Gastroenterology 2022;162:1891–1910

Higher vs Standard Adalimumab Induction and Maintenance Dosing Regimens for Treatment of Ulcerative Colitis: SERENE UC Trial Results

Julián Panés,[1] Jean-Frederic Colombel,[2] Geert R. D'Haens,[3] Stefan Schreiber,[4] Remo Panaccione,[5] Laurent Peyrin-Biroulet,[6] Edward V. Loftus Jr,[7] Silvio Danese,[8] Satoshi Tanida,[9] Yusuke Okuyama,[10] Edouard Louis,[11] Alessandro Armuzzi,[12,*] Marc Ferrante,[13] Harald Vogelsang,[14] Toshifumi Hibi,[15] Mamoru Watanabe,[16] Jessica Lefebvre,[17] Tricia Finney-Hayward,[18] Yuri Sanchez Gonzalez,[17] Thao T. Doan,[17] Nael M. Mostafa,[17] Kimitoshi Ikeda,[19] Wangang Xie,[17] Bidan Huang,[17] Joel Petersson,[17] Jasmina Kalabic,[20] Anne M. Robinson,[17] and William J. Sandborn[21]

[1]Hospital Clinic de Barcelona, August Pi i Sunyer Biomedical Research Institute, Biomedical Research Networking Center in Hepatic and Digestive Diseases, Barcelona, Spain; [2]Icahn School of Medicine at Mt Sinai, New York, New York; [3]Amsterdam Gastroenterology Endocrinology Metabolism and Gastroenterology and Hepatology Departments, Amsterdam University Medical Centers, Amsterdam, The Netherlands; [4]Department of Internal Medicine, University Hospital Schleswig-Holstein, Kiel University, Kiel, Germany; [5]Department of Medicine, University of Calgary, Calgary, Alberta, Canada; [6]Department of Gastroenterology, Centre Hospitalier Régional Universitaire de Nancy, Nutrition-Genetics and Exposure to Environmental Risks, Institut National de la Santé et de la Recherche Médicale, University of Lorraine, Nancy, France; [7]Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; [8]Gastroenterology and Endoscopy, Istituto di Ricovero e Cura a Carattere Scientifico, Ospedale San Raffaele and University Vita-Salute San Raffaele, Milan, Italy; [9]Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan; [10]Department of Gastroenterology, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Japan; [11]Department of Gastroenterology, University Hospital Centre Hospitalier Universitaire de Liège, Liège, Belgium; [12]Inflammatory Bowel Diseases Unit, Fondazione Policlinico Universitario A. Gemelli Istituto di Ricovero e Cura a Carattere Scientifico, Rome, Italy; [13]Department of Gastroenterology and Hepatology, University Hospitals Leuven, Katholieke Universiteit Leuven, Leuven, Belgium; [14]Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria; [15]Center for Advanced Inflammatory Bowel Disease Research and Treatment, Kitasato University, Kitasato Institute Hospital, Tokyo, Japan; [16]Advanced Research Institute and Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Tokyo, Japan; [17]AbbVie Inc, North Chicago, Illinois; [18]AbbVie Ltd, Maidenhead, Berkshire, England, United Kingdom; [19]AbbVie GK, Minato-ku, Tokyo, Japan; [20]AbbVie Deutschland GmbH & Co KG, Ludwigshafen, Germany; and [21]Gastroenterology Department, University of California San Diego, La Jolla, California

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BACKGROUND & AIMS: SERENE UC (Study of a Novel Approach to Induction and Maintenance Dosing With Adalimumab in Patients With Moderate to Severe Ulcerative Colitis) evaluated the efficacy of higher adalimumab induction and maintenance dose regimens in patients with ulcerative colitis. **METHODS:** This phase 3, double-blind, randomized trial included induction and maintenance studies, with a main study (ex-Japan) and Japan substudy. Eligible patients (18–75 years, full Mayo score 6–12, centrally read endoscopy subscore 2–3) were randomized 3:2 to higher induction regimen (adalimumab 160 mg at weeks 0, 1, 2, and 3) or standard induction regimen (160 mg at week 0 and 80 mg at week 2); all received 40 mg at weeks 4 and 6. At week 8, all patients were rerandomized 2:2:1 (main study) to 40 mg every week (ew), 40 mg every other week (eow), or exploratory therapeutic drug monitoring; or 1:1 (Japan substudy) to 40 mg ew or 40 mg eow maintenance regimens. **RESULTS:** In the main study, 13.3% vs 10.9% of patients receiving the higher induction regimen vs standard induction regimen achieved clinical remission (full Mayo score $\leq$2 with no subscore $>$1) at week 8 (induction primary end point; $P = .265$); among week-8 responders, 39.5% vs 29.0% receiving 40 mg ew vs 40 mg eow achieved clinical remission at week 52 (maintenance primary end point; $P = .069$). In the integrated (main + Japan) population, 41.1% vs 30.1% of week-8 responders receiving 40 mg ew vs 40 mg eow achieved clinical remission at week 52 (nominal $P = .045$). Safety profiles were comparable between dosing regimens. **CONCLUSION:** Although primary end points were not met, a $>$10% absolute difference in clinical remission was demonstrated with higher adalimumab maintenance dosing. Higher dosing regimens were generally well tolerated and consistent with the known safety profile of adalimumab in ulcerative colitis. ClinicalTrials.gov, Number: NCT002209456.

CLINICAL AT

Keywords: Adalimumab; Monoclonal Antibody; Inflammatory Bowel Disease; Moderately to Severely Active Ulcerative Colitis; Clinical Trial Result.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Adalimumab is approved for moderately to severely active ulcerative colitis. SERENE UC evaluated higher vs standard adalimumab induction and maintenance dosing regimens and was conducted to fulfill post-marketing approval requirements.

NEW FINDINGS

Higher and standard induction adalimumab dosing did not differ in efficacy. In the integrated (ex-Japan + Japan) population, higher maintenance adalimumab dosing regimen demonstrated superior efficacy compared with the standard maintenance regimen.

LIMITATIONS

The study was not placebo-controlled. Study design differences (eg, rerandomization vs treat-through, central vs local endoscopy, steroid tapering vs continuation) limit comparisons with previous clinical trials of adalimumab in ulcerative colitis.

IMPACT

SERENE UC confirms the approved adalimumab induction-dosing regimen is appropriate. Clinical remission was ≥10% higher with weekly vs every-other-week maintenance dosing. Safety was consistent with the known safety profile.

Ulcerative colitis (UC), one of the major subtypes of inflammatory bowel disease, is idiopathic, chronic, and progressive in nature, and is associated with a substantial burden of disease and profound negative impact on health-related quality of life.[1] The efficacy of conventional treatments[2] for UC (eg, anti-inflammatory agents [mesalamine derivatives and corticosteroids] and/or immunosuppressives [thiopurines]) for achieving therapeutic goals (ie, abatement of inflammatory symptoms, induction/maintenance of clinical and endoscopic remission, and reduction of disability) is limited.[3]

Adalimumab is a subcutaneously administered recombinant human IgG1 monoclonal antibody that binds with high affinity and specificity to tumor necrosis factor (TNF)-α. Adalimumab is approved in the United States,[4] Europe,[5] Japan,[6] and elsewhere for treating adults with moderately to severely active UC with inadequate response to conventional therapy. Based on results from the 8-week, randomized, phase 3 ULTRA 1 (Ulcerative Colitis Long-Term Remission and Maintenance With Adalimumab 1) study (ClinicalTrials.gov, Number: NCT00385736), an induction dosing regimen of adalimumab 160 mg at week 0, followed by 80 mg at week 2 and then 40 mg every other week (eow) starting at week 4 is approved for the treatment of adults with moderately to severely active UC.[4-6] However, logistic regression model predictions based on pharmacokinetic and pharmacodynamic data from the 52-week, randomized, phase 3 ULTRA 2 study[7] (ClinicalTrials.gov, Number: NCT00408629) suggest that a higher induction dose of adalimumab may provide greater efficacy in some patients with moderately to severely active UC.[8]

According to the current European label, the recommended adalimumab maintenance dosing regimen is 40 mg eow; patients who experience a decrease in their response to adalimumab 40 mg eow may benefit from an increase in adalimumab dose to 40 mg every week (ew) or 80 mg eow.[5] Weekly adalimumab maintenance dosing is not approved for patients with UC in the United States or Japan. A recent systematic review of real-world evidence indicates that, on average, dose escalation occurs within 1 year in approximately 36% of patients with UC taking an anti-TNF/anti-integrin therapy (ranging from 5% to 55% across 14 studies reporting dose escalation of adalimumab).[9] A retrospective multicenter cohort study of patients with UC on an adalimumab maintenance regimen found that after adalimumab dose escalation, 41%–58% and 17%–26% of patients achieved clinical response and remission, respectively.[10] A retrospective multicenter observational cohort study found most patients with UC (56%) required adalimumab dose escalation, which was successful in 60%.[11] Use of therapeutic drug monitoring (TDM)—measuring drug concentrations and adjusting dosage to optimize the clinical benefit of individual therapies and overall patient care—is increasing in the ever-evolving field of inflammatory bowel disease management.[12–14]

SERENE UC (Study of a Novel Approach to Induction and Maintenance Dosing With Adalimumab in Patients With Moderate to Severe Ulcerative Colitis) was designed to evaluate higher vs standard adalimumab dosing regimens for induction and maintenance therapy in patients with moderately to severely active UC in a main study (ex-Japan) and a Japan substudy. The objective of the Japan substudy was to evaluate the safety and efficacy of higher induction and maintenance adalimumab dosing regimens and to demonstrate the consistency of efficacy between the Japanese population and integrated population of Japanese and Western patients. Here, the results of the SERENE UC main study and a prespecified integrated analysis of patients from both the main study and the Japan substudy are reported,

* Alessandro Armuzzi is now at Istituto di Ricovero e Cura a Carattere Scientifico Humanitas Research Hospital, Rozzano, Milan, Italy.

Abbreviations used in this paper: AAA, anti-adalimumab antibody; AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; eow, every other week; ew, every week; FMS, full Mayo score; HIR, higher induction regimen; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; IFX, infliximab; ITT, intent-to-treat; ITT-RP, intent-to-treat responder patient; RBS, rectal bleeding subscore; RHI, Robarts Histopathology Index; SFS, stool frequency subscore; SIR, standard induction regimen; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor; UC, ulcerative colitis.

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2022.02.033

including efficacy, safety, pharmacokinetics, quality of life, and histologic outcomes.

Methods

Study Design

SERENE UC was a phase 3, double-blind, randomized, multicenter study that evaluated the safety and efficacy of higher vs standard adalimumab dosing regimens for induction and maintenance therapy in adults with moderately to severely active UC. It included a main study (ex-Japan) conducted across 120 clinical study sites in 19 countries (Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Romania, Slovakia, Spain, Switzerland, Ukraine, United Kingdom, and United States) and a Japan substudy conducted across 22 clinical centers in Japan. The SERENE UC main study and the Japan substudy were post-marketing commitments for US Food and Drug Administration and Japanese Pharmaceuticals and Medical Devices Agency approvals, respectively. SERENE UC was registered at ClinicalTrials.gov (Number: NCT02065622). The induction and the maintenance studies had separate, standalone end points, which were analyzed independently. The SERENE UC study included a 3-week screening period, an 8-week double-blind induction study, a 44-week double-blind maintenance study, and a 70-day follow-up period (Supplementary Figure 1).

Per Good Clinical Practice, independent Ethics Committees/Institutional Review Boards ensured the ethical, scientific, and medical appropriateness of this study and approved all relevant documents (eg, protocol, informed consent, and patient information) before authorization of drug shipment to each study site. The SERENE UC study was conducted according to the protocol, International Conference for Harmonisation guidelines, applicable regulations and clinical study conduct guidelines, and ethical principles originating from the Declaration of Helsinki. Patients provided informed written consent before screening- and study-specific procedures. All authors had access to the study data and reviewed and approved the final manuscript.

Patient Eligibility Criteria

Eligible patients were adults (aged 18–75 years at baseline) with moderately to severely active UC, which was defined as full Mayo score (FMS) of 6–12 and endoscopy subscore (confirmed by a central reader) of 2–3, despite concurrent or prior treatment with a full/adequate course of 1 or more protocol-defined oral corticosteroid or immunosuppressant. Patients had a diagnosis of UC for $\geq$90 days before baseline, confirmed by endoscopy (colonoscopy or flexible sigmoidoscopy) during the screening period. Patients with current infection, dysplasia, and/or malignancy were excluded, as were primary nonresponders to infliximab (IFX), a chimeric monoclonal anti–TNF-α antibody.[15] The main study and the Japan substudy allowed enrollment of up to 25% of patients with previous IFX exposure. Eligible patients with prior IFX exposure either lost response (ie, overall lack of improvement or worsening of UC-related symptoms) after the initial benefit from IFX or were intolerant (ie, needed to stop IFX due to toxicity). Patients with a diagnosis and/or history of Crohn's disease or indeterminate colitis, current diagnosis of fulminant colitis and/or toxic megacolon, disease limited to the rectum (ulcerative proctitis) during the screening endoscopy, and/or history of chronic recurring infections or active tuberculosis, subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Kock pouch, ileostomy, or planned bowel surgery were also excluded from the study. Patients who entered the study on concomitant corticosteroids were mandated to taper steroid use from week 4 onward. See Supplementary Material for full inclusion and exclusion criteria.

Treatment

In the induction study (both main and Japan substudy), patients were randomized 3:2 using an interactive response system to receive the higher induction regimen (HIR) of adalimumab (Humira; AbbVie Inc, North Chicago, IL) 160 mg at weeks 0, 1, 2, and 3, followed by 40 mg at weeks 4 and 6 or the standard induction regimen (SIR) of adalimumab 160 mg at week 0, followed by adalimumab 80 mg at week 2 and 40 mg at weeks 4 and 6 (placebo received at weeks 1 and 3 to maintain blinding). Randomization was stratified by previous IFX use (yes/no) and baseline corticosteroid use (yes/no). In the maintenance study (main study), all patients who completed week 8 of the induction study were rerandomized 2:2:1 to receive either adalimumab 40 mg ew maintenance regimen, adalimumab 40 mg eow maintenance regimen, or a TDM (ex-Japan only) exploratory maintenance regimen (see Supplementary Material for dose-escalation criteria and additional details). Rerandomization was stratified by induction treatment regimen and response status (FMS) at week 8; among week-8 responders, the randomization was further stratified by remission status at week 8. The TDM regimen was an exploratory regimen in the main study designed to assess the efficacy and safety of aiming for serum adalimumab levels within a targeted concentration range for making decisions regarding dosing. The targeted concentration range for TDM dosing was based on adalimumab serum concentrations and rectal bleeding subscore (RBS). The Japan substudy did not include a TDM arm and patients were rerandomized 1:1 to receive either the adalimumab 40 mg ew or the adalimumab 40 mg eow maintenance regimen with the same stratification criteria as the main study.

All SERENE UC investigators, study site personnel, and patients remained blinded to each patient's treatment throughout the study.

Assessments

Efficacy assessments–induction study. In the induction study, the primary efficacy end point was the proportion of patients who achieved clinical remission, defined as FMS $\leq$2 with no subscore $>$1, at week 8. The following ranked (hierarchically 1–5) secondary efficacy end points were assessed at week 8: endoscopic improvement (endoscopic subscore 0 or 1; rank no. 1), with fecal calprotectin $<$ 150 mg/kg (rank no. 2), with Inflammatory Bowel Disease Questionnaire (IBDQ) response (IBDQ increase from baseline $\geq$ 16; rank no. 3), clinical response (FMS decrease from baseline $\geq$3 and $\geq$30% plus $\geq$1-point decrease from baseline in RBS or absolute RBS of 0 or 1; rank no. 4), and endoscopic subscore of 0 (rank no. 5).

Efficacy assessments–maintenance study. In the maintenance study, the primary efficacy end point was the proportion of patients who achieved clinical remission at week 52 among week-8 responders. The following ranked secondary efficacy end points were also assessed at week 52: the proportion of week-8 responders who achieved endoscopic improvement (rank no. 1), who took steroids at baseline and were steroid-free for ≥90 days (rank no. 2), and who took steroids at baseline who were steroid-free for ≥90 days and in clinical remission (rank no. 3); patients with clinical remission at week 8 (week-8 remitters) who achieved clinical remission (rank no. 4), who achieved endoscopic improvement (rank no. 5), who took steroids at baseline and were steroid-free for ≥90 days (rank no. 6), and who took steroids at baseline and were steroid-free for ≥90 days and in clinical remission (rank no. 7); the proportion of week-8 responders with IBDQ response (rank no. 8); patients without clinical response at week 8 (week-8 nonresponders) with clinical remission (rank no. 9); patients without clinical remission at week 8 (week-8 nonremitters) with clinical remission (rank no. 10); week-8 responders who achieved endoscopic subscore of 0 (rank no. 11); and week-8 remitters who achieved endoscopic subscore of 0 (rank no. 12).

For the primary efficacy end point in both the induction and maintenance studies, the following subgroups were assessed in prespecified analyses: sex, age, race, region, prior anti-TNF exposure, baseline corticosteroid use, immunosuppressant use, FMS, weight, presence of extensive colitis, disease duration, high-sensitivity C-reactive protein (hs-CRP), and albumin.

Safety assessments. Adverse events (AEs), vital signs, and laboratory parameters (ie, hemoglobin, platelets, neutrophils, lymphocytes, alanine transaminase, and aspartate transaminase) were assessed throughout the induction and maintenance studies. Patients were contacted for assessment of any new or ongoing AEs 70 days after the last dose of study drug, except those who continued commercially available treatment after the end of the study. In the induction study, treatment-emergent AEs were defined as events that began or worsened on or after the first dose of study drug and up to the first dose of study drug in the maintenance study for patients rerandomized at week 8 or within 70 days after the last dose of induction study drug for patients who prematurely discontinued during the induction study. In the maintenance study, treatment-emergent AEs were defined as events that began or worsened on or after the first dose of maintenance study drug and within 70 days after the last dose of study drug. AEs, AEs of special interest (AESIs), and AEs leading to death or premature discontinuation were organized using the Medical Dictionary for Drug Regulatory Activities, version 22.0 (https://www.meddra.org/) by system organ class, preferred term, relationship to study drug, and severity.

Patient-reported outcomes. Changes from baseline in IBDQ total score[16] were assessed at weeks 2, 4, and 8 (induction study) and weeks 12, 24, 37, and 52 (maintenance study). Changes from baseline in Work Productivity and Impairment Questionnaire[17] and 36-Item Short Form Health Survey[18,19] scores were assessed at week 8 (induction study) and week 52 (maintenance study).

Histology-related end points. Patients underwent endoscopy (colonoscopy or flexible sigmoidoscopy) with biopsy (2 from each observed colonic segment, including every inflamed segment) for histologic assessment during screening and at weeks 8 and 52 or premature discontinuation (for patients who remained in the study through week 24) (see Supplementary Material for more details). Biopsy samples were processed by ICON Central Laboratories, Inc (Farmingdale, NY) and histology was evaluated by an independent blinded central reader. Changes from baseline in Geboes score[20] and Robarts Histopathology Index (RHI)[21] were assessed at week 8 (induction study) and week 52 (maintenance study). Histologic scores were derived from the maximum score for the rectum and sigmoid segments. Histologic remission (Geboes score <2 or RHI score <3) and endoscopy improvement were assessed at week 8 (induction study); and the proportion of week-8 responders with histologic remission was assessed at week 52 (maintenance study). A cross-tabulation was completed for patients with histologic remission and endoscopic improvement at week 8 (induction study) and week 52 (maintenance study).

Pharmacokinetics and immunogenicity. Pharmacokinetics and immunogenicity of adalimumab treatment were assessed in all patients (the main and Japan populations combined; ie, integrated analysis). Serum adalimumab concentrations were assessed using an enzyme-linked immunosorbent assay at baseline and at weeks 2, 4, 8, 10, 12, 16, 22, 24, 29, 35, 37, 42, 48, and 52/early termination, and unscheduled visit if applicable. Serum anti-adalimumab antibody (AAA) concentrations were assessed using a validated double antigen immunoassay at baseline and at weeks 4, 8, 12, 24, 37, and 52/early termination, and unscheduled visit if applicable.

Statistical Analyses

Although the study was ongoing, the study protocol was amended to divide the structure into 2 distinct studies (induction study and maintenance study) that each had their own study-specific end points and type I error control, based on the fact that patients were rerandomized into the maintenance study with blinded treatment. The sample sizes for each induction and maintenance study were increased to provide each study with higher statistical power (see Supplementary Material for details).

For the induction study, the primary efficacy analyses were conducted in the intent-to-treat (ITT) population comparing HIR and SIR groups, and for the maintenance study, primary efficacy analyses were conducted in the ITT responder patient (ITT-RP) population comparing adalimumab 40 mg ew and 40 mg eow groups (TDM was exploratory). The ITT population in the induction study (main study) was defined as all randomized patients; and the ITT-RP population in the maintenance study was defined as all rerandomized patients who achieved a response at week 8. Overall type I error rate of the primary and ranked secondary end points were strongly controlled using the fixed-sequence multiple testing procedure approach in the induction and maintenance studies, respectively. As prespecified in the Japan substudy protocol, efficacy analyses were conducted in the integrated population (the Japan-only population was not statistically powered to achieve any end point alone), which included all randomized patients (main and Japan populations), to demonstrate consistency between the Japanese population and Western population in the induction (ITT) and maintenance (ITT-RP) studies. For the integrated analyses, no

multiplicity adjustment was applied for the induction study; the overall type I error rate for the primary and ranked secondary end points was controlled using a fixed-sequence multiple testing procedure approach in the maintenance study.

FMS was defined as the composite score of UC disease activity based on endoscopy (0–3), Physician's Global Assessment (0–3), rectal bleeding (0–3), and stool frequency (0–3), with a range from 0–12 (higher scores represent more severe disease).

Mean (SD) adalimumab concentrations (μg/mL) were assessed over time by induction dose and by maintenance dose. A patient was considered AAA positive (AAA+) if they had 1 or more AAA concentrations >20 ng/mL within 30 days after an adalimumab dose (time points assessed listed in the Pharmacokinetics and Immunogenicity section). The number and proportion of patients who developed AAA+ were summarized by treatment dose in both induction and maintenance studies.

Safety analyses included all patients who received 1 or more doses of study drug. Safety data (number and percentage of patients summarized by treatment group) were analyzed from baseline to week 8 (induction study) and from week 8 to the end of the study. The number and percentage of patients with change from baseline in laboratory parameters of grade ≥3 (Common Toxicity Criteria for Adverse Events, version 3.0 or later[22]) were summarized.

Analyses were performed using SAS (SAS Institute Inc, Cary, NC). Both 95% confidence intervals (CI) and *P* values between treatment arms were calculated using the Cochran–Mantel–Haenszel test, which was adjusted for previous IFX use and baseline corticosteroid use (induction study), and induction treatment regimen, and week-8 remission status (maintenance study). For the primary analysis, missing data were handled by nonresponder imputation for categorical/binary end points and mixed-effect model for repeated measure for continuous end points, when applicable. Patients who needed to restart steroids during the maintenance study as rescue treatment per investigator judgment were considered nonresponders for categorical/binary end points and data were censored from analysis for continuous end points, when applicable. Sensitivity analyses were conducted using observed case analysis, which did not impute values for missing evaluations—patients who did not have a scheduled evaluation were excluded from the analysis for that visit—and last observation carried forward, which was also conducted for missing continuous and categorical efficacy end points. All statistical tests were 2-sided with a .05 significance level.

Results

Patients

The number of patients who were randomized, allocated to treatment, and completed the study are listed in Figure 1*A* (induction study) and Figure 1*B* (maintenance study). Overall, the rates of discontinuation from the induction and maintenance studies were low and comparable between dosing regimens; the leading reason for premature discontinuation was lack of efficacy in both the main (ex-Japan) and Japan populations.

Demographic and baseline characteristics were generally well balanced between dosing regimen groups in the induction (HIR vs SIR) and maintenance (40 mg ew vs 40 mg eow) studies for both the main (ex-Japan) and Japan populations (Table 1 [safety population] and Supplementary Table 1 [ITT and ITT-RP populations]). The Japan population's demographic and baseline characteristics were generally similar to those of the main study population, with the exception of lower weight (overall mean [SD], 62 [12] kg), higher use of concomitant immunosuppressants at baseline, and higher prior exposure to IFX.

Induction Study

In the main study population, the proportion of patients who achieved clinical remission at week 8 (primary efficacy end point) was 13.3% vs 10.9% in the HIR and SIR groups, respectively (95% CI, −1.9 to 7.1; $P = .265$) (Figure 2). Clinical remission rates in the integrated population were consistent with the main study population; no significant difference was observed between HIR and SIR groups ($P = .297$). In the main study population, all ranked secondary end points at week 8 were slightly numerically higher in patients receiving the HIR compared with SIR, with 2 ranked secondary end points reaching nominal *P* value ≤ .05 (IBDQ response and clinical response) (Table 2). Similarly, in the integrated population, all ranked secondary end points were slightly numerically higher in the HIR group compared with the SIR group; 1 (clinical response) had a nominal *P* value ≤ .05.

Prespecified subgroup analyses in the main study were consistent with the primary analysis (Figure 4*A*). A higher proportion of patients with longer disease duration achieved clinical remission on the HIR compared with the SIR (nominal $P < .05$).

Clinical responses over time are shown in Supplementary Figure 2. At week 4, greater proportions of patients in the HIR group compared with the SIR group achieved clinical response and clinical remission per partial Mayo Score (nominal $P < .05$).

During the induction study, in the main study population, the overall incidence of AEs, severe AEs, and AEs leading to discontinuation of the study drug were similar between the HIR and the SIR groups (Table 3). Approximately one-half of patients in each induction dosing regimen had 1 or more AEs; most were mild or moderate in severity. Although injection-site reaction was reported more frequently by patients in the HIR group compared with the SIR group (12.1% vs 3.8%), most injection-site–related AEs were mild in severity and did not lead to study drug discontinuation. Two deaths were reported during the induction study, both in patients receiving the HIR, and were assessed by the investigator as not related to the study drug. Similar proportions of patients in the HIR and SIR groups reported an AESI of infection (13.5% and 17.1%, respectively); most were nonserious and assessed by the investigator as not related to study drug. One patient in each the HIR and SIR groups reported an opportunistic infection. Only 1 case of tuberculosis (severe, possibly study drug related) was reported for a patient in the HIR group, who discontinued study treatment. One case

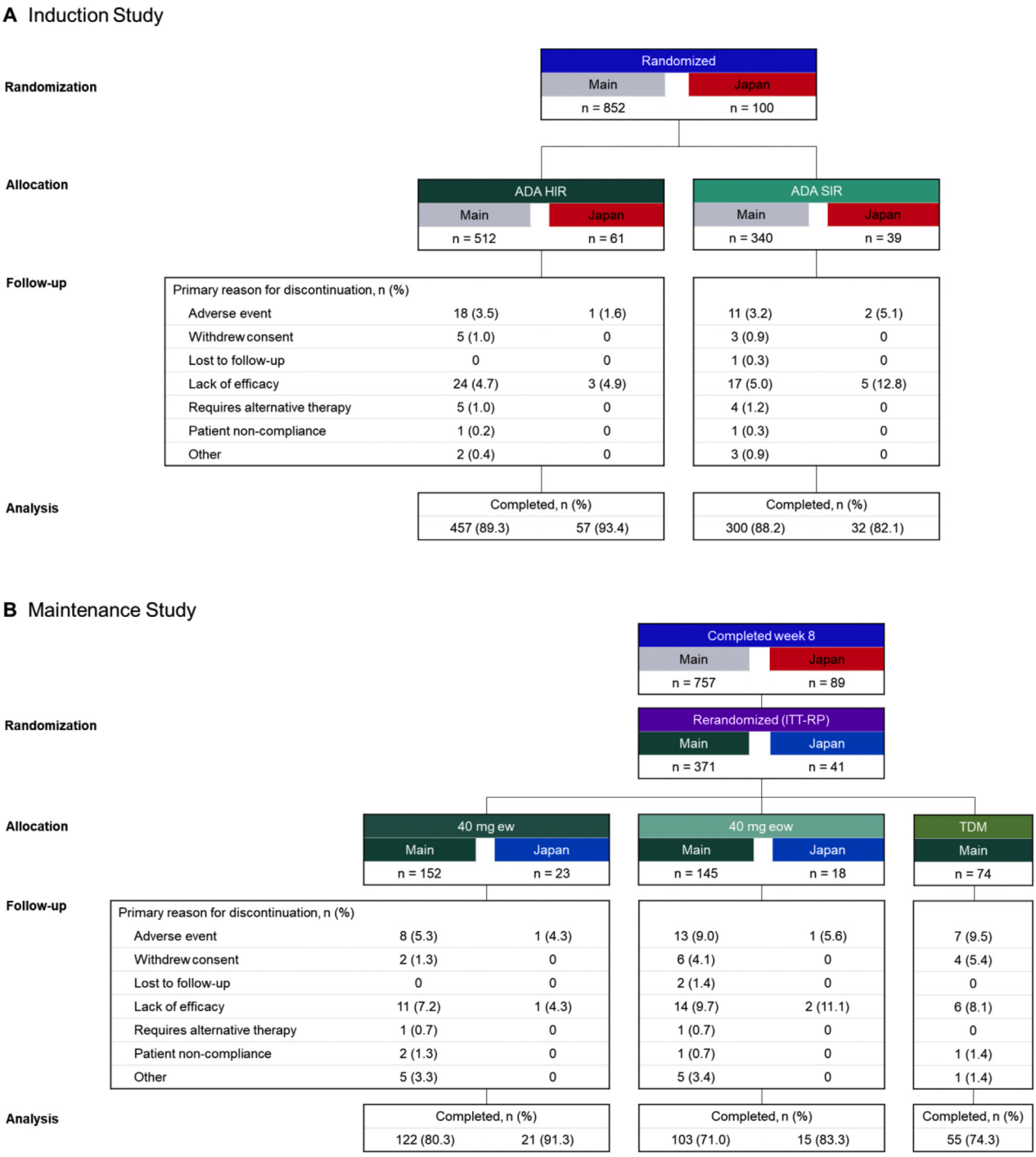

Figure 1. Patient disposition. (*A*) Induction study. (*B*) Maintenance study. ADA, adalimumab.

of each of the following malignancies was reported: melanoma in situ (study drug related), squamous cell carcinoma of the cervix (study drug unrelated), and basal cell carcinoma (study drug unrelated). Rates of Common Terminology Criteria for Adverse Events[22] grade 3 or 4 AEs of laboratory values, and clinically significant vital signs were infrequent and broadly similar across both induction dosing regimens. Mean changes in laboratory parameters were not considered clinically relevant, according to the investigator.

In the Japan study population, 50% of patients had 1 or more treatment-emergent AEs, and most were assessed by the investigator as mild or moderate in severity; the proportion of patients with AEs was higher in the HIR vs the SIR group (Table 3). The number of patients with serious AEs or AEs leading to discontinuation of the study drug was low (≤5% and comparable between treatment regimens). No deaths, malignancies, or cases of tuberculosis occurred during the induction study. The most frequently reported AEs (≤5% in either treatment group) were nasopharyngitis,

Table 1. Demographics and Baseline Characteristics at Induction Study Entry (Safety Population)

	Adalimumab							
	Induction study				Maintenance study			
	Main population (ex-Japan)		Japan population		Main population (ex-Japan)		Japan population	
Characteristic	HIR (n = 512)	SIR (n = 340)	HIR (n = 61)	SIR (n = 39)	40 mg ew (n = 304)	40 mg eow (n = 302)	40 mg ew (n = 46)	40 mg eow (n = 43)
Sex, n (%)								
Male	289 (56.4)	189 (55.6)	45 (73.8)	24 (61.5)	166 (54.6)	170 (56.3)	34 (73.9)	28 (65.1)
Race, n (%)								
White	484 (94.7)	326 (95.9)	0	0	290 (95.4)	286 (94.7)	0	0
Black/African American	16 (3.1)	8 (2.4)	0	0	11 (3.6)	7 (2.3)	46 (100)	43 (100)
Asian	9 (1.8)	5 (1.5)	61 (100)	39 (100)	3 (1.0)	6 (2.0)	0	0
American Indian/Alaska Native	0	0	0	0	0	0	0	0
Native Hawaiian/other Pacific Islander	1 (0.2)	0	0	0	0	1 (0.3)	0	0
Multirace	1 (0.2)	1 (0.3)	0	0	0	2 (0.7)	0	0
Missing	1 (0.2)	0	0	0	0	0	0	0
Age, *y*, median (range)	39.0 (18–75)	38.0 (18–73)	41.0 (19–71)	43.0 (20–66)	40.0 (18–75)	37.5 (18–69)	41.5 (22–65)	43.0 (20–71)
Disease duration, *y*, mean (SD)	7.2 (7.2)	7.0 (7.0)	8.4 (8.1)	6.6 (6.2)	6.8 (6.7)	7.4 (6.9)	9.7 (8.1)	6.5 (6.6)
Weight, *kg*, mean (SD)	75.9 (18.3)	75.2 (17.2)	63.6 (12.2)	60.2 (11.3)	76.3 (17.0)	74.7 (17.8)	62.2 (11.2)	63.2 (11.6)
Albumin, *g/L*, mean (SD)	39.9 (4.2)	40.0 (3.8)	39.9 (3.5)	38.6 (5.5)	40.0 (4.0)	40.2 (3.6)	39.6 (4.8)	39.4 (3.4)
Fecal calprotectin, *μg/g*, median (range)	1667.0 (10–9600)	1578.5 (11–9600)	1812.0 (113–9600)	1888.0 (29–9600)	1563.0 (10–9600)	1468.0 (34–9600)	1704.0 (39–9600)	2034.5 (29–9600)
hs-CRP, *mg/L*								
Median (range)	4.9 (0.1–172.3)	4.9 (0.1–145.7)	2.6 (0.2–88.2)	3.1 (0.1–167.9)	5.1 (0.2–129.1)	4.1 (0.1–94.1)	1.8 (0.2–82.8)	4.1 (0.1–167.9)
≤5 mg/L, n (%)	259 (50.6)	172 (50.6)	41 (67.2)	24 (61.5)	83 (54.6)	82 (56.6)	19 (82.6)	11 (61.1)
>5 mg/L, n (%)	253 (49.4)	168 (49.4)	20 (32.8)	15 (38.5)	69 (45.4)	63 (43.4)	4 (17.4)	7 (38.9)
Extensive colitis, n (%)	245 (47.9)	151 (44.4)	35 (57.4)	23 (59.0)	139 (46.0)	137 (45.4)	29 (63.0)	23 (53.5)
IBDQ total score, mean (SD)	114.2 (33.7)	117.7 (31.7)	138.7 (30.6)	133.8 (31.8)	114.6 (33.1)	118.2 (34.0)	139.9 (30.1)	132.3 (31.4)
Corticosteroid use,[a] n (%)	296 (57.8)	208 (61.2)	32 (52.5)	19 (48.7)	186 (61.2)	185 (61.3)	22 (47.8)	23 (53.5)
Immunosuppressant use, n (%)	131 (25.6)	81 (23.8)	33 (54.1)	23 (59.0)	64 (21.1)	84 (27.8)	30 (65.2)	23 (53.5)
Prior infliximab use,[a] n (%)	67 (13.1)	43 (12.6)	15 (24.6)	10 (25.6)	35 (11.5)	45 (14.9)	12 (26.1)	9 (20.9)

Table 1. Continued

Characteristic	Adalimumab								
	Induction study				Maintenance study				
	Main population (ex-Japan)		Japan population		Main population (ex-Japan)		Japan population		
	HIR (n = 512)	SIR (n = 340)	HIR (n = 61)	SIR (n = 39)	40 mg ew (n = 304)	40 mg eow (n = 302)	40 mg ew (n = 46)	40 mg eow (n = 43)
FMS[b]								
Mean (SD)	8.9 (1.6)	8.7 (1.5)	8.6 (1.4)	8.7 (1.8)	8.8 (1.6)	8.7 (1.5)	8.6 (1.6)	8.5 (1.5)
≤9, n (%)	283 (55.6)	220 (64.7)	42 (68.9)	24 (61.5)	87 (57.2)	90 (62.1)	14 (60.9)	11 (61.1)
>9, n (%)	226 (44.4)	120 (35.3)	19 (31.1)	15 (38.5)	65 (42.8)	55 (37.9)	9 (39.1)	7 (38.9)

[a]Stratification factors for randomization.
[b]Stratification factor for rerandomization (along with induction treatment regimen).

injection site reaction, and pyrexia. Induction study safety results for the integrated (main and Japan substudy) population are also presented in Table 3.

Maintenance Study

In the main study population, 39.5% of week-8 responders taking adalimumab 40 mg ew achieved clinical remission at week 52 compared with 29.0% in the 40 mg eow group (absolute difference, 10.5%; 95% CI, −0.8 to 20.6; $P = .069$) (Figure 3). In the larger integrated study population, the differences in the proportion of week-8 responders achieving clinical remission with adalimumab 40 mg ew (41.1%) compared with 40 mg eow (30.1%) at week 52 was associated with a nominal P value ≤.05 (absolute difference, 11.0%; 95% CI, 0.2 to 20.4; $P = .045$) (Figure 3).

Although all ranked secondary efficacy end points in the main study population were slightly numerically higher in the adalimumab 40 mg ew group compared with the adalimumab 40 mg eow group (Table 2), in only 1 case was the difference between treatment groups associated with a nominal P value ≤ .05 (week-8 responders who took steroids at baseline and were steroid-free for ≥90 days at week 52). Similar results for all ranked secondary efficacy end points were observed in the integrated population, the following 2 end points were associated with a nominal P value ≤ .05: week-8 responders who took steroids at baseline and were steroid-free for ≥90 days at week 52 and clinical remission at week 52 among patients without week-8 clinical remission.

Overall, prespecified subgroup analyses in the main study were consistent with the primary analysis (Figure 4*B*). More patients with high/elevated hs-CRP, extensive UC, low albumin, or long disease duration treated with adalimumab 40 mg ew achieved clinical remission compared with those treated with adalimumab 40 mg eow (nominal $P < .05$ for all).

Results from a post-hoc Cochran–Mantel–Haenszel test with an additional covariate for the primary end point of clinical remission in the main study population demonstrated that including UC duration (median ≤4.65 years, >4.65 years; ≤2, >2 years; or ≤5, >5 years), or week 8 RBS (0, >0), or region (Eastern Europe, non-Eastern Europe) as covariates (1 covariate at a time in addition to the original randomization factors) yielded P values < .05 (Supplementary Table 2).

Among the patients who completed the 52-week maintenance therapy in the TDM arm (Supplementary Table 3), approximately 84% were dose-escalated from eow to ew adalimumab dosing. Although exploratory, the observed clinical remission rate with TDM was intermediate between adalimumab 40 mg ew and 40 mg eow (Supplementary Table 4).

In the main study population of the maintenance study, the overall incidence of AEs, serious AEs, severe AEs, and AEs leading to discontinuation of study drug was similar between the adalimumab 40 mg ew and 40 mg eow maintenance dosing regimens (Table 3). Approximately three-quarters of patients in each maintenance dosing

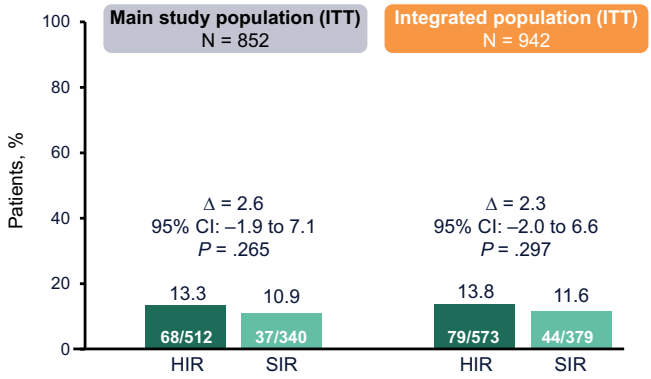

Figure 2. Clinical remission at week 8 (primary efficacy end point–induction study). Clinical remission was defined as FMS ≤2 with no subscore >1 (ITT analysis set). Adjusted difference by stratification factors. Central reviewer scoring of endoscopy results was used for all efficacy assessments. RBS and SFS components of FMS were based on entries into patient diary averaged over 5 days before each study visit. Missing data were handled by nonresponder imputation.

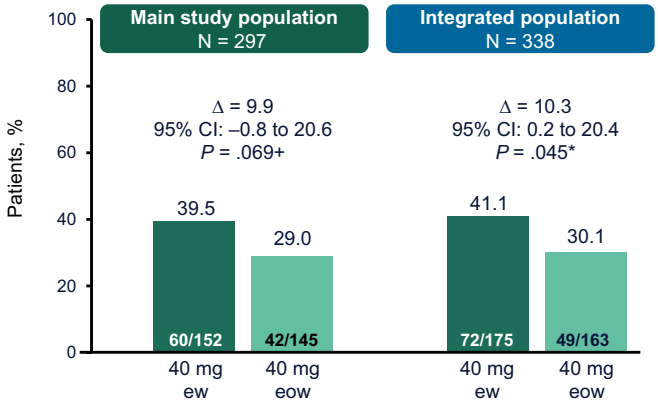

Figure 3. Clinical remission among patients with week-8 response (primary efficacy end point–maintenance study). Clinical response was defined per FMS; FMS decrease from baseline ≥3 and ≥30%, plus RBS decrease from baseline ≥1 or absolute RBS of 0 or 1. *P* values for comparison between 40 mg ew and 40 mg eow calculated using Cochran–Mantel–Haenszel test adjusted for stratification factors. Missing data were handled by nonresponder imputation.

regimen had 1 or more AEs. No opportunistic infections were reported. Four and 2 malignancies were reported in the adalimumab 40 mg ew and 40 mg eow maintenance dosing regimens, respectively. There were 4 deaths reported, 2 in each maintenance dosing regimen; all were assessed by the investigator as not related to the study drug. Overall, the proportion of patients experiencing AESIs was low (<5%), with the exception of infections (34.5% in adalimumab 40 mg ew group and 36.4% in the 40 mg eow group), and relatively balanced across dosing regimens. Most AEs of infection were nonserious, mild, or moderate, and assessed by the investigator as not related to the study drug; 3 cases (1%) in each of the 40 mg ew and 40 mg eow groups lead to discontinuation of study drug. Two cases of tuberculosis (active or latent) were reported in patients in the 40 mg ew group (both severe, 1 related and led to discontinuation of study treatment and 1 unrelated to study treatment). There were no notable changes in AEs of Common Terminology Criteria for Adverse Events[22] grade 3 or 4 laboratory values; shifts were infrequent, broadly similar across both maintenance dosing regimens, and not considered clinically meaningful by the investigator.

In the Japan study population, most patients reported 1 or more treatment-emergent AEs, most were mild or moderate in severity; rates of AEs were similar between adalimumab 40 mg ew and 40 mg eow maintenance regimens (Table 3). Although the proportion of patients who reported serious AEs or severe AEs was higher in the 40 mg ew group compared with the 40 mg eow group, the incidences were lower than what was reported in the main population, and most events were due to underlying disease (ie, flare). Of the 7 patients who reported 1 or more AEs that led to discontinuation of the study drug (the most frequently reported was UC), 2 patients (1 in each maintenance group) experienced events (hepatobiliary disease and lupus-like syndrome) assessed by the investigator as possibly related to the study drug. No deaths occurred in the Japan population. The proportions of patients experiencing AESIs were low and relatively balanced between dosing regimens. There were no notable changes in laboratory parameter values from baseline. Maintenance study safety results in the integrated (main and Japan substudy) population are presented in Table 3. The incidence rates of infection were higher in the Japan population compared with the integrated population; however, most infections were events of nasopharyngitis.

An overview of the exploratory TDM maintenance regimen safety profile is reported in Supplementary Table 4. Overall, fewer patients in the TDM arm reported a treatment-emergent AE compared with the adalimumab 40 mg ew and 40 mg eow maintenance regimens. No deaths occurred in the TDM group.

Patient-Reported Outcomes

During induction in the main study population, no statistically significant difference was observed for the mean change from baseline in IBDQ total score in patients receiving the HIR compared with the SIR (Supplementary Figure 3*A*). The mean percent reductions from baseline in Work Productivity and Activity Impairment Questionnaire were greater for activity impairment (nominal $P \leq .001$) in patients receiving the HIR compared with the SIR (Supplementary Figure 3*B*). The mean change from baseline in 36-Item Short-Form Health Survey was not different between the HIR and SIR groups (Supplementary Figure 3*C*). Similar trends were observed in the integrated population.

During maintenance in the main study population, mean change from baseline in IBDQ (Supplementary Figure 3*D*), percent reductions from baseline in Work Productivity and Activity Impairment Questionnaire (Supplementary Figure 3*E*), and change from baseline in 36-Item Short-Form Health Survey (Supplementary Figure 3*F*) were not

Table 2. Ranked Secondary Efficacy End Points

	Adalimumab					
	Main study population			Integrated population		
Induction study (wk 8; ITT population)	HIR, n (%) (n = 512)	SIR, n (%) (n = 340)	Adjusted risk difference (95% CI) *P* value[a]	HIR, n (%) (n = 573)	SIR, n (%) (n = 379)	Adjusted risk difference (95% CI) *P* value[a]
1. Endoscopic improvement	159 (31.1)	92 (27.1)	4.3 (–1.9 to 10.5) .18	175 (30.5)	102 (26.9)	3.8 (–2.0 to 9.7) .20
2. Fecal calprotectin < 150 mg/kg	115 (22.5)	67 (19.7)	3.1 (–2.5 to 8.7) .28	129 (22.5)	74 (19.5)	3.2 (–2.1 to 8.5) .24
3. IBDQ response	344 (67.2)	207 (60.9)	6.5 (0.0 to 13.1) .05	374 (65.3)	230 (60.7)	4.8 (–1.4 to 11.1) .13
4. Clinical response	241 (47.1)	136 (40.0)	7.3 (0.5 to 14.1) .03	271 (47.3)	147 (38.8)	8.7 (2.3 to 15.1) .008
5. Endoscopic remission	67 (13.1)	34 (10.0)	3.2 (–1.2 to 7.6) .16	74 (12.9)	38 (10.0)	3.0 (–1.2 to 7.1) .16

	Adalimumab					
Maintenance study (wk 52)	40 mg ew, n/n (%)	40 mg eow, n/n (%)	Adjusted risk difference (95% CI) *P* value[b]	40 mg ew, n/n (%)	40 mg eow, n/n (%)	Adjusted risk difference (95% CI) *P* value[b]
1. Endoscopic improvement in patients with wk-8 clinical response (ITT-RP)	78/152 (51.3)	60/145 (41.4)	9.5 (–1.7 to 20.8) .10	91/175 (52.0)	68/163 (41.7)	9.9 (–0.7 to 20.5) .07
2. Steroid-free for ≥90 d in patients with wk-8 clinical response who took steroids at baseline (ITT-RP)	72/96 (75.0)	49/92 (53.3)	21.7 (7.8 to 35.6) .002	81/109 (74.3)	56/103 (54.4)	19.9 (6.8 to 32.9) .003
3. Steroid-free for ≥90 d and in clinical remission in patients with wk-8 clinical response who took steroids at baseline (ITT-RP)	38/96 (39.6)	25/92 (27.2)	11.9 (–1.5 to 25.3) .08	44/109 (40.4)	29/103 (28.2)	11.4 (–1.3 to 24.1) .08
4. Clinical remission in patients with wk-8 clinical remission (ITT-RM)	24/42 (57.1)	15/37 (40.5)	15.9 (–6.3 to 38.2) .16	29/52 (55.8)	20/45 (44.4)	10.4 (–9.8 to 30.6) .31
5. Endoscopic improvement in patients with wk-8 clinical remission (ITT-RM)	27/42 (64.3)	19/37 (51.4)	12.3 (–9.7 to 34.4) .27	32/52 (61.5)	25/45 (55.6)	5.3 (–14.6 to 25.2) .60
6. Steroid-free for ≥90 d in patients with wk-8 clinical remission who took steroids at baseline (ITT-RM)	22/28 (78.6)	14/26 (53.8)	24.5 (–1.3 to 50.3) .06	26/36 (72.2)	18/32 (56.3)	15.6 (–7.6 to 38.8) .19
7. Steroid-free for ≥90 d and in clinical remission in patients with wk-8 clinical remission who took steroids at baseline (ITT-RM)	16/28 (57.1)	9/26 (34.6)	21.2 (–5.9 to 48.3) .12	19/36 (52.8)	12/32 (37.5)	13.7 (–10.2 to 37.6) .26

Table 2. Continued

Maintenance study (wk 52)	Adalimumab					
	40 mg ew, n/n (%)	40 mg eow, n/n (%)	Adjusted risk difference (95% CI) *P* value[b]	40 mg ew, n/n (%)	40 mg eow, n/n (%)	Adjusted risk difference (95% CI) *P* value[b]
8. IBDQ response in patients with wk-8 clinical response (ITT-RP)	101/152 (66.4)	90/145 (62.1)	4.5 (–6.4 to 15.3) .42	115/175 (65.7)	102/163 (62.6)	3.4 (–6.8 to 13.6) .51
9. Clinical remission in patients without wk-8 clinical response (ITT-NRP)	24/152 (15.8)	19/157 (12.1)	3.7 (–4.1 to 11.4) .35	28/175 (16.0)	22/182 (12.1)	3.9 (–3.3 to 11.1) .29
10. Clinical remission in patients without wk-8 clinical remission (ITT-NRM)	60/262 (22.9)	46/265 (17.4)	5.4 (–1.4 to 12.1) .12	71/298 (23.8)	51/300 (17.0)	6.5 (0.1 to 12.8) .046
11. Endoscopic remission in patients with wk-8 clinical response (ITT-RP)	54/152 (35.5)	40/145 (27.6)	7.5 (–2.9 to 17.9) .16	62/175 (35.4)	44/163 (27.0)	8.0 (–1.8 to 17.9) .11
12. Endoscopic remission in patients with wk-8 clinical remission (ITT-RM)	20/42 (47.6)	17/37 (45.9)	1.4 (–21.0 to 23.8) .90	23/52 (44.2)	19/45 (42.2)	1.3 (–18.8 to 21.3) .90

NOTE. End points are in ranked order from top to bottom.
ITT-NRM, intent-to-treat nonremitter; ITT-NRP, intent-to-treat nonresponder; ITT-RP, intent-to-treat responder patient; ITT-RM, intent-to-treat-remitter.
[a]Induction study: 95% CI for the difference in the proportions between the treatment groups and *P* value were calculated using Cochran–Mantel–Haenszel test adjusted for induction treatment regimen and wk-8 remission status. ITT analysis set: Endoscopic improvement: endoscopic subscore of 0 or 1. IBDQ response: increase from baseline $\geq$16. Clinical response: FMS decrease from baseline $\geq$3 points and $\geq$30% plus RBS decrease from baseline $\geq$1 or absolute RBS of 0 or 1. Endoscopic remission: endoscopic subscore of 0. Clinical remission: FMS $\leq$2 with no subscore $>$1. Central reviewer scoring of endoscopy results was used for all efficacy assessments.
[b]Maintenance study: nominal *P* values are presented for comparison between 40 mg ew and 40 mg eow maintenance dosing regimens calculated using Cochran–Mantel–Haenszel test adjusted for stratification.

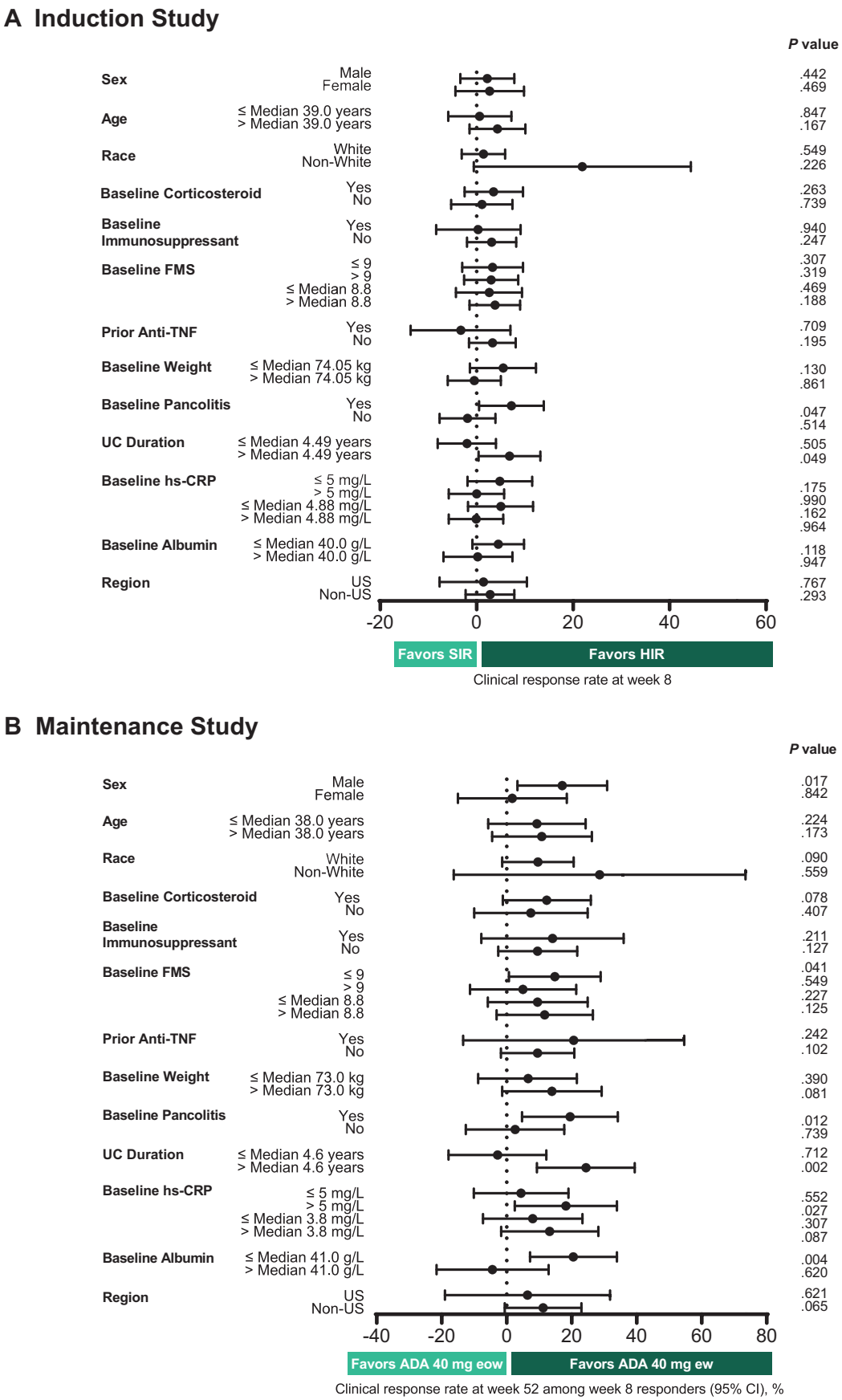

Figure 4. Subgroup analysis. Clinical remission was defined as full Mayo score $\leq$2 with no subscore $>$1 using the endoscopy subscore provided by the central reader. (*A*) Induction study: risk difference = adalimumab (ADA) HIR – ADA SIR. (*B*) Maintenance study: risk difference = ADA 40 mg ew – ADA 40 mg eow. 95% CIs for risk difference were calculated based on normal approximation using PROC FREQ. *P* value was calculated based on χ^2 test (or Fisher exact test if $\geq$20% of the cells have expected cell count $<$5).

Table 3. Safety Results From Week 0 to 8 (Induction Study) and From Week 8 to 52 (Maintenance Study)

	Adalimumab											
	Induction study (safety population)						Maintenance study (safety population)					
	Main		Japan		Integrated		Main		Japan		Integrated	
Variable	HIR (n = 512)	SIR (n = 340)	HIR (n = 61)	SIR (n = 39)	HIR (n = 573)	SIR (n = 379)	40 mg ew (n = 304)	40 mg eow (n = 302)	40 mg ew (n = 46)	40 mg eow (n = 43)	40 mg ew (n = 350)	40 mg eow (n = 345)
Overview, n (%)												
TEAE	271 (52.9)	184 (54.1)	34 (55.7)	16 (41.0)	305 (53.2)	200 (52.8)	222 (73.0)	220 (72.8)	41 (89.1)	37 (86.0)	263 (75.1)	257 (74.5)
Serious AE	19 (3.7)	17 (5.0)	3 (4.9)	2 (5.1)	22 (3.8)	19 (5.0)	40 (13.2)	42 (13.9)	4 (8.7)	2 (4.7)	44 (12.6)	44 (12.8)
AE leading to discontinuation of study drug	30 (5.9)	19 (5.6)	1 (1.6)	3 (7.1)	31 (5.4)	22 (5.8)	30 (9.9)	38 (12.6)	5 (10.9)	2 (4.7)	35 (10.0)	40 (11.6)
Severe TEAE	23 (4.5)	16 (4.7)	1 (1.6)	1 (2.6)	24 (4.2)	17 (4.5)	38 (12.5)	28 (9.3)	3 (6.5)	1 (2.3)	41 (11.7)	29 (8.4)
TEAE possibly related to study drug[a]	138 (27.0)	75 (22.1)	11 (18.0)	8 (20.5)	149 (26.0)	83 (21.9)	104 (34.2)	82 (27.2)	13 (28.3)	7 (16.3)	117 (33.4)	89 (25.8)
AE leading to death	1 (0.2)	0	0	0	1 (0.2)	0	2 (0.7)	2 (0.7)	0	0	2 (0.6)	2 (0.6)
Death[b]	2 (0.4)[c]	0	0	0	2 (0.3)[c]	0	2 (0.7)[d]	2 (0.7)[e]	0	0	2 (0.6)[d]	2 (0.6)[e]
AEs reported by ≥5% of patients (in any group), n (%)												
Colitis ulcerative	29 (5.7)	30 (8.8)	2 (3.3)	2 (5.1)	31 (5.4)	32 (8.4)	60 (19.7)	74 (24.5)	5 (10.9)	2 (4.7)	76 (22.0)	65 (18.6)
Nasopharyngitis	19 (3.7)	14 (4.1)	10 (16.4)	2 (5.1)	29 (5.1)	16 (4.2)	30 (9.9)	31 (10.3)	16 (34.8)	16 (37.2)	46 (13.1)	47 (13.6)
Arthralgia	17 (3.3)	9 (2.6)	1 (1.6)	2 (5.1)	18 (3.1)	11 (2.9)	24 (7.9)	24 (7.9)	1 (2.2)	0	25 (7.1)	24 (7.0)
Upper RTI	6 (1.2)	3 (0.9)	0	0	6 (1.0)	3 (0.8)	17 (5.6)	21 (7.0)	2 (4.3)	1 (2.3)	19 (5.4)	22 (6.4)
Headache	47 (9.2)	23 (6.8)	1 (1.6)	0	48 (8.4)	23 (6.1)	20 (6.6)	16 (5.3)	2 (4.3)	1 (2.3)	22 (6.3)	17 (4.9)
Anemia	16 (3.1)	13 (3.8)	2 (3.3)	2 (5.1)	18 (3.1)	15 (4.0)	13 (4.3)	12 (4.0)	5 (10.9)	3 (7.0)	18 (5.1)	15 (4.3)
Influenza	1 (0.2)	6 (1.8)	1 (1.6)	0	2 (0.3)	6 (1.6)	11 (3.6)	13 (4.3)	4 (8.7)	3 (7.0)	15 (4.3)	16 (4.6)
Pyrexia	7 (1.4)	5 (1.5)	3 (4.9)	2 (5.1)	10 (1.7)	7 (1.8)	12 (3.9)	8 (2.6)	4 (8.7)	2 (4.7)	16 (4.6)	10 (2.9)
Nausea	17 (3.3)	9 (2.6)	1 (1.6)	1 (2.6)	18 (3.1)	10 (2.6)	6 (2.0)	13 (4.3)	4 (8.7)	1 (2.3)	10 (2.9)	14 (4.1)
Cystitis	1 (0.2)	0	0	0	1 (0.2)	0	0	1 (0.3)	3 (6.5)	2 (4.7)	3 (0.9)	3 (0.9)
Back pain	12 (2.3)	3 (0.9)	2 (3.3)	1 (2.6)	14 (2.4)	4 (1.1)	9 (3.0)	6 (2.0)	1 (2.2)	3 (7.0)	10 (2.9)	9 (2.6)

Table 3. Continued

Variable	Adalimumab											
	Induction study (safety population)						Maintenance study (safety population)					
	Main		Japan		Integrated		Main		Japan		Integrated	
	HIR (n = 512)	SIR (n = 340)	HIR (n = 61)	SIR (n = 39)	HIR (n = 573)	SIR (n = 379)	40 mg ew (n = 304)	40 mg eow (n = 302)	40 mg ew (n = 46)	40 mg eow (n = 43)	40 mg ew (n = 350)	40 mg eow (n = 345)
AESIs, n (%)												
Infection	69 (13.5)	58 (17.1)	14 (23.0)	4 (10.3)	83 (14.5)	62 (16.4)	105 (34.5)	110 (36.4)	25 (54.3)	22 (51.2)	130 (37.1)	132 (38.3)
Serious infection	3 (0.6)	2 (0.6)	1 (1.6)	1 (2.6)	4 (0.7)	3 (0.8)	9 (3.0)	10 (3.3)	0	1 (2.3)	9 (2.6)	11 (3.2)
Opportunistic infection[f]	1 (0.2)	1 (0.3)	0	0	1 (0.2)	1 (0.3)	0	0	0	0	0	0
Oral candidiasis	0	0	0	0	0	0	1 (0.3)	1 (0.3)	0	1 (2.3)	1 (0.3)	2 (0.6)
Tuberculosis (active or latent)	1 (0.2)	0	0	0	1 (0.2)	0	2 (0.7)	0	0	0	2 (0.6)	0
Parasitic infection	1 (0.2)	0	0	0	1 (0.2)	0	2 (0.7)	0	0	0	2 (0.6)	0
Malignancy	0	3 (0.9)[g]	0	0	0	3 (0.8)[g]	4 (1.3)[h]	2 (0.7)[i]	0	0	4 (1.1)[h]	2 (0.6)[i]
NMSC	0	1 (0.3)	0	0	0	1 (0.3)	1 (0.3)	1 (0.3)	0	0	1 (0.3)	1 (0.3)
Melanoma	0	1 (0.3)	0	0	0	1 (0.3)	1 (0.3)	0	0	0	1 (0.3)	0
Other malignancy[j]	0	1 (0.3)	0	0	0	1 (0.3)	2 (0.7)	1 (0.3)	0	0	2 (0.6)	1 (0.3)
Allergic reaction[k]	8 (1.6)	5 (1.5)	1 (1.6)	1 (2.6)	9 (1.6)	6 (1.6)	6 (2.0)	4 (1.3)	1 (2.2)	0	7 (2.0)	4 (1.2)
Vasculitis (including cutaneous and noncutaneous)	0	0	0	0	0	0	1 (0.3)	0	0	0	1 (0.3)	0
Myocardial infarction	0	0	0	0	0	0	0	1 (0.3)	0	0	0	1 (0.3)
Congestive heart failure	0	0	0	0	0	0	0	1 (0.3)	0	0	0	1 (0.3)
Cerebrovascular accident	0	0	0	0	0	0	0	0	0	0	0	0
Pulmonary embolism	0	0	0	0	0	0	3 (1.0)	1 (0.3)	0	0	3 (0.9)	1 (0.3)
Pancreatitis	1 (1.3)	0	0	0	1 (0.2)	0	0	1 (0.3)	0	0	0	1 (0.3)
Worsening/new-onset psoriasis	1 (0.2)	2 (0.6)	0	0	1 (0.2)	2 (0.5)	1 (0.3)	2 (0.7)	0	0	1 (0.3)	2 (0.6)
Demyelinating disorder	0	0	0	0	0	0	0	0	0	0	0	0
Hematologic disorders[l]	22 (4.3)	16 (4.7)	4 (6.6)	2 (5.1)	26 (4.5)	18 (4.7)	17 (5.6)	14 (4.6)	6 (13.0)	3 (7.0)	23 (6.6)	17 (4.9)
Liver failure and other liver event[m]	2 (0.4)	0	0	0	2 (0.3)	0	1 (0.3)	1 (0.3)	1 (2.2)	1 (2.3)	2 (0.6)	2 (0.6)
Injection-site reaction	62 (12.1)	13 (3.8)	7 (11.5)	3 (7.7)	69 (12.0)	16 (4.2)	14 (4.6)	8 (2.6)	2 (4.3)	0	16 (4.6)	8 (2.3)

Table 3. Continued

Variable	Adalimumab											
	Induction study (safety population)						Maintenance study (safety population)					
	Main		Japan		Integrated		Main		Japan		Integrated	
	HIR (n = 512)	SIR (n = 340)	HIR (n = 61)	SIR (n = 39)	HIR (n = 573)	SIR (n = 379)	40 mg ew (n = 304)	40 mg eow (n = 302)	40 mg ew (n = 46)	40 mg eow (n = 43)	40 mg ew (n = 350)	40 mg eow (n = 345)
Laboratory parameters (CTCAE criteria, grade ≥3), n/n (%)[n]												
Hemoglobin	11/505 (2.2)	6/332 (1.8)	1/61 (1.6)	0/38	12/566 (2.1)	6/370 (1.6)	9/299 (3.0)	7/297 (2.4)	1/45 (2.2)	0/43 (0)	10/344 (2.9)	7/340 (2.1)
Platelets	1/508 (0.2)	1/337 (0.3)	0/61	0/39	1/569 (0.2)	1/376 (0.3)	0/300	0/297	0/46 (0)	0/43 (0)	0/343	0/343
Neutrophils	5/509 (1.0)	5/338 (1.5)	3/60 (5.0)	1/39 (2.6)	8/569 (1.4)	6/377 (1.6)	5/300 (1.7)	5/301 (1.7)	3/46 (6.5)	1/42 (2.4)	8/346 (2.3)	6/343 (1.7)
Lymphocytes	8/508 (1.6)	2/335 (0.6)	4/58 (6.9)	3/37 (8.1)	12/566 (2.1)	5/372 (1.3)	2/300 (0.7)	6/297 (2.0)	2/43 (4.7)	2/41 (4.9)	4/343 (1.2)	8/338 (2.4)
ALT	0/509	0/339	0/61	0/39	0/570	0/378	1/300 (0.3)	2/300 (0.7)	0/46 (0)	0/43 (0)	1/346 (0.3)	2/343 (0.6)
AST	1/510 (0.2)	1/339 (0.3)	0/61	0/39	1/571 (0.2)	1/377 (0.3)	1/300 (0.3)	2/299 (0.7)	0/45 (0)	0/43 (0)	1/345 (0.3)	2/342 (0.6)

ALT, alanine transaminase; AST, aspartate transaminase; CTCAE, Common Terminology Criteria for Adverse Events; HSTCL, hepatosplenic T-cell lymphoma; NMSC, nonmelanoma skin cancer; RTI, respiratory tract infection; TEAE, treatment-emergent adverse event.

[a]Any TEAE assessed with reasonable possibility of being related to study drug by the investigator.

[b]Assessed by the investigator and AbbVie.

[c]One was postsurgical peritonitis (surgery performed was a laparotomy, resection of transverse colon, descending colon, and two-thirds of sigmoid colon, a partial colon resection and abdominal drainage) developed on day 121 in a male patient aged 65 years (died post treatment, day 78); and 1 was cardiac arrest in a male patient aged 30 years with history of hypertension, diabetes mellitus, and left ventricular hypertrophy who fell down the stairs on day 20 and was examined and discharged from the emergency department, the patient was found unresponsive in his bed 11 hours later (both not related to study drug).

[d]One was a White male (aged 52 years) with a history of anemia and former smoker for 20 years who experienced an event of pneumonia with an outcome of death and 1 was a White male (aged 63 years) with a history of gastroesophageal reflux disease, hypertension, and was a former smoker for 28 years, who was diagnosed with esophageal adenosquamous carcinoma (stage IV) with an outcome of death (both not related to study drug).

[e]One was a White male (aged 68 years) with history of diabetes mellitus, hypercholesteremia, hypertension, myocardial infarction, and former smoker for 44 years, who experienced an event of disseminated non–small cell lung carcinoma resulting in death and 1 was a White female (aged 69 years) with a history of hypertension and asthma who experienced an event of pulmonary embolism with an outcome of death (both not related to study drug).

[f]Excluding oral candidiasis and tuberculosis.

[g]One case of malignant melanoma in situ (study drug related, severe), 1 case of squamous cell carcinoma of the cervix (study drug unrelated), and 1 case of basal cell carcinoma (study drug unrelated).

[h]One case of esophageal adenocarcinoma and 1 case of bladder cancer (both serious and unrelated to study drug), 1 case of serious malignant melanoma (unrelated to study drug), and 1 basal cell carcinoma moderate in severity (nonserious, study drug related).

[i]One serious TEAE of non–small cell lung cancer (study drug unrelated) and 1 serious TEAE of malignant melanoma (related to study drug).

[j]Excluding NMSC, melanoma, lymphoma, HSTCL, and leukemia.

[k]Including angioedema/anaphylaxis.

[l]Including pancytopenia.

[m]With the exception of gall bladder–related events.

[n]The n values for each of the laboratory parameters reflect missing values.

different between dosing groups. Similar trends were observed in the integrated population.

Histology

During induction in the main study population, the mean (SD) change from baseline at week 8 in Geboes score, RHI, and the proportions of patients (ITT population) who achieved histologic remission was numerically higher in the HIR group compared with the SIR group (Supplementary Table 5). Cross-tabulation of histologic remission and endoscopy improvement at week 8 followed a similar pattern but revealed no notable trends across dosing regimens. Similar trends were observed in the integrated population.

During maintenance in the main study population, the proportion of patients (ITT-RP population) who received the adalimumab 40 mg ew dosing regimen and achieved histologic remission at week 52 was numerically lower for Geboes score <2 and for RHI score <3 compared with patients receiving the 40 mg eow dosing regimen (Supplementary Table 5). Cross-tabulation of histologic remission and endoscopy improvement at week 52 revealed no notable trends across dosing regimens. Similar trends were observed in the integrated population.

Pharmacokinetics and Immunogenicity

Pharmacokinetics and immunogenicity data demonstrated that the fixed adalimumab dosing regimens resulted in differences in exposure (Supplementary Figure 4). At the end of the 8-week induction study, the mean trough adalimumab concentration was more than 2-fold higher in the HIR group (19.2 μg/mL) compared with the SIR (8.0 μg/mL) group (Supplementary Figure 4*A*). In the 44-week maintenance study, the 40 mg ew dosing regimen resulted in higher concentrations of adalimumab than the 40 mg eow regimen (Supplementary Figure 4*B*). In patients previously on HIR, the mean steady-state adalimumab concentrations in patients taking the 40 mg ew dosing regimen were approximately 2-fold higher than for patients taking the 40 mg eow dosing regimen (15–18 μg/mL vs 7–10 μg/mL from weeks 16 to 52). In those previously on SIR, the mean steady-state adalimumab concentrations in patients taking the 40 mg ew dosing regimen were also approximately 2-fold higher than in patients taking the 40 mg eow dosing regimen (14–17 μg/mL vs 5–8 μg/mL from weeks 16 to 52). A total of 21 patients became AAA+ during the study; the AAA+ rate was 2.2% (21 of 949) (Supplementary Figure 4*C*). Overall, immunogenicity did not appear to impact the safety or efficacy of adalimumab in patients with UC. Detailed pharmacokinetics and immunogenicity results will be reported in a subsequent publication.

Discussion

Adalimumab is approved and well established for the treatment of UC.[4–6] Results from the SERENE UC study confirm previous findings that adalimumab is an effective and well-tolerated therapy for inducing and maintaining clinical remission in patients with moderately to severely active UC who did not adequately respond to conventional therapies. In the induction study, main and integrated study populations, the higher adalimumab dosing regimen (with 160 mg at weeks 0, 1, 2, and 3) did not lead to superior clinical and/or endoscopic efficacy at week 8 compared with the approved standard dosing regimen. Serum adalimumab concentrations were higher in patients taking the HIR compared with the SIR; however, increased serum adalimumab concentrations did not translate into increased efficacy. Several factors may contribute to the lack of association between adalimumab concentration and efficacy; these include interpatient variability, the possibility that the studied doses are close to the exposure–response relationship plateau, and the possibility that efficacy differences between dose groups may take longer than 8 weeks to emerge. Previous studies reporting adalimumab exposure–response relationships may be limited by the narrow concentration range observed when evaluating a single-dose regimen.[23] In the main and integrated study populations, the safety profile of adalimumab in patients receiving the HIR was comparable with that of patients receiving the SIR, and both were consistent with the known safety profile of adalimumab in inflammatory bowel disease.[4,7,24]

In the maintenance study, for week 52 remission rates among week-8 responders, a clinically meaningful difference in clinical remission was observed with adalimumab 40 mg ew dosing, as evidenced by the $>10\%$ absolute difference for clinical remission rates between groups (39.5% vs 29.0% among week-8 responders receiving 40 mg ew vs 40 mg eow). Although the difference did not achieve statistical significance in the main study population, in the larger integrated study population, the difference in clinical remission rates was associated with a P value of .045 (absolute difference, 11.0%; 95% CI, 0.2–20.4). These results may indicate that the eow maintenance regimen is not sufficient for some patients due to differences in pharmacokinetics variability or other unknown factors; these patients may benefit from an ew maintenance regimen.

Not all patients experienced an increased response to weekly adalimumab maintenance dosing. When adjusted for UC disease duration (eg, $\leq$4.65, $>$4.65 years), week-8 RBS (0, $>$0), or geographic region (Eastern Europe, non-Eastern Europe) as covariates in a post-hoc analysis, significantly greater proportions of patients receiving higher vs standard adalimumab maintenance regimens achieved clinical remission ($P < .05$), suggesting that some patients may benefit from 40 mg ew adalimumab maintenance dosing. In addition, efficacy was greater with adalimumab 40 mg ew compared with adalimumab 40 mg eow among subgroups of patients with factors indicating more severe disease (eg, higher/elevated hs-CRP, extensive UC, low albumin). Patients with a high inflammatory burden, often characterized by elevated hs-CRP and lower albumin levels, may have higher drug clearance[25] and require higher drug exposure to achieve favorable therapeutic outcomes. However, these factors describe only a portion of the variability in pharmacokinetic parameters,[26–28] and additional evidence is

needed to elucidate whether subgroup-specific differences in pharmacokinetic parameters affect the efficacy of adalimumab in patients with UC.

Patients in this study were required to taper corticosteroid use from week 4 onward. A total of 27.2% and 39.6% of patients in the standard and higher adalimumab maintenance dosing regimens, respectively, achieved steroid-free (≥90 days) clinical remission at week 52, suggesting the 40 mg ew maintenance dosing regimen may provide additional clinical benefit, given the steroid tapering, potentially reducing the AEs associated with long-term corticosteroid use.

Among patients with week-8 response, adalimumab serum concentrations were higher with 40 mg ew maintenance dosing compared with 40 mg eow maintenance dosing. Overall, neither serum concentrations nor immunogenicity appeared to have a significant impact on the efficacy and safety of adalimumab in patients with UC. In the main and integrated patient populations, the adalimumab 40 mg ew maintenance dosing regimen was generally well tolerated and similar to the 40 mg eow maintenance dosing regimen. No new safety concerns were identified compared with what has been observed for adalimumab previously.[29,30]

The proactively designed, exploratory TDM arm demonstrated clinical remission rates between those observed for adalimumab 40 mg ew and 40 mg eow. A detailed report of TDM efficacy and safety results is forthcoming in a separate publication.

Although differences in patient-reported outcomes across higher vs standard dosing groups were not statistically significant, marked improvements from baseline demonstrate important quality-of-life benefits from adalimumab regardless of dosing regimen. The prespecified histology-related end points were exploratory in nature, no assumptions were made regarding the impact of higher vs standard adalimumab doses on histologic remission. Analyses of histology-related end points did not reveal significant differences between patients receiving the standard vs higher induction dosing regimen or patients receiving the 40 mg ew or 40 mg eow maintenance dosing regimen.

The SERENE UC study design was limited by the absence of a placebo control group. Direct comparison of results from SERENE UC with previous studies of adalimumab in patients with moderately to severely active UC (ie, ULTRA 2) is limited due to study design differences (eg, rerandomization vs treat-through, centralized vs decentralized endoscopy reading, and mandatory steroid tapering vs continuation of steroid use at stable dose). The exploratory arm added to assess the role of proactive TDM was not powered to evaluate the primary end points, limiting interpretations of the TDM results

In conclusion, results from the SERENE UC study confirm that currently approved doses of adalimumab are effective and well tolerated for inducing and maintaining clinical remission in patients with moderately to severely active UC who do not respond adequately to conventional therapies. Although the primary end point for the induction study was not met, a >10% absolute difference in clinical remission was demonstrated with ew vs eow adalimumab dosing regimens (maintenance study primary end point), a difference that was statistically significant in the integrated study population. Weekly adalimumab maintenance dosing, which is approved for loss of response in the European Union, may be appropriate for some patients (eg, those with extensive colitis or low albumin levels, based on results from the subgroup analyses). The safety profile of higher adalimumab induction and maintenance dosing regimens was comparable with that of the standard dosing regimens, indicating no additional risk. The benefit–risk profile of the adalimumab standard induction and maintenance dosing regimen as approved for patients with moderately to severely active UC remains unchanged.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2022.02.033.

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Received July 20, 2021. Accepted February 20, 2022.

Correspondence
Address correspondence to: Julián Panés, MD, Hospital Clínic i Provincial de Barcelona, August Pi i Sunyer Biomedical Research Institute, Biomedical Research Networking Center in Hepatic and Digestive Diseases, Barcelona 08036, Spain. e-mail: jpanes@clinic.cat.

Acknowledgments
AbbVie and the authors thank all study investigators for their contributions and the patients who participated in this study. The authors thank Lynn Randall (AbbVie) for contributing to data interpretation and James W. Butler, a former AbbVie employee, for contributing to statistical analysis and data interpretation. William Sandborn was supported in part by the National Institute of Diabetes and Digestive and Kidney Diseases–funded San Diego Digestive Diseases Research Center (P30 DK120515). Medical writing assistance, funded by AbbVie, was provided by Caroline W. Cazares, PhD, of JB Ashtin.

CRediT Authorship Contributions
Julián Panés, MD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Jean-Frederic Colombel, MD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Geert R. D'Haens, MD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Stefan Schreiber, MD, PhD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Remo Panaccione, MD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Laurent Peyrin-Biroulet, MD, PhD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Edward V. Loftus Jr, MD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Silvio Danese, MD, PhD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Satoshi Tanida, MD, PhD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Yusuke Okuyama, MD, PhD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Edouard Louis, MD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Alessandro Armuzzi, MD, PhD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

Marc Ferrante, MD, PhD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Harald Vogelsang, MD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Toshifumi Hibi, MD, PhD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Mamoru Watanabe, MD, PhD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Jessica Lefebvre, MD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Tricia Finney-Hayward, PhD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Yuri Sanchez Gonzalez, PhD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Thao T. Doan, MD (Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Nael M. Mostafa, PhD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Kimitoshi Ikeda, PhD (Data curation: Equal; Formal analysis: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Wangang Xie, PhD (Data curation: Equal; Formal analysis: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Bidan Huang, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Joel Petersson, MD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Jasmina Kalabic, MD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
Anne M. Robinson, PharmD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).
William J. Sandborn, MD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)

Data Availability

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 (eg, 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 and execution of a data sharing agreement. 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

Conflicts of interest

These authors disclose the following: Julián Panés has received research grants from AbbVie and Pfizer; speaker's fees from AbbVie, Ferring, Janssen, Merck, Pfizer, Shire, Takeda, and Theravance; and has been a consultant for AbbVie, Arena, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Genentech, GlaxoSmithKline, GoodGut, Janssen, Merck, Nestlé, Origo, Pandion, Pfizer, Progenity, Robarts Clinical Trials, Roche, Takeda, Theravance, and Wassermann. Jean-Frederic Colombel has received research grants from AbbVie, Janssen, and Takeda; speaker's fees from AbbVie, Allergan, Amgen, Ferring, Shire, and Takeda; and consulting fees from AbbVie, Amgen, Arena, Boehringer Ingelheim, BMS, Celgene, Ferring, Galmed, Genentech, GlaxoSmithKline, Imedex, Immunic, Iterative Scopes, Janssen, Kaleido, LillyMerck, Microba, Novartis, PBM Capital, Pfizer, Sanofi, Takeda, TiGenix, and Vifor; he also holds stock options in Intestinal Biotech Development. Geert R. D'Haens has served as advisor for AbbVie, Ablynx, Active Biotech AB, Agomab Therapeutics, Alimentiv, Allergan, Alphabiomics, Amakem, Amgen, AM Pharma, Applied Molecular Therapeutics, Arena, AstraZeneca, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Celltrion, DSM Pharma; Echo Pharmaceuticals, Eli Lilly, Engene, Exeliom Biosciences, Ferring, DrFALK Pharma, Galapagos, Genentech/Roche, Gilead, Glaxo Smith Kline, Gossamerbio, Pfizer, Immunic, Johnson and Johnson, Kintai Therapeutics, Lument, Lycera, Takeda, Medtronic, Mitsubishi Pharma, Merck Sharp Dome, Novonordisk, Otsuka, Photopill, ProciseDx, Prodigest, Prometheus laboratories/Nestle, Progenity, Protagonist, RedHill, Samsung Bioepis, Sandoz, Seres, Setpoint, Shire, Teva, Tillotts, Topivert, Versant, and Vifor. Stefan Schreiber has been a consultant for AbbVie, Amgen, Arena, Bristol Myers Squibb; Boehringer Ingelheim, Celltrion, Dr Falk Pharma, Ferring, Fresenius, Galapagos, Genentech, GlaxoSmithKline, Gilead, IMAB-Biopharma, Janssen, Lilly, Merck, Novartis/Sandoz, Pfizer, Protagonist, Takeda, and Theravance. Remo Panaccione has received consulting fees from AbbVie, Abbott, Alimentiv (formerly Robarts), Amgen, Arena, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Eli Lilly, Ferring, Galapagos, Genentech, Gilead Sciences, Glaxo-Smith Kline, Janssen, Merck, Mylan, Oppilan Pandion, Pharma, Pandion Pharma, Pfizer, Progenity, Protagonist Therapeutics, Roche, Satisfai Health, Sandoz, Schering-Plough, Shire, Sublimity Therapeutics, Theravance, UCB, and Takeda; speaker fees from AbbVie, Arena, Celgene, Eli Lilly, Ferring, Gilead Sciences, Janssen, Merck, Pfizer, Roche, Sandoz, Shire, and Takeda; research/educational support from AbbVie, Ferring, Janssen, Pfizer, and Takeda; and has served on an advisory board for AbbVie, Amgen, Arena, Bristol Myers Squibb, Celgene, Celltrion, Eli Lilly, Ferring, Galapagos, Genentech, Gilead Sciences, Glaxo-Smith Kline, Janssen, Merck, Mylan, Oppilan Pharma, Pandion Pharma, Pfizer, Sandoz, Shire, Sublimity Therapeutics, Theravance, and Takeda. Laurent Peyrin-Biroulet has received personal fees from AbbVie, Allergan, Amgen, Arena, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Enthera, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead, Gossamer Bio, Index Pharmaceuticals, Inotrem, Janssen, Lilly, Merck, Mylan, Norgine, OSE Immunotherapeutics, Pandion Therapeutics, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, Theravance, Thermofisher, Tillotts, Viatris, and Vifor; and grants from AbbVie, Fresenius Kabi, Merck, and Takeda. He also holds CTMA stock options. Edward V. Loftus Jr has been a consultant for AbbVie, Allergan, Amgen, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Calibr, Celgene, Celltrion, Genentech, Gilead, Iterative Scopes, Janssen, Lilly, Ono Pharma, Pfizer, Sun Pharma, Takeda, and UCB; and received research grants from AbbVie, Amgen, Bristol Myers Squibb, Genentech, Gilead, Janssen, Pfizer, Receptos (Celgene), Robarts Clinical Trials, Takeda, Theravance, and UCB. Silvio Danese has received research grants from AbbVie, Amgen, Celgene, Genentech, Gilead, Janssen, Pfizer, Receptos (Celgene), Robarts Clinical Trials, Seres Therapeutics, Takeda, and UCB; and been a consultant for AbbVie, Allergan, Amgen, Bristol Myers Squibb, Celgene, Celltrion, Janssen, Lilly, Pfizer, Takeda, and UCB. Satoshi Tanida has received research grants from AbbVie and EA Pharma. Edouard Louis has received research grants from Takeda, Pfizer, and Janssen; educational grants from AbbVie, Takeda, and Janssen; speaker fees from AbbVie, Ferring, MSD, Falk, Takeda, Janssen, Pfizer, and Celgene; participated in advisory boards for AbbVie, Ferring, MSD, Takeda, Celgene, Janssen, Gilead-Galapagos, Arena, Pfizer, and Eli Lilly; and has been a consultant for AbbVie. Alessandro Armuzzi has been a consultant or advisory board member for AbbVie, Allergan, Amgen, Arena, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Ferring, Galapagos, Gilead, Janssen, Lilly, Merck, Mylan, Pfizer, Roche, Samsung Bioepis, Sandoz, Sofar SpA, and Takeda; has received speaker's fees from AbbVie, Amgen, Arena, Biogen, Bristol Myers Squibb, Ferring, Galapagos, Gilead, Janssen, Medtronic, Merck, Mitsubishi Tanabe Pharma, Nikkiso, Novartis, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, and TiGenix; and received research grants from Merck, Pfizer, and Takeda. Marc Ferrante has been a consultant for AbbVie, Boehringer Ingelheim, Celltrion, Janssen, Lilly, Medtronic, Merck, Pfizer, Sandoz, Takeda, and Thermo Fisher; has received research grants from AbbVie, Amgen, Biogen, Janssen, Pfizer, and Takeda; and received speaker's fees from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Dr Falk Pharma, Ferring, Janssen, Lamepro BV, Merck, Mylan, Pfizer, Sandoz, Takeda, and Truvion Healthcare. Harald Vogelsang has received consulting and/or speaker's fees from AbbVie, Amgen, Astro Pharma, Bristol Myers Squibb, Dr Falk Pharma, Ferring, Gilead, Janssen, Merck, MSD, Pfizer, and Takeda. Toshifumi Hibi is an editor of *Intestinal Research* and has received grants, personal fees, and/or other funds from AbbVie, Aspen Pharmacare, Celltrion, EA Pharma, Ferring, Gilead, Janssen, JIMRO, Kissei Pharmaceutical, Kyorin Pharmaceutical, Lilly, Mitsubishi Tanabe Pharma, Miyarisan Pharmaceutical, Mochida Pharmaceutical, Nichi-Iko, Nippon Kayaku, Otsuka, Pfizer, Takeda, and Zeria Pharmaceutical. Mamoru Watanabe has received grants, personal fees, and/or other funds from AbbVie, Alfresa Pharma, Asahi Kasei Medical, Astellas, Ayumi Pharmaceutical, Celgene, Celltrion, Chugai, Daiichi Sankyo, EA Pharma, Eisai, Fujirebio, Gilead, Janssen, JIMRO, Kaken Pharmaceutical, Kissei Pharmaceutical, Kyorin Pharmaceutical, Kyowa Kirin, Lilly, Merck, Mitsubishi Tanabe Pharma, Miyarisan Pharmaceutical, Mochida Pharmaceutical, Nippon Kayaku, Pfizer, Taiho Pharmaceutical, Takeda, Toray Industries, and Zeria Pharmaceutical. Jessica Lefebvre, Thao T. Doan, Nael M. Mostafa, Wangang Xie, Bidan Huang, Joel Petersson, Tricia Finney-Hayward, Jasmina Kalabic, Kimitoshi Ikeda, Yuri Sanchez Gonzalez, and Anne M. Robinson are full-time employees of AbbVie, and may own AbbVie stock or options. William J. Sandborn has received research grants from AbbVie, Abivax, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Genentech, Gilead Sciences, Glaxo Smith Kline, Janssen, Lilly, Pfizer, Prometheus Biosciences, Seres Therapeutics, Shire, Takeda, and Theravance Biopharma; consulting fees from AbbVie, Abivax, Alfasigma, Alimentiv (previously Robarts Clinical Trials, owned by Alimentiv Health Trust), Allakos, Amgen, Arena, AstraZeneca, Atlantic Pharmaceuticals, Beigene, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Clostrabio, Forbion, Galapagos, GlaxoSmithKline, Gossamer Bio, Index Pharmaceuticals, Iota Biosciences, Janssen, Lilly, Morphic Therapeutics, Novartis, Oppilan Pharma (now Venytx Biosciences), Pfizer, Pharm Olam, Polpharm, Progenity, Prometheus Biosciences, Protagonists Therapeutics, PTM Therapeutics, Seres Therapeutics, Shoreline Biosciences, Sublimity Therapeutics, Surrozen, Takeda, Theravance Biopharma, Vendata Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivreon Gastrosciences, Xencor, and Zealand Pharmaceuticals; stock or stock options from Allakos, BeiGene, Gossamer Bio, Oppilan Pharma (now Ventyx Biosciences), Prometheus Biosciences,

Prometheus Laboratories Protagonists Therapeutics, Shoreline Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivreon Gastrosciences; and employee at Shoreline Biosciences. Spouse: Iveric Bio - consultant, stock options; Progenity - stock; Oppilan Pharma (now Ventyx Biosciences) - stock; Prometheus Biosciences - employee, stock, stock options; Prometheus Laboratories – stock, stock options, consultant; Ventyx Biosciences – stock, stock options; Vimalan Biosciences – stock, stock options. The remaining author discloses no conflicts.

Funding
AbbVie funded the research for this study and provided writing support for this manuscript. AbbVie Inc participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving of this manuscript. All authors had access to the data, and participated in the development, review, and approval, and in the decision to submit this manuscript for publication. Medical writing assistance was funded by AbbVie.