-IR					
n (%)	4 (33.3)	6 (46.2)	9 (69.2)	9 (81.8)	9 (75.0)
Risk difference (95% CI)		12.8 (-25.2 to 50.8)	35.9 (-0.7 to 72.5)	48.5 (13.4 to 83.6)	41.7 (5.5 to 77.9)
P value		0.688	0.073	0.036	0.041

Biologic inadequate response (Bio-IR)=patients who had inadequate response, loss of response or intolerance to an TNF antagonist or other biologic agent; Non biologic inadequate response (Non Bio-IR)= patients who had no inadequate response, loss of response or intolerance to an TNF antagonist or other biologic agent. QD=once daily; CI=confidence interval

The confidence intervals have not been adjusted for multiplicity and inferences drawn from the intervals may not be reproducible.

Table S8. Patient demographics and baseline disease characteristics in patients from U-ACHIEVE study 1 part 1 and part 2

		Upadacitinib			
	Placebo	**7.5 mg QD**	**15 mg QD**	**30 mg QD**	**45 mg QD**
Characteristic	**n=46**	**n=47**	**n=49**	**n=117**	**n=123**
Female, n (%)	17 (37.0)	24 (51.1)	19 (38.8)	47 (40.2)	44 (35.8)
Age, years, median (range)	40.0 (21- 67)	41.0 (18- 75)	47.0 (22-71)	41.0 (19.0-75)	39.0 (19-74)
UC duration, years, median (range)	5.86 (0.4-30.8)	6.59 (0.8-43.7)	4.58 (0.2-43.0)	7.03 (0.3-28.0)	5.99 (0.2-35.3)
Disease extent, n (%)					
Rectosigmoid	0	1 (2.1)	0	0	0
Left-sided colitis	18 (39.1)	20 (42.6)	25 (51.0)	53 (45.3)	54 (43.9)
Extensive colitis or pancolitis	28 (60.9)	26 (55.3)	24 (49.0)	64 (54.7)	69 (56.1)
Total Mayo score, median (range)	9.3 (7-12)	9.0 (7-12)	9.7 (7-12)	9.0 (5-12)	9.0 (6-12)
Adapted Mayo score, median (range)	6.9 (5-9)	7.0 (5-9)	7.0 (4-9)	6.7 (3-9)	6.9 (4-9)
Baseline corticosteroid use, n (%)	26 (56.5)	25 (53.2)	27 (55.1)	50 (42.7)	53 (43.1)
Baseline immunosuppressant use, n (%)	1 (2.2)	2 (4.3)	2 (4.1)	3 (2.6)	5 (4.1)
Baseline aminosalicylates use, n (%)	26 (56.5)	27 (57.4)	25 (51.0)	64 (54.7)	67 (54.5)

Table S9. Stool frequency subscore and Rectal bleeding subscore at Week 8 in the U-ACHIEVE study 1 part 1 and part 2

		Upadacitinib			
Adapted Mayo Score Component at Week 8, n (%)	**Placebo N=46**	**7.5 mg QD N=47**	**15 mg QD N=49**	**30 mg QD N=52**	**45 mg QD N=56**
Stool Frequency Subscore ≤1	6 (13.0)	15 (31.9)	13 (26.5)	46 (39.3)	54 (43.9)
Rectal Bleeding Subscore =0	12 (26.1)	18 (38.3)	20 (40.8)	73 (62.4)	69 (56.1)

Table S10: Efficacy outcomes in the U-ACHIEVE study 1 part 1 and part 2

		Upadacitinib			
	Placebo	**7.5 mg QD**	**15 mg QD**	**30 mg QD**	**45 mg QD**
End Point	**N=46**	**N=47**	**N=49**	**N=117**	**N=123**
Clinical remission according to the Adapted Mayo score at week 8					
n (%)	0	4 (8.5)	7 (14.3)	25 (21.4)	22 (17.9)
Adjusted risk difference (95% CI)		8.2 (-0.1 to 16.6)	13.5 (3.3 to 23.8)	21.2 (8.9 to 33.4)	17.8 (6.9 to 28.8)
P value		0.054	0.010	<0.001	0.001
Endoscopic improvement at week 8					
n (%)	1 (2.2)	7 (14.9)	15 (30.6)	40 (34.2)	42 (34.1)
Adjusted risk difference (95% CI)		12.9 (1.1 to 24.8)	27.6 (13.1 to 42.1)	31.1 (16.8 to 45.3)	33.0 (18.2 to 47.8)
P value		0.033	<0.001	<0.001	<0.001
Clinical response according to the Adapted Mayo score at week 8					
n (%)	6 (13.0)	13 (27.7)	22 (44.9)	63 (53.8)	65 (52.8)
Adjusted risk difference (95% CI)		13.8 (-1.4 to 29.0)	31.1 (13.8 to 48.4)	38.2 (22.4 to 54.0)	40.1 (23.5 to 56.7)
P value		0.074	<0.001	<0.001	<0.001

Clinical response according to the Partial Mayo score					
at week 2					
n (%)	7 (15.2)	11 (23.4)	18 (36.7)	52 (44.4)	63 (51.2)
Adjusted risk difference (95% CI)		8.0 (-8.6 to 24.7)	20.3 (2.7 to 37.8)	29.2 (12.8 to 45.6)	39.6 (22.7 to 56.5)
P value		0.345	0.024	<0.001	<0.001
Endoscopic remission at week 8					
n (%)	0	3 (6.4)	2 (4.1)	19 (16.2)	20 (16.3)
Adjusted risk difference (95% CI)		6.5 (-0.8 to 13.7)	3.8 (-2.0 to 9.6)	16.0 (5.8 to 26.1)	15.3 (4.6 to 25.9)
P value		0.079	0.199	0.002	0.005
Histologic improvement at week 8					
n (%)	3 (6.5)	16 (34.0)	25 (51.0)	55 (47.0)	62 (50.4)
Adjusted risk difference (95% CI)		27.4 (10.3 to 44.5)	43.6 (25.4 to 61.8)	39.1 (23.3 to 54.9)	45.1 (28.1 to 62.2)
P value		0.002	<0.001	<0.001	<0.001

QD=once daily; CI=confidence interval

The confidence intervals have not been adjusted for multiplicity and inferences drawn from the intervals may not be reproducible

Table S11: Safety outcomes at Week 8 in patients from U-ACHIEVE study 1 part 1 and part 2

		Upadacitinib			
Adverse event	**Placebo n=46**	**7.5 mg QD n=47**	**15 mg QD n=49**	**30 mg QD n=117**	**45 mg QD n=123**
Any AE, n (%)	33 (71.7)	30 (63.8)	30 (61.2)	81 (69.2)	79 (64.2)
Colitis ulcerative, n (%)	6 (13.0)	1 (2.1)	3 (6.1)	8 (6.8)	6 (4.9)
Any serious AE, n (%)	5 (10.9)	0	2 (4.1)	5 (4.3)	6 (4.9)
Any AE leading to discontinuation, n (%)	4 (8.7)	1 (2.1)	2 (4.1)	5 (4.3)	7 (5.7)
Infections and infestations, n (%)	16 (34.8)	9 (19.1)	10 (20.4)	24 (20.5)	28 (22.8)
Serious infections	2 (4.3)	0	1 (2.0)	1 (0.9)	2 (1.6)
Opportunistic infection	1 (2.2)	0	0	0	1 (0.8)
Herpes zoster	0	0	0	0	1 (0.8)
Any hepatic disorder, n (%)	1 (2.2)	2 (4.3)	0	0	6 (4.9)
Anemia, n (%)	3 (6.5)	1 (2.1)	4 (8.2)	5 (4.3)	5 (4.1)
Any creatine phosphokinase elevation, n (%)	0	0	3 (6.1)	4 (3.4)	8 (6.5)
Adjudicated cardiovascular events, n (%)	0	0	0	0	1 (0.8)
Abnormal laboratory test results					
Hemoglobin (g/L)					
Grade 3 (<80)	1/46 (2.2)	2/47 (4.3)	2/49 (4.1)	3/115 (2.6)	1/122 (0.8)
Lymphocytes ($x10^9$/L)					
Grade 3 (<0.5-0.2)	0/46	2/47 (4.3)	1/49 (2.0)	4/115 (3.5)	4/122 (3.3)
Grade 4 (<0.2)	0/46	0/47	0/49	0/115	0/122

Neutrophils (x10^9/L)					
Grade 3 (0.5-<1.0)	0/46	0/47	1/49 (2.0)	1/115 (0.9)	4/122 (3.3)
Grade 4 (<0.5)	0/46	0/47	0/49	0/115	0/122
Alanine aminotransferase (U/L)					
Grade 3 (5.0-<20.0*ULN)	0/46	0/47	0/49	0/117	0/122
Grade 4 (>20.0*ULN)	0/46	0/47	0/49	0/117	0/122
Aspartate aminotransferase (U/L)					
Grade 3 (5.0-<20.0*ULN)	0/46	0/47	0/49	0/117	1/122 (0.8)
Grade 4 (>20.0*ULN)	0/46	0/47	0/49	0/117	0/122
Creatine Kinase (U/L)					
Grade 3 (>5.0-10.0 x ULN)	0/46	0/47	1/49 (2.0)	1/117 (0.9)	4/121 (3.3)
Grade 4 (>10.0 x ULN)	0/46	0/47	1/49 (2.0)	1/117 (0.9)	3/121 (2.5)

AE=adverse event. QD=once daily.

What you need to know:

BACKGROUND AND CONTEXT: Studies are needed to evaluate the efficacy and safety of upadacitinib, an oral selective inhibitor of Janus kinase 1, for treatment of ulcerative colitis (UC).

NEW FINDINGS: In a phase 2b trial, 8 weeks treatment with upadacitinib was more effective than placebo for induction of remission in patients with moderately to severely active UC.

LIMITATIONS: This study comprised 250 patients with UC; further studies are needed.

IMPACT: Upadacitinib might be used as a new therapy in patients with moderate to severe UC.

Lay Summary: In a clinical trial, the drug upadacitinib was effective in inducing remission in patients with moderate to severe UC.