Journal Pre-proof

Higher vs Standard Adalimumab Induction Dosing Regimens and 2 Maintenance Strategies: Randomized SERENE CD Trial Results

Geert R. D'Haens, William J. Sandborn, Edward V. Loftus, Jr., Stephen B. Hanauer, Stefan Schreiber, Laurent Peyrin-Biroulet, Remo Panaccione, Julian Panés, Filip Baert, Jean-Frederic Colombel, Marc Ferrante, Edouard Louis, Alessandro Armuzzi, Qian Zhou, Venkata S. Goteti, Nael M. Mostafa, Thao T. Doan, Joel Petersson, Tricia Finney-Hayward, Alexandra P. Song, Anne M. Robinson, Silvio Danese

PII: S0016-5085(22)00099-3
DOI: https://doi.org/10.1053/j.gastro.2022.01.044
Reference: YGAST 64871

To appear in: *Gastroenterology*
Accepted Date: 25 January 2022

Please cite this article as: D'Haens GR, Sandborn WJ, Loftus Jr EV, Hanauer SB, Schreiber S, Peyrin-Biroulet L, Panaccione R, Panés J, Baert F, Colombel J-F, Ferrante M, Louis E, Armuzzi A, Zhou Q, Goteti VS, Mostafa NM, Doan TT, Petersson J, Finney-Hayward T, Song AP, Robinson AM, Danese S, Higher vs Standard Adalimumab Induction Dosing Regimens and 2 Maintenance Strategies: Randomized SERENE CD Trial Results, *Gastroenterology* (2022), doi: https://doi.org/10.1053/j.gastro.2022.01.044.

Higher vs Standard Adalimumab Induction Dosing Regimens and 2 Maintenance Strategies: Randomized SERENE CD Trial Results

Running Title: Adalimumab Dosing Regimens for Crohn's Disease

Geert R. D'Haens,[1] William J. Sandborn,[2] Edward V. Loftus, Jr,[3] Stephen B. Hanauer,[4] Stefan Schreiber,[5] Laurent Peyrin-Biroulet,[6] Remo Panaccione,[7] Julian Panés,[8] Filip Baert,[9] Jean-Frederic Colombel,[10] Marc Ferrante,[11] Edouard Louis,[12] Alessandro Armuzzi,[13] Qian Zhou,[14] Venkata S. Goteti,[14] Nael M. Mostafa,[14] Thao T. Doan,[14] Joel Petersson,[14] Tricia Finney-Hayward,[15] Alexandra P. Song,[14] Anne M. Robinson,[14] and Silvio Danese[16]

[1]Amsterdam Gastroenterology Endocrinology Metabolism and Gastroenterology and Hepatology Departments, Amsterdam University Medical Centers, Amsterdam, The Netherlands; [2]Gastroenterology Department, University of California San Diego, La Jolla, California; [3]Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; [4]Department of Medicine (Gastroenterology and Hepatology), Northwestern University, Chicago, Illinois; [5]Department of Internal Medicine, University Hospital Schleswig-Holstein, Kiel, Germany; [6]Department of Gastroenterology, University Hospital of Nancy, Lorraine University, Vandoeuvre, France; [7]Department of Medicine, University of Calgary, Calgary, AB, Canada; [8]Department of Gastroenterology, Hospital Clinic Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain; [9]Department of Gastroenterology, AZ Delta, Roeselare-Menen, Belgium; [10]Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; [11]Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium; [12]Department of Gastroenterology, University Hospital CHU of Liège, Liège, Belgium; [13]CEMAD-IBD Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [14]AbbVie Inc.,

North Chicago, Illinois; [15]AbbVie Ltd, Maidenhead, United Kingdom; and [16]Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milan, Italy

Word Count: 6977

Study Sponsor:

AbbVie Inc. participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving of this manuscript. AbbVie funded the research for this study and provided writing support for this manuscript.

Abbreviations used in this paper: Anti-adalimumab antibody positivity, AAA+; AE, adverse event; AESI, adverse event of special interest; CA, clinically adjusted; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; EQ-5D-5L, 5-level European Quality of Life 5 Dimensions; ew, every week; eow, every other week; HIR, higher induction regimen; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; IOIBD, International Organization for the Study of Inflammatory Bowel Disease; ITT, intent to treat; OLE, open-label extension; PRO, patient-reported outcome; SAE, serious adverse event; SES-CD, Simple Endoscopic Score for CD, SIR, standard induction regimen; TDM, therapeutic drug monitoring; TEAE, treatment-emergent adverse event; TNFα, tumor necrosis factor α; WPAI, Work Productivity and Activity Impairment Questionnaire.

Correspondence

Address correspondence to: Geert D'Haens MD, PhD, Amsterdam University Medical Centers, Meibergdreef 9 - C2-208, 1105 AZ Amsterdam, The Netherlands. Phone: +31 20 5661768. Fax: +31 20 6917033. E-mail: g.dhaens@amsterdamumc.nl.

Conflicts of interest

The authors disclose the following: Geert R. D'Haens has served as advisor for AbbVie, Ablynx, Active Biotech AB, Agomab Therapeutics, Alimentiv, Allergan, Alphabiomics, Amgen, AM Pharma, Applied Molecular Therapeutics, Arena Pharmaceuticals, AstraZeneca, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Celltrion, Cosmo, Dr Falk Pharma, DSM Pharma, Echo Pharmaceuticals, Engene, Exeliom Biosciences, Ferring, Galapagos, Genentech/Roche, Gilead, GlaxoSmithKline, Gossamerbio, Immunic, Johnson and Johnson, Kintai Therapeutics, Lilly, Lument, Medtronic, Mitsubishi Pharma, Merck Sharp and Dome, Mundipharma, Novo Nordisk, Otsuka, Pfizer, ProciseDx, Prodigest, Prometheus Laboratories/Nestle, Progenity, Protagonist, RedHill, Salix, Samsung Bioepis, Sandoz, Seres/Nestec/Nestle, Setpoint, Takeda, Teva, Tigenix, Tillotts, Topivert, Versant, and Vifor. He has received speaker fees from AbbVie, Biogen, Ferring, Galapagos/Gilead, Johnson and Johnson, Merck Sharp and Dome, Mundipharma, Norgine, Pfizer, Samsung Bioepis, Shire, Millenium/Takeda, Tillotts, and Vifor. 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-Meyers 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. 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. He has received research grants from AbbVie, Amgen, Bristol-Myers Squibb, Genentech, Gilead, Janssen, MedImmune, Pfizer, Receptos (Celgene), Robarts Clinical Trials, Takeda, Theravance, and UCB. Stephen B Hanauer has been a consultant and/or speaker for AbbVie, Actavis, Allergan, Amgen, Arena Pharmaceuticals, Astra-Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Ferring, Genentech, Gilead, GlaxoSmithKline, Gossamer, Janssen, Lilly, Merck, Nestlé, Novartis, Pfizer, Prometheus Biosciences, Protagonist, Salix, Samsung Bioepis, Sanofi, Seres Therapeutics, Shire, Takeda, and Therakos. He has received research grants from AbbVie, Allergan, Amgen, Celgene, Genentech, GlaxoSmithKline, Janssen, Lilly, Novartis, Pfizer, Prometheus Biosciences, Receptos (Celgene), and Sanofi. Stefan Schreiber has been a consultant for AbbVie, Amgen, Arena, Bristol-Myers Squibb, Boehringer Ingleheim, Celltrion, Dr Falk Pharma, Ferring, Fresenius, Galapagos, Genentech, GlaxoSmithKline, Gilead, IMAB-Biopharma, Janssen, Lilly, Merck, Novartis/Sandoz, Pfizer, Protagonist, Takeda, and

Theravance. Laurent Peyrin-Biroulet has received personal fees from AbbVie, Allergan, Alma Bio Therapeutics, Amgen, Arena, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Enterome, Ferring, Genentech, Gilead, Hikma, InDex Pharmaceuticals, Janssen, Merck, Nestlé, Pfizer, Pharmacosmos, Roche, Samsung Bioepis, Sandoz, Sterna Biological, Takeda, and Tillotts Pharma; and grants from AbbVie, Merck, and Takeda. He also holds Clementia Pharmaceuticals stock options. 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, Ferring, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Lilly, Merck, Mylan, Oppilan Pharma, Pandion Pharma, Pfizer, Progenity, Protagonist Therapeutics, Roche, Sandoz, Satisfai Health, Schering-Plough, Shire, Sublimity Therapeutics, Takeda, Theravance, and UCB. He has received speaker fees from AbbVie, Arena, Celgene, Ferring, Gilead Sciences, Janssen, Lilly, Merck, Pfizer, Roche, Sandoz, Shire, and Takeda. He has received 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, Ferring, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Lilly, Merck, Mylan, Oppilan Pharma, Pandion Pharma, Pfizer, Sandoz, Shire, Sublimity Therapeutics, Takeda, and Theravance. Julian Panés has received research grants from AbbVie and Pfizer; speaker's fees from AbbVie, Ferring, Janssen, Pfizer, and Takeda; and has been a consultant for AbbVie, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Genentech, GlaxoSmithKline, Janssen, Origo, Pandion, Pfizer, Progenity, Robarts Clinical Trials, Roche, Takeda, Theravance, and Wassermann. Filip Baert has been a consultant and/or speaker from AbbVie, Arena, Biogen, Bristol-Myers Squibb, Celgene, Celltrion, Dr Falk Pharma, Ferring, Galapagos, Janssen, Merck, Mundipharma, Pfizer, Sandoz, Takeda, and Vifor Pharma. He has received research grants from AbbVie, Amgen, Chiesi, Janssen, Ipsen, and Merck. Jean-Frederic Colombel reports receiving research grants from

AbbVie, Janssen, and Takeda; receiving payment for lectures from AbbVie, Amgen, Allergan, Ferring, Shire, and Takeda; receiving consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Ferring, Galmed Research, Genentech, GlaxoSmithKline, Janssen, Kaleido Biosciences, Lilly, Imedex, Immunic, Iterative Scopes, Merck, Microba, Novartis, PBM Capital, Pfizer, Sanofi, Takeda, TiGenix, and Vifor. He holds stock options in Intestinal Biotech Development. Marc Ferrante has been a consultant for AbbVie, Boehringer Ingelheim, Celltrion, Janssen, Lilly, Medtronic, Merck, Pfizer, Sandoz, Takeda, and Thermo Fisher. He has received research grants from AbbVie, Amgen, Biogen, Janssen, Pfizer, and Takeda; and speaker's fees from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Dr Falk Pharma, Ferring, Janssen, Lamepro BV, Merck, Mylan, Pfizer, Sandoz, Takeda, and Truvion Healthcare. Edouard Louis has received research grants from Janssen, Pfizer, and Takeda; educational grants from AbbVie, Janssen, and Takeda; speaker fees from AbbVie, Celegene, Dr Falk Pharma, Ferring, Janssen, Merck, Pfizer, and Takeda; and has participated on advisory boards for AbbVie, Arena, Celgene, Ferring, Gilead-Galapagos, Janssen, Lilly, Merck, Pfizer, and Takeda; 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. He has received speaker's fees from AbbVie, Amgen, Arena, Biogen, Bristol-Myers Squibb, Ferring, Galapagos, Gilead, Janssen, Medtronic, Merck, Mitsubishi Tanabe Pharma, Novartis, Nikkiso, Novartis, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda and TiGenix.; and research grants from Merck, Pfizer, and Takeda. Qian Zhou, Venkata S. Goteti, Nael M. Mostafa, Thao T. Doan, Joel Petersson, Tricia Finney-Hayward, Alexandra P. Song, and Anne M. Robinson are full-time employees of AbbVie, and may own AbbVie stock or options. Silvio Danese has received research grants from AbbVie, Amgen, Genentech, Gilead, Janssen, Pfizer, Receptos (Celgene), Robarts Clinical Trials, Seres Therapeutics, Takeda, and UCB. He has been a consultant for

AbbVie, Allergan, Amgen, Bristol-Myers Squibb, Celgene, Celltrion, Janssen, Lilly, Pfizer, Takeda, and UCB.

Transcript Profiling

N/A

Writing Assistance

Medical writing assistance, funded by AbbVie, was provided by Lisa M Pitchford, PhD, of JB Ashtin.

CRediT Authorship Contributions

Geert R. D'Haens (Study conceptualization and design: Equal; Data acquisition and interpretation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); William J. Sandborn (Data acquisition and interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Edward V. Loftus, Jr (Data acquisition and interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Stephen B. Hanauer (Data acquisition and interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Stefan Schreiber (Data acquisition and interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Laurent Peyrin-Biroulet (Data interpretation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Remo Panaccione (Study conceptualization and design: Equal; Data interpretation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Julian Panés (Data acquisition and interpretation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Filip Baert (Data acquisition and interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Jean-Frederic Colombel (Study conceptualization and design: Equal;

Data acquisition and interpretation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Marc Ferrante (Data acquisition and interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Edouard Louis (Data acquisition and interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Alessandro Armuzzi (Data interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Qian Zhou (Data acquisition and interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Venkata S. Goteti (Statistical analysis: Equal; Data interpretation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Nael M. Mostafa (Data acquisition and interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Thao T. Doan (Data interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Joel Petersson (Study conceptualization and design: Equal; Data acquisition and interpretation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Tricia Finney-Hayward (Data interpretation: Equal; Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Alexandra P. Song (Study conceptualization and design: Equal; Data acquisition and interpretation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Anne M. Robinson (Study conceptualization and design: Equal; Data interpretation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); and Silvio Danese (Study conceptualization and design: Equal; Data acquisition and interpretation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal)

Acknowledgments

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, approval, and decision to submit this manuscript for publication. AbbVie and the authors thank all study investigators for their contributions and the patients who participated in this study. AbbVie would also like to acknowledge Jasmina Kalabic, Senior Medical Director at AbbVie, for her medical expertise and support throughout the study; James W Butler, a former AbbVie employee, for support of data analysis; Donyalle Richardson, Study Management Associate III at AbbVie, and Cordula Ubrig, Study Project Manager I at AbbVie, for operational leadership and oversight; Yuri Sanchez Gonzales, Director of Health Economics and Outcomes Research at AbbVie, for support of patient-reported outcomes analysis; and Bidan Huang, Senior Director, and Statistics TA Head, Specialty Data and Statistical Science at AbbVie, for her central role in the statistical analysis and design of the study. AbbVie funded the research for this study and provided writing support for this manuscript. Medical writing assistance, funded by AbbVie, was provided by Lisa M Pitchford, PhD, of JB Ashtin.

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.

Abstract

BACKGROUND & AIMS: Dose-optimization strategies for biologic therapies in Crohn's disease (CD) are not well established. SERENE CD evaluated higher vs standard adalimumab induction dosing and clinically adjusted (CA) vs therapeutic drug monitoring (TDM) maintenance strategies in patients with moderately to severely active CD. **METHODS:** In this phase 3, randomized, double-blind, multicenter trial, eligible adults (CD Activity Index [CDAI] of 220–450, endoscopic evidence of mucosal inflammation, and previous failure of standard therapies) were randomized to higher induction regimen (HIR; adalimumab 160mg at weeks 0, 1, 2, and 3; N = 308) or standard induction regimen (SIR; adalimumab 160mg at week 0 and 80mg at week 2; N = 206) followed by 40mg every other week from week 4 onward. Coprimary endpoints included clinical remission at week 4 and endoscopic response at week 12. At week 12, patients were rerandomized to maintenance therapy optimized by CDAI and C-reactive protein (CA; N = 92) or serum adalimumab concentrations ± clinical criteria (TDM; N = 92); exploratory endpoints were evaluated at week 56. **RESULTS:** Similar proportions of patients receiving HIR and SIR achieved clinical remission at week 4 (44% in both; *P*=.939) and endoscopic response at week 12 (43% vs 39%, respectively, *P* = .462). Week 56 efficacy was similar between CA and TDM. Safety profiles were comparable between dosing regimens. **CONCLUSIONS:** HIR was not superior to SIR, and CA and TDM maintenance strategies were similarly efficacious. Adalimumab therapy was well tolerated, and no new safety concerns were identified. (Clinicaltrials.gov, Number: NCT02065570)

Keywords: Biologic agent; monoclonal antibody; inflammatory bowel disease; TNF inhibitor

Abstract Word Count: 260

.

INTRODUCTION

Crohn's disease (CD) is a chronic, progressive, and transmural inflammatory bowel disease with gastrointestinal and systemic symptoms, including abdominal pain, diarrhea, weight loss, and fatigue, that negatively impact patients' quality of life.[1] Treatment for CD has traditionally focused on symptomatic improvement, clinical remission, and withdrawal of corticosteroids. In recent years, endoscopic outcomes have also become important treatment goals. Improvement in endoscopic outcomes has been associated with favorable patient outcomes, including higher rates of persistent clinical remission[2] and fewer hospitalizations and surgeries.[3] However, as endoscopic outcomes may be more difficult to achieve than clinical outcomes, we hypothesized that more intensive treatment may be required to achieve the treatment goal of endoscopic improvement in addition to clinical remission and symptomatic improvement.[4]

Adalimumab is a human immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to tumor necrosis factor alpha (TNFα) and inhibits this cytokine's activity by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab is approved in the United States,[5] Europe,[6] and globally[7] for treating adults with moderately to severely active CD. The standard approved adalimumab induction dose regimen for adults with CD is 160 mg followed by 80 mg 2 weeks later.[5, 8, 9] The recommended maintenance-dose regimen is 40 mg every other week (eow) from week 4 onward.[10] Patients who experience a decrease in their response to adalimumab 40 mg eow may benefit from a dose increase to adalimumab 40 mg every week (ew) or 80 mg eow. These approaches are approved in the European label[6]; however, dose escalation is not approved in the United States.

Exposure-response relationships from the CLASSIC and GAIN studies suggested that higher adalimumab serum concentrations were associated with greater efficacy (data on file), and

adalimumab trough concentrations were higher in patients who achieved endoscopic response in the Japanese DIAMOND study.[11] Thus, it was hypothesized that a higher induction dose regimen may lead to increased efficacy for more stringent endpoints, including endoscopic improvement. During maintenance therapy, dose escalation may improve outcomes for patients who experience a loss of response to adalimumab. In the CHARM study, over a quarter of patients met protocol-defined criteria for adalimumab dose escalation; of these, 37% achieved clinical remission after dose escalation.[12] Approaches used to guide and optimize dose adjustment during maintenance therapy may provide another strategy to further enhance efficacy. One of the suggested approaches is proactive therapeutic drug monitoring (TDM), where measurements of serum drug concentrations are used to optimize the clinical benefit of therapies. TDM is an area of considerable interest in the ever-evolving field of inflammatory bowel disease management.[13-15]

SERENE CD (Study of a novEl appRoach to induction and maintenance dosing with adalimumab in patiENts with modErate to severe Crohn's Disease) was designed to evaluate the efficacy and safety of higher vs standard adalimumab induction regimens and to compare the efficacy and safety of TDM vs clinically adjusted (CA) maintenance strategies in adult patients with moderately to severely active CD.

Methods

Study Design

The SERENE CD study was a phase 3, randomized, double-blind, multicenter clinical trial conducted across 93 sites in 19 countries (Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, The Netherlands, Poland, Romania, Slovakia, Spain, Switzerland, Ukraine, United Kingdom, and the United States). As originally designed, the SERENE CD study included a 12-week, 2-arm induction study followed by a separate 40-week open-label extension (OLE) study. While the study was ongoing, a consensus paper from the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) recommended that endoscopic remission be defined using the Simple Endoscopic Score for CD (SES-CD) 0–2, while emphasizing that further research was warranted to define endoscopic targets predicting favorable outcomes.[16] Based on this evolving interest in more stringent endoscopic endpoints as well as the evaluation of TDM, the study was amended. The sample size was increased to provide sufficient power to include an additional ranked secondary endpoint (IOIBD-defined endoscopic remission [ie, SES-CD ≤2]) to the induction study. This increased sample size also allowed the addition of an exploratory 44-week, double-blind maintenance study to investigate TDM, maximizing the study design to address the high interest in TDM for adalimumab.[13-15] (**Figure 1**). Patients entering the study after this amendment received induction and maintenance treatment under the amended protocol and were not enrolled into the OLE study (see **Supplementary Methods** for a summary of key protocol amendments). OLE study methods and results are reported in the supplement.

Per Good Clinical Practice guidelines, independent ethics committees/institutional review boards ensured the ethical, scientific, and medical appropriateness of the study and approved

the study documents before drug shipment to study sites. The study was conducted in accord with the protocol; International Council for Harmonisation guidelines; and applicable regulations, guidelines, and ethical principles originating from the Declaration of Helsinki. Patients provided written informed consent prior to screening or undergoing study-specific procedures. The SERENE CD study was registered at ClinicalTrials.gov (NCT02065570). 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) with moderately to severely active CD (CD Activity Index [CDAI] 220–450) despite full/adequate current or previous treatment with standard therapies (ie, oral corticosteroid and/or immunosuppressant therapies), and centrally read endoscopic evidence of mucosal inflammation defined as SES-CD ≥6 or ≥4 for isolated ileal disease, excluding the presence of the narrowing component. Patients diagnosed with ulcerative or indeterminate colitis were ineligible, as were patients with symptomatic bowel stricture, abdominal or perianal abscess, any ostomy or ileoanal pouch, or short bowel syndrome. The study allowed enrollment of patients with secondary loss of response or intolerance to infliximab (up to 25% of the total study population). Full inclusion and exclusion criteria are listed in the **Supplementary Methods**.

Study Treatment

In the induction study, eligible patients were randomized (3:2, stratified by baseline high-sensitivity C-reactive protein [hs-CRP levels <10 or ≥10 mg/L], prior infliximab use, and CD activity [CDAI ≤300 or >300]) to receive adalimumab using a higher induction regimen (HIR) or the standard induction regimen (SIR). For HIR, patients received adalimumab 160 mg at baseline, and at week 1, week 2, and week 3. For SIR, patients received adalimumab 160 mg at

baseline, placebo (adalimumab vehicle) at week 1, adalimumab 80 mg at week 2, and placebo at week 3. Starting at week 4, patients in both groups received adalimumab 40 mg eow through week 12. Concomitant medication use remained stable, except for corticosteroids, for which patients were required to taper their dose starting at week 4 per the protocol-defined taper schedule (see **Supplementary Methods** for details).

After addition of the exploratory 44-week double-blind maintenance study, all patients completing the induction study were rerandomized at week 12 (1:1) to adalimumab maintenance using clinically adjusted (CA) or TDM strategies. Randomization was stratified based on induction treatment regimen, clinical response (defined as reduction of CDAI by 70 points) at week 12, and SES-CD (>50% decrease from baseline at week 12, further stratified by endoscopic remission at week 12). All patients received 40 mg eow beginning at week 12. For the CA strategy, the adalimumab dose was escalated to 40 mg ew if the patient's CDAI was ≥220 or hs-CRP level (measured at weeks 12, 26, and 40, and unscheduled visits) was ≥10 mg/L (based on measured hematocrit and hs-CRP levels from the previous or current study visit); to reflect clinical practice, dose escalation could occur at weeks 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, or 54. The TDM strategy was intended to proactively achieve a minimum adalimumab concentration (5 µ/mL) in all patients based on assessment of concentration in conjunction with clinical criteria at 3 timepoints during the maintenance study (**Supplementary Figure 1**). While pharmacokinetic analyses from previous trials of adalimumab did not identify a serum concentration level that significantly and reliably predicted remission of CD (data on file), approximately 75% of the patients who were in clinical remission at week 56 in CLASSIC II had serum adalimumab concentrations >5 µg/mL and the median adalimumab concentration among patients in clinical remission was nearly 10 µg/mL.[17] The TDM dose adjustment criteria were designed to achieve adalimumab serum concentrations above 5 µg/mL and not exceeding ~20 µg/mL, which is an exposure range associated with

efficacy but does not exceed the maximum observed range in CLASSIC II. Based on blinded serum adalimumab concentrations from the previous study visit 2 weeks earlier, patients with adalimumab concentrations <5 µg/mL were escalated to 40 mg ew dosing, and patients with serum adalimumab concentrations >10 µg/mL remained at 40 mg eow dosing, regardless of clinical parameters. Patients with serum adalimumab concentrations ≥5 and ≤10 µg/mL were escalated to 40 ew dosing only if their CDAI was ≥220 or their hs-CRP level was ≥10 mg/L. Because of the time required for serum adalimumab levels to reach steady state after dose adjustments, dose escalation for patients in the TDM group could only occur at weeks 14, 28, or 42 **(Supplementary Figure 1)**. For both the CA and TDM strategies, once the adalimumab dose was escalated, it remained at 40 mg ew for the remainder of the study. To maintain blinding, all patients received weekly syringes from week 12 through the end of the study, with patients remaining on adalimumab 40 mg eow receiving placebo on alternate weeks.

Assessments

Efficacy Assessments–Induction Study. The coprimary endpoints were the proportions of patients who achieved (1) clinical remission (CDAI <150) at week 4, and (2) endoscopic response (>50% decrease from baseline in SES-CD [or a ≥2-point reduction in patients with a baseline SES-CD of 4]) at week 12. All endoscopic assessments were confirmed by a central reader.

Ranked secondary endpoints included, in order, (1) sustained clinical remission (clinical remission at both weeks 4 and 12); (2) clinical remission at week 4 and endoscopic response at week 12; (3) clinical remission at week 12; (4) steroid-free clinical remission (clinical remission among patients who were taking corticosteroids at baseline and discontinued their use) at week 12; (5) endoscopic remission (SES-CD ≤4, ≥2-point reduction in SES-CD from baseline, and no

subscore >1 in any individual variable) at week 12; (6) change from baseline in fecal calprotectin level at week 4; (7) hs-CRP levels <5 mg/L and fecal calprotectin <250 µg/g at week 4; (8) clinical remission, hs-CRP levels < 5 mg/L, and fecal calprotectin <250 µg/g at week 4; (9) clinical remission, hs-CRP levels <5 mg/L, endoscopic remission, and fecal calprotectin <250 µg/g at week 12; (10) SES-CD ≤2 at week 12; (11) clinical response (≥70-point decrease in CDAI from baseline) at week 4; (12) clinical response at week 12; (13) Inflammatory Bowel Disease Questionnaire (IBDQ)[18] bowel symptom domain response (≥8-point increase in IBDQ bowel symptom domain score) at week 4; (14) IBDQ bowel symptom domain response at week 12; and (15) IBDQ fatigue item response (≥1-point increase in IBDQ fatigue item score) at week 12. Selected other endpoints are listed in the **Supplementary Methods**.

Efficacy Assessments–Maintenance Study. All maintenance study endpoints were exploratory and were evaluated at week 56. These endpoints included: (1) clinical remission (among 3 populations: patients overall, patients who achieved clinical remission at week 12, and patients who underwent dose escalation); (2) steroid-free clinical remission (patients who discontinued corticosteroid use and achieved clinical remission among patients taking corticosteroids at baseline; (3) endoscopic response (among 3 populations: patients overall, patients who achieved endoscopic response at week 12, and patients who underwent dose escalation); (4) endoscopic remission (among 3 populations: patients overall, patients who achieved endoscopic remission at week 12, and patients who underwent dose escalation); (5) deep remission (both clinical remission and endoscopic remission); (6) change from baseline in fecal calprotectin concentration; (7) hs-CRP levels <5 mg/L and fecal calprotectin <250 µg/g; (8) clinical remission, hs-CRP levels <5 mg/L, and fecal calprotectin <250 µg/g; (9) clinical remission, hs-CRP levels <5 mg/L, endoscopic remission, and fecal calprotectin <250 µg/g; (10) SES-CD ≤2; (11) change from baseline in CDAI; (12) clinical response; (13) enhanced clinical

response; (14) IBDQ bowel symptom domain response; (15) IBDQ fatigue item response; (16) symptomatic remission; (17) symptomatic response; (18) IBDQ response; and (19) IBDQ remission.

Safety Assessments. Adverse events (AEs), vital signs, and laboratory parameters were assessed throughout the induction and maintenance studies. Except for those patients who continued commercially available adalimumab after the end of the study, patients were contacted 70 days after the last dose of study drug to assess any new or ongoing AEs. AEs and AEs of special interest (AESIs) were organized using the Medical Dictionary for Drug Regulatory Activities, version 20.1 or later, by system organ class, preferred term, relationship to study drug, and severity.

Patient-Reported Outcomes. Changes from baseline in IBDQ total scores, 5-level European Quality of Life 5 Dimensions (EQ-5D-5L)[19] index, and Work Productivity and Impairment Questionnaire (WPAI)[20] scores were assessed at weeks 4, 8, 12, 26, 40, and 56.

Pharmacokinetics and Immunogenicity. Serum adalimumab concentrations and anti-adalimumab antibody positivity (AAA+) were determined using a validated ligand binding assay.[21] The anti-adalimumab antibody assay was able to detect immunogenicity only when adalimumab concentrations were <2 µg/mL (meaning the assay was not drug-tolerant). Adalimumab concentrations were determined at baseline and weeks 2, 4, 6, 8, 12, 26, 40, and 56. Anti-adalimumab antibody positivity was determined prior to baseline and at weeks 4, 12,

26, 40, and 56. AAA+ was defined as ≥1 AAA concentration ≥20 ng/mL within 30 days of an adalimumab dose.

Statistical Analyses

All analyses were performed using SAS software (SAS Institute Inc., Cary, NC). All statistical tests were 2-sided with a 0.05 significance level. Sample size calculations and randomization procedures are described in the **Supplementary Methods**.

Induction study efficacy endpoints were analyzed for the intent-to-treat (ITT) population, which included all patients who were randomized at baseline; missing data were imputed using the nonresponder imputation (NRI) method. For binary variables, proportions of patients were compared between the HIR and SIR groups using the Cochran-Mantel-Haenszel test adjusting for the baseline stratification factors. For continuous variables, differences in change from baseline of the variable between treatment groups were analyzed using an analysis of covariance model including factors for treatment, baseline hs-CRP, prior infliximab use, CDAI at baseline, and the variable's baseline values. Patients who required initiation of corticosteroids or increased corticosteroid doses above their baseline dose were considered nonresponders and were censored from efficacy analyses.

Maintenance study endpoints were analyzed for the modified intent-to-treat (mITT) population, which included all patients in the ITT population who achieved clinical response at week 12. The NRI method was used to impute missing data for categorical endpoints, and the last observation carried forward method was used to impute continuous endpoints. Proportions of patients were compared between CA and TDM groups using the Cochran-Mantel-Haenszel test adjusted induction treatment (HIR or SIR) and achievement of endoscopic response at week 12.

Differences in change from baseline between treatment groups were analyzed using an analysis of covariance model including factors for treatment, induction regimen, achievement of endoscopic response at week 12, and respective induction baseline value.

All safety analyses included all patients who received ≥1 dose of study drug. Safety data were analyzed from baseline to week 12 (induction study) and from week 12 to the end of the study.

Adalimumab trough serum concentrations and AAA+ rates were summarized by treatment group at each time point using descriptive statistics. For the maintenance study, adalimumab concentrations were analyzed separately for patients receiving adalimumab 40 mg eow vs those whose dose was escalated to adalimumab 40 mg ew within each group (ie, CA eow, CA ew, TDM eow, and TDM ew).

Results

Patients

Of the 514 patients enrolled in the induction study, 308 and 206 patients were randomized to the HIR and SIR groups, respectively. The completion rate was high, with 479 patients (93.2% in both groups) completing the induction study **(Figure 2*A*)**. Nine patients who completed the induction study chose not to continue from induction to maintenance. Of the remaining 470 patients, 252 entered the OLE study, and 198 patients (78.6%) completed the OLE study. After the protocol amendment, all patients who completed the induction study (N = 218) were rerandomized into the 44-week maintenance study (safety population). Patients who achieved clinical response at week 12 (84%) were included in the maintenance study efficacy analyses (N = 184; 92 per arm); of these, 155 patients (CA group, 76/92 [82.6%]; TDM group, 79/92 [85.9%]) completed the maintenance study **(Figure 2*B*)**. Key demographics and baseline characteristics of patients were balanced between groups in both the induction (HIR vs SIR groups) and maintenance studies (CA vs TDM groups). Baseline characteristics were consistent with moderately to severely active CD; the mean (SD) disease duration was 7.3 (8.5) years **(Table 1)**. Approximately 17% of patients had previous failure of and/or intolerance to infliximab. Concomitant use of corticosteroids and immunosuppressants at baseline was reported by nearly 50% and 27% of patients, respectively.

Induction Study

Similar proportions of patients in the HIR and SIR groups achieved the coprimary efficacy endpoints of clinical remission at week 4 (43.5% and 43.7%; *P* = .939) and endoscopic response at week 12 (42.9% and 39.3%; *P* = .462; **Figure 3**). Interestingly, a larger treatment effect was seen for endoscopic response rates at week 12 in patients with ileal vs colonic

disease (Δ = 19.0 vs 6.1; **Supplemental Figure 2**). The proportions of patients who achieved the ranked secondary endpoints were also similar between groups, except for clinical remission and clinical response at week 12, which were numerically higher for HIR vs SIR. Clinical remission was achieved by 62.3% of patients in the HIR group vs 51.5% of patients in SIR group at week 12 (*P* = .008); 83.4% vs 74.8%, respectively, achieved clinical response at week 12 (*P* = .015; **Table 2**). Although rates were similar between groups, ~ 50% of patients in both the HIR and SIR group achieved steroid-free remission at week 12.

For other endpoints, the mean change in CDAI increased from baseline from week 2 through week 12 in both groups; at weeks 8 and 12, the mean change in CDAI from baseline was numerically greater for those in the HIR group than in the SIR group (*P* = .006 at week 12; **Supplementary Figure 3**). Similar patterns were observed for the proportion of patients who achieved clinical remission and clinical response over time. Numerically higher rates for the HIR group vs the SIR group were also observed for several nonranked induction study endpoints, including proportions of patients who achieved enhanced clinical response (*P* = .011), IBDQ response (*P* = .044), and symptomatic response (clinical response per reduction in stool frequency and abdominal pain criteria; *P* = .011) at week 12 (**Supplementary Table 1**). Clinical remission and endoscopic response rates at week 12 in the stratified subgroups (baseline hs-CRP, CD disease severity, and prior infliximab use) are presented in **Supplemental Table 2**.

AEs, severe AEs, serious adverse events (SAEs), treatment-related AEs, and AEs leading to discontinuation of the study drug were reported for similar proportions of patients receiving HIR vs SIR **(Table 3)**. The most frequently reported AEs in either group were headache, worsening of CD, nasopharyngitis, arthralgia, nausea, and dizziness. Most AEs were mild or moderate; severe AEs were reported for 17 patients (5.5%) in the HIR group and 13 patients (6.3%) in the SIR group. Of these, only worsening of CD occurred in >1 patient receiving either treatment

regimen. There were no treatment-emergent deaths. One case of renal papillary cell carcinoma assessed by the investigator as having no reasonable possibility of relationship to the study drug. This case of renal papillary cell carcinoma was reported at week 8 in the HIR group. Infections were reported for similar proportions of patients receiving HIR (22.4%) and SIR (23.8%), with most being nonserious. Serious infections were reported for 2 patients in each group (detailed in **Table 3**). A total of 3 opportunistic infections were reported for 1 patient in the HIR group and 2 patients in the SIR group (detailed in **Table 3**). One case of intestinal tuberculosis was reported for a patient in the SIR group (detailed in **Table 3**). Injection site reactions were reported for approximately 8% of patients in each group; all events were nonserious. Clinically significant (grade ≥3) laboratory parameter values were rare, and there were no notable mean changes in laboratory parameter or vital sign values.

Maintenance Study

The adalimumab maintenance dose was escalated to 40 mg ew for 28% of patients in the CA group **(Supplementary Figure 4*A*)** and 39% of patients in the TDM group **(Supplementary Figure 4*B*)**. In the CA group, the most frequent reason for dose escalation was hs-CRP levels ≥10 mg/L (69% of patients had their dose escalated based on hs-CRP alone; an additional 4% also had a CDAI ≥220). In the TDM group, the most frequent reason was a serum adalimumab concentration <5 µg/mL (58% of patients). While patients could have their doses escalated due to adalimumab concentration <5 µg/mL, irrespective of CDAI or hs-CRP level, 33% of patients had low serum concentrations alone and 25% also had hs-CRP levels ≥10 mg/L with or without a CDAI ≥220 in conjunction with low serum levels. Among patients who underwent dose escalation, similar proportions of patients receiving each maintenance strategy achieved clinical remission (CA: 53.8%, TDM: 55.6%; *P* = .789), endoscopic response (CA: 34.6%, TDM: 25.0%;

P = .501), and endoscopic remission (CA: 23.1%, TDM: 19.4%; *P* = .966; **Supplementary Figure 4*C***) at week 56.

Similar proportions of patients in the CA and TDM groups achieved each week 56 efficacy endpoint (all exploratory) in the maintenance study **(Figure 4*A*)**. At week 56, 70.7% of patients in the CA group and 66.3% of patients in the TDM group achieved clinical remission (*P* = .497). More than 70% of patients taking corticosteroids at induction baseline achieved steroid-free clinical remission (76.9% and 73.2% in CA and TDM groups, respectively; *P* = .636). Slightly more than 40% (44.6% and 43.5% in the CA and TDM groups, respectively) of patients achieved endoscopic response, and approximately 30% (31.5% and 29.3%) achieved endoscopic remission (*P* = .824 and .621, respectively). Similar proportions of patients also met the more stringent endpoint of both clinical remission and endoscopic remission (ie, deep remission) in each group (29.3% in the CA group and 26.1% in the TDM group; *P* = .507). The proportions of patients who achieved other efficacy endpoints, including symptomatic remission/response per stool frequency and abdominal pain criteria, were also similar between CA and TDM groups **(Supplementary Table 3)**.

The proportions of patients who maintained clinical remission, endoscopic response, or endoscopic remission at week 56 among those who had achieved the same endpoint at week 12 of the induction study are shown in **Figure 4*B***. More than 70% of patients with clinical remission at week 12 maintained clinical remission at week 56, with similar rates between the CA and TDM groups. Endoscopic response and endoscopic remission were maintained by more than 50% of patients in both groups; rates were slightly numerically higher among patients in the CA group vs the TDM group.

During the maintenance study, rates of AEs, severe AEs, SAEs, treatment-related AEs, and AEs leading to discontinuation of the study drug were similar between groups **(Table 3)**. AEs reported for ≥5% of patients included worsening of CD, nasopharyngitis, headache, arthralgia, and diarrhea. No deaths or malignancies were reported. Except for infections, the overall rates of AESIs were low. Infections were reported for similar proportions of patients in the CA and TDM groups (33.9% and 34.9%, respectively), and most infections were nonserious. Serious infections were reported for 3 patients in the TDM group (detailed in **Table 3**); none were reported in the CA group. No opportunistic infections were reported during the maintenance study. There were no notable mean changes in laboratory values; shifts in laboratory values were infrequent and not considered clinically meaningful.

Patient-Reported Outcomes

The mean changes from baseline in IBDQ total score, responses on the WPAI, and responses on the EQ-5D-5L indicated overall improvements in patient-reported outcomes (PROs) from baseline to week 4 of the induction study and through week 56 (**Supplementary Figure 5**). Changes in PROs were similar between the HIR and SIR groups during the induction study and between CA and TDM groups during the maintenance study.

Pharmacokinetics and Immunogenicity

Pharmacokinetic and immunogenicity data demonstrated that different induction dosing regimens of adalimumab resulted in differences in exposure (**Supplementary Figure 6**). Throughout the 12-week induction study, the mean adalimumab concentration was higher in the HIR group compared with the SIR group. At the beginning of the maintenance study (week 12), mean adalimumab concentrations were similar between the CA and TDM groups overall, however the concentrations trended lower among patients who subsequently had their doses

escalated. This difference appeared to be larger in the TDM group compared with the CA group. At week 56, mean adalimumab concentrations in the CA group were slightly higher among patients who had their doses escalated to adalimumab 40 mg ew compared with patients who continued receiving adalimumab 40 mg eow (13.9 vs 9.7 µg/mL, respectively). However, in the TDM group, mean adalimumab concentrations were similar (~10 µg/mL), regardless of whether patients were receiving adalimumab 40 mg eow or had their dose escalated to adalimumab 40 mg ew. AAA+ rates during the entire study were low; a total of 11 patients (5/308 [1.6%] originally randomized to HIR and 6/206 [2.9%] originally randomized to SIR group) experienced AAA+ through week 56.

OLE Study

Key demographics and baseline characteristics at OLE study entry were consistent with moderately to severely active CD **(Supplementary Table 4).** Clinical remission, endoscopic response, and endoscopic remission were maintained by 68.2%, 45.4%, and 31.6% of patients, respectively, at week 40 of the OLE study (week 52 from baseline) among patients who entered the OLE at week 0 achieving the same endpoint **(Supplementary Table 5)**; patients who underwent dose escalation (N = 55) to 40 mg ew were censored for efficacy analyses. Safety results for the OLE study were similar to those reported for the maintenance study **(Supplementary Table 6)**.

Discussion

Adalimumab is approved[5, 6] and well established for the treatment of CD.[8, 22] Results from the SERENE CD study confirm safety and efficacy findings from previous trials of adalimumab in patients with moderately to severely active CD and show adalimumab to be well tolerated. Further, these results demonstrate no significant effect of either higher induction dosing or dose adjustment based on proactive TDM during maintenance on the efficacy and safety of adalimumab.

In the induction study, although HIR dosing resulted in increased adalimumab serum concentrations, this did not translate into significantly greater clinical or endoscopic efficacy compared with the approved SIR. The lack of significant difference between induction regimens confirms the appropriateness of the approved 160/80 mg induction dose for patients with moderately to severely active CD. Safety findings were similar for both induction regimens and were consistent with the known safety profile of adalimumab. Dose-dependent toxicity was not observed.

In the maintenance study, adalimumab was efficacious for the long-term treatment of CD, with approximately two-thirds of patients who responded to induction therapy achieving clinical remission at week 56, demonstrating the durability of clinical efficacy. Also notable was the high proportion of patients (>70%) who achieved corticosteroid-free clinical remission after an early corticosteroid taper beginning at week 4, demonstrating the observed clinical efficacy rates were not driven by corticosteroids and a benefit of reduced reliance on concomitant corticosteroids use for patients. The clinical remission rates observed in the SERENE CD study are higher than those observed in prior pivotal adalimumab trials,[8, 9] despite potentially more severe baseline endoscopic inflammation among patients in the present study as documented by a central

reviewer, which was not an entry criterion in the earlier studies. For endoscopic outcomes, approximately 40% of patients achieved endoscopic response and approximately 33% of patients achieved endoscopic remission during the maintenance study at week 56. A majority (>50% in TDM and >70% in CA) of patients who achieved endoscopic response or remission at week 12 maintained achievement of the same endpoint at week 56, providing further evidence that adalimumab is efficacious for the long-term treatment of CD.

For patients who experience a lack and/or loss of response to adalimumab, dose adjustment may allow achievement of response/remission. In the present study, 28% of patients in the CA group had their dose escalated, a rate that is similar to that reported for patients in the CHARM study (27%)[12] and the annual risk of dose escalation for initial responders reported in a systematic literature review (24.8% per patient-year).[23] The dose escalation rate for the TDM group was higher (39%), with most patients (58%) qualifying for dose escalation based on low serum adalimumab concentrations, regardless of hs-CRP or CDAI. In the SERENE CD study, more than half of the patients who had their doses escalated in either group achieved clinical remission at week 56. This surpasses the rate observed among patients who had their doses escalated due to lack of response or recurrent flares in the CHARM study (37%), though differences in study design between CHARM and SERENE CD (eg, different inclusion criteria, lack of placebo group, lower induction dose regimen, no endoscopy at baseline or follow up in CHARM) limit direct comparison between the 2 studies.[12] Though the maintenance study comparing the CA and TDM strategies was exploratory, key efficacy endpoints were similar among patients who had an escalation in dose, regardless of strategy, suggesting that use of a proactive TDM strategy does not lead to additional clinical benefit over dose adjustment based on the evaluation of symptoms and/or hs-CRP alone.

While the practice of measuring serum drug concentrations and using TDM to optimize treatment is an area of considerable interest among gastroenterologists who treat inflammatory bowel disease, supportive evidence from prospective, randomized controlled trials is limited. The American Gastroenterological Association currently recommends TDM only as a reactive strategy (ie, in patients with active disease) and notes that this recommendation is based on "very low quality evidence".[13] Results from the exploratory SERENE CD study, suggesting there is no clinical benefit of a proactive TDM strategy over a CA strategy for optimizing adalimumab maintenance dosing, align with the results from previous studies evaluating TDM of anti-TNF therapies in adult patients with inflammatory bowel disease. In the TAXIT study, proactive TDM was not superior to CA dose optimization for achieving remission at 1 year in patients with CD or ulcerative colitis.[24] Similarly, in the TAILORIX study of patients with CD, proactive TDM failed to improve clinical and endoscopic remission rates over a CA approach.[25] In contrast, proactive TDM led to a higher clinical remission rate than did reactive TDM among pediatric patients with CD in the PAILOT trial, but this trial was nonblinded and lacked endoscopic assessments.[26]

As expected, induction adalimumab serum concentrations were higher among patients receiving HIR compared with SIR. The difference between groups peaked at week 4 and decreased thereafter; serum concentrations were largely similar by week 12. However, the higher serum adalimumab concentrations seen with higher induction dosing in the SERENE CD study were not associated with increased efficacy beyond the SIR dose for clinical remission at week 4 or endoscopic response at week 12. One reason the previous pharmacokinetic/pharmacodynamic modeling did not conform with results of this study may be that the hypothesis was based on extrapolation of exposure-response relationships outside the previously studied dose and timepoint ranges (ie, 160/80 mg was the highest previously studied induction dose; efficacy endpoints beyond week 4 had not been previously modeled). Further, as endoscopic endpoints were not routinely assessed in historic CD trials, exposure-endoscopic response relationships

were not available at the time of pharmacokinetic/pharmacodynamic modeling. Previous studies have identified exposure-response relationships between adalimumab serum concentrations and clinical remission at week 4[17] or endoscopic response at weeks 26 and 52.[11] The complexity of the pharmacokinetic/pharmacodynamic relationship is reflected in the considerable interpatient variability and overlap between patients with and without remission or response. Additional factors such as differences in study design, serum concentrations associated with different doses, and assessment of endpoints at different timepoints should be considered. The lack of a dose-response relationship for efficacy with the HIR vs the SIR may also reflect that the studied doses are close to the plateau of the exposure-response relationship for the overall population.

In the maintenance study, adalimumab concentrations were similar between groups at week 12 (ie, prior to dose escalation for any patient). Differences in adalimumab concentrations among patients who remained on eow dosing or were escalated to ew dosing within the CA and TDM groups reflect the nature of each strategy. In the CA group, dose escalation decisions per protocol were independent of adalimumab concentration, which may have resulted in dose escalation among patients with higher pre-escalation adalimumab concentrations and may be reflected in the mean serum concentration at week 56 for the subset of patients who underwent dose escalation in the CA group. In the TDM group, dose escalation was primarily driven by low serum adalimumab concentrations, reflecting a higher clearance. The lower week 12 adalimumab concentrations among patients whose dose was subsequently escalated reflects the algorithm used for dose escalation (ie, dose escalation in response to low adalimumab concentrations, regardless of hs-CRP level or CDAI). Dose escalation in these patients resulted in similar concentrations of adalimumab among patients in the TDM group at week 56, regardless of final dose level. Despite the differences in escalation criteria between the CA and TDM strategies, the overall differences in adalimumab concentrations between patients who

continued with adalimumab 40 mg eow and those who were escalated to 40 mg ew, even in the CA group, were not large.

Although no significant differences in PROs were observed between groups, the marked improvements in PROs from baseline demonstrate important quality-of-life benefits associated with adalimumab therapy, regardless of dose regimen. Both induction dosing regimens and both maintenance strategies were well tolerated, confirming the known safety profile of adalimumab in treating CD. OLE study results were similar to the CA/TDM populations and generally supportive of the maintenance study outcomes.

With respect to limitations, the SERENE CD trial did not include a placebo control arm for ethical reasons; hence, there was no control for placebo-adjusted effects. High remission rates observed at week 56 may be due to the open-label nature of the study. The exploratory nature of the maintenance study and the lack of a group receiving adalimumab ew limits the conclusions that can be drawn from the results. Dose escalation occurred earlier and more often overall in the TDM group vs the CA group, and the interpretation of serum drug concentrations is limited by differences in dose escalation timepoints and criteria (eg, the nature of the algorithm selecting dose escalation for patients with low serum levels in the TDM group, the potential for dose escalation based on symptoms alone in the CA group). Therapeutic cutoff values for dose escalation have not been defined, and the results may be limited by the selected cutoff values. For this trial, the cutoff values were based on clinical outcomes but not endoscopic outcomes as were relied on in the pivotal trials. The choice of a different minimum serum concentration value (eg, using a threshold adalimumab concentration of 12 µg/mL, as suggested by the prospective, multicenter observational PANTS study[27]) or removing the maximum serum concentration value above which dose escalation could not occur may have

yielded different results. Further trials that are adequately powered to investigate TDM strategies are still needed.

In conclusion, results from the SERENE CD study confirm the appropriateness of the approved standard 160/80-mg dose of adalimumab for patients with moderately to severely active CD. In the induction study, HIR did not demonstrate significantly greater clinical or endoscopic efficacy over the approved SIR. The safety profile of the higher adalimumab induction dosing regimen was comparable with the standard dosing regimen, with no new safety signals identified. Dose adjustment based primarily on serum adalimumab levels did not provide additional clinical benefit over clinical adjustment based on symptoms and biomarkers. The benefit-risk profile of adalimumab in moderately to severely active CD remains unchanged.

References

1. Becker HM, Grigat D, Ghosh S, et al. Living with inflammatory bowel disease: a Crohn's and Colitis Canada survey. Can J Gastroenterol Hepatol 2015;29:77-84.

2. Shah SC, Colombel JF, Sands BE, et al. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. Aliment Pharmacol Ther 2016;43:317-333.

3. Reinink AR, Lee TC, Higgins PD. Endoscopic mucosal healing predicts favorable clinical outcomes in inflammatory bowel disease: a meta-analysis. Inflamm Bowel Dis 2016;22:1859-1869.

4. Picco MF, Farraye FA. Targeting mucosal healing in Crohn's disease. Gastroenterol Hepatol (N Y) 2019;15:529-538.

5. Humira (adalimumab). Prescribing information. AbbVie Inc.; 2021. Accessed March 22, 2021. https://www.rxabbvie.com/pdf/humira.pdf.

6. Humira (INN-adalimumab). Summary of product characteristics. AbbVie Biotechnology GmbH; 2020. Accessed January 8, 2021. https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf.

7. Humira (adalimumab): Crohn's disease. http://www.e-humira.jp/medical/dcd.

8. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130:323-333; quiz 591.

9. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med 2007;146:829-838.

10. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52-65.

11. Watanabe K, Matsumoto T, Hisamatsu T, et al. Clinical and pharmacokinetic factors associated with adalimumab-induced mucosal healing in patients with Crohn's disease. Clin Gastroenterol Hepatol 2018;16:542-549 e541.

12. Sandborn WJ, Colombel JF, Schreiber S, et al. Dosage adjustment during long-term adalimumab treatment for Crohn's disease: clinical efficacy and pharmacoeconomics. Inflamm Bowel Dis 2011;17:141-151.

13. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute Guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology 2017;153:827-834.

14. Su HY, Ward MG, Sparrow MP. Therapeutic drug monitoring in inflammatory bowel disease: too little too early?—comments on the American Gastroenterology Association Guideline. Transl Gastroenterol Hepatol 2017;2:113.

15. Cheifetz A. Overview of therapeutic drug monitoring of biologic agents in patients with inflammatory bowel disease. Gastroenterol Hepatol (N Y) 2017;13:556-559.

16. Vuitton L, Marteau P, Sandborn WJ, et al. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. Gut 2016;65:1447-1455.

17. Chiu YL, Rubin DT, Vermeire S, et al. Serum adalimumab concentration and clinical remission in patients with Crohn's disease. Inflamm Bowel Dis 2013;19:1112-1122.

18. Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Gastroenterology 1994;106:287-296.

19. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727-1736.

20. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353-365.

21. Weisman MH, Moreland LW, Furst DE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther 2003;25:1700-1721.

22. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007;56:1232-1239.

23. Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. Am J Gastroenterol 2011;106:674-684.

24. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015;148:1320-1329 e1323.

25. D'Haens G, Vermeire S, Lambrecht G, et al. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. Gastroenterology 2018;154:1343-1351 e1341.

26. Assa A, Matar M, Turner D, et al. Proactive monitoring of adalimumab trough concentration associated with increased clinical remission in children with Crohn's disease compared with reactive monitoring. Gastroenterology 2019;157:985-996 e982.

27. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol 2019;4:341-353.

FIGURE LEGENDS

Figure 1. Study design. ADA, adalimumab; CA, clinically adjusted; eow, every other week; CDAI, Clinical Disease Activity Index; hs-CRP, high-sensitivity C-reactive protein; SES-CD, Simple Endoscopic Score for Crohn's Disease; TDM, therapeutic drug monitoring.

Figure 2. Patient disposition. (*A*) Induction study. (*B*) Maintenance study. Clinical response: ≥70-point reduction from baseline in CDAI. ADA, adalimumab; CA, clinically adjusted; CDAI, Crohn's Disease Activity Index; HIR, higher induction regimen; mITT, modified intent to treat; SIR, standard induction regimen; TDM, therapeutic drug monitoring.

Figure 3. Clinical remission at week 4 and endoscopic response at week 12 (coprimary efficacy endpoints–induction study; ITT population). Delta adjusted by stratification factors. Central reviewer scoring of endoscopy results was used for all efficacy assessments. Missing data were handled by nonresponder imputation. BL, baseline; CDAI, Clinical Disease Activity Index; ITT, intent to treat; HIR, higher induction regimen; SES-CD, Simple Endoscopic Score for Crohn's Disease; SIR, standard induction regimen.

Figure 4. Selected week 56 efficacy endpoints (maintenance study; mITT population). (*A*) Achievement of key efficacy endpoints at week 56. (*B*) Sustained efficacy at week 56 among patients who achieved key efficacy endpoints at week 12. Clinical remission was defined as CDAI <150. Steroid-free clinical remission was defined as CDAI <150 and discontinuation of corticosteroids among patients taking corticosteroids at baseline. Endoscopic response was defined as SES-CD >50% from induction baseline (or for an induction baseline SES-CD of 4, ≥2-point reduction from induction baseline). Endoscopic remission was defined as SES-CD ≤4 and ≥2-point reduction from induction baseline, and no subscore >1 in any individual variable.

Deep remission was defined as clinical remission and endoscopic remission. Central reviewer scoring of endoscopy results was used. CA, clinically adjusted; CDAI, Crohn's Disease Activity Index; mITT, modified intent to treat; SES-CD, Simple Endoscopic Score for Crohn's Disease; TDM, therapeutic drug monitoring.

Table 1. Demographics and Baseline Characteristics at Induction Study Entry

Characteristic	ADA	Induction (ITT)		Maintenance (mITT)	
		HIR N = 308	SIR N = 206	CA N = 92	TDM N = 92
Female, n (%)		158 (51.3)	109 (52.9)	45 (48.9)	43 (46.7)
Race, n (%)					
White		288 (93.8)	182 (88.3)	87 (94.6)	85 (92.4)
Black/African American		11 (3.6)	18 (8.7)	4 (4.3)	6 (6.5)
Asian		6 (2.0)	5 (2.4)	0	1 (1.1)
American Indian/Alaska Native		1 (0.3)	0	1 (1.1)	0
Multirace		1 (0.3)	1 (0.5)	0	0
Ethnicity, not Hispanic/Latino, n (%)		298 (96.8)	201 (97.6)	90 (97.8)	90 (97.8)
Age, y, median (range)		34 (18–73)	34 (18–71)	32 (18–73)	34 (18–73)
CD duration, y, mean (SD)		7.0 (7.9)	7.8 (9.3)	6.2 (7.5)	6.4 (8.2)
Weight, *kg*, mean (SD)		73.1 (18.3)	75.0 (20.8)	71.7 (19.6)	74.1 (18.6)
SES-CD, mean (SD)		13.6 (6.6)	13.6 (6.4)	13.3 (6.1)	12.3 (6.1)
IBDQ total score, mean (SD)		114.4 (31.7)	116.4 (31.2)	116.3 (33.0)	120.6 (27.5)
Daily AP, mean (SD)		5.7 (2.0)	5.6 (2.0)	5.7 (1.7)	5.4 (2.1)
SFPS, mean (SD)		134.1 (44.2)	131.8 (38.8)	132.5 (46.2)	138.9 (39.1)
Fecal calprotectin, *μg/g*, median (range)		1076 (10–9600)	1136 (22–9600)	918 (25–9600)	786 (10–9600)
hs-CRP[a] levels (mg/L)					
<10, n (%)		175 (56.8)	113 (54.9)	50 (54.3)	52 (56.5)
≥10, n (%)		133 (43.2)	93 (45.1)	42 (45.7)	40 (43.5)
Mean (SD)		20.7 (30.9)	20.2 (31.6)	21.6 (31.5)	18.8 (26.6)

Characteristic	ADA	Induction (ITT)		Maintenance (mITT)	
		HIR N = 308	SIR N = 206	CA N = 92	TDM N = 92
Corticosteroid use, n (%)		155 (50.3)	100 (48.5)	39 (42.4)	56 (60.9)
Immunosuppressant use, n (%)		78 (25.3)	61 (29.6)	31 (33.7)	25 (27.2)
Previous infliximab use[a], n (%)		53 (17.2)	36 (17.5)	15 (16.3)	10 (10.9)
CDAI[a]					
≤300, n (%)		179 (58.1)	119 (57.8)	58 (63.0)	46 (50.0)
>300, n (%)		129 (41.9)	87 (42.2)	34 (37.0)	46 (50.0)
Mean (SD)		295.8 (53.8)	298.0 (50.3)	296.1 (57.5)	303.4 (56.3)
Disease location per SES-CD, n (%)					
Ileal only		80 (26.0)	42 (20.4)	20 (21.7)	27 (29.3)
Colonic only		96 (31.2)	73 (35.4)	36 (39.1)	25 (27.2)
Ileocolonic		131 (42.5)	91 (44.2)	36 (39.1)	40 (43.5)

ADA, adalimumab; AP, abdominal pain; CDAI, Crohn's Disease Activity Index; CA, clinically adjusted; CD, Crohn's disease; HIR, higher induction regimen; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; ITT, intent to treat; mITT, modified intent to treat; SES-CD, Simple Endoscopic Score for Crohn's Disease; SFPS, Stool (liquid/soft) frequency + AP score (CDAI components); SIR, standard induction regimen; TDM, therapeutic drug monitoring.
[a]Stratification factors for randomization.

Table 2. Ranked Secondary Efficacy Endpoints (Induction Study, ITT Population)

ADA	HIR N = 308	SIR N = 206	*P* value
1) Sustained clinical remission: clinical remission at both weeks 4 and 12	120 (39.0)	72 (35.0)	.269
2) Clinical remission at week 4 and endoscopic response at week 12	68 (22.1)	42 (20.4)	.610
3) Clinical remission at week 12	192 (62.3)	106 (51.5)	.008
4) Discontinued corticosteroid use and achieved clinical remission at week 12 among patients taking corticosteroids at baseline	82/155 (52.9)	48/100 (48.0)	.336
5) Endoscopic remission at week 12	88 (28.6)	54 (26.2)	.694
6) Change from baseline in fecal calprotectin concentration at week 4, *μg/g*, mean (SD)	−1157.0 (2000.7)	−1045.7 (1648.5)	.946
7) hs-CRP level <5 mg/L and fecal calprotectin <250 μg/g at week 4	100 (32.5)	57 (27.7)	.293
8) Clinical remission, hs-CRP level <5 mg/L, and fecal calprotectin <250 μg/g at week 4	44 (14.3)	23 (11.2)	.304
9) Clinical remission, hs-CRP level <5 mg/L, endoscopic remission, and fecal calprotectin <250 μg/g at week 12	36 (11.7)	15 (7.3)	.092
10) SES-CD ≤2 at week 12	62 (20.1)	33 (16.0)	.278
11) Clinical response at week 4	229 (74.4)	146 (70.9)	.353
12) Clinical response at week 12	257 (83.4)	154 (74.8)	.015

13) IBDQ bowel symptom response at week 4	230 (74.7)	147 (71.4)	.394
14) IBDQ bowel symptom response at week 12	237 (76.9)	151 (73.3)	.349
15) IBDQ fatigue response at week 12	234 (76.0)	141 (68.4)	.054

NOTE. Data are presented as n (%) or n/N (%), unless otherwise noted.
Endpoints are in ranked order from top to bottom.
Nonresponder imputation for categorical endpoints, observed cases for change in fecal calprotectin.
Clinical remission: CDAI <150.
Clinical response: ≥70-point reduction from baseline in CDAI.
Endoscopic remission: SES-CD ≤4 and ≥2-point reduction from baseline, and no subscore >1 in any individual variable.
IBDQ bowel symptom response: ≥8-point increase in IBDQ bowel symptom domain from baseline.
IBDQ fatigue response: ≥1-point increase in IBDQ fatigue item score.
ADA, adalimumab; CDAI, Clinical Disease Activity Index; HIR, higher induction regimen; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; ITT, intent to treat; SES-CD, Simple Endoscopic Score for Crohn's Disease; SIR, standard induction regimen.

Table 3. Safety Results From Week 0 to 12 (Induction Study) and From Week 12 to 56 (Maintenance Study)

	Induction		Maintenance	
	ADA			
	HIR N = 308	SIR N = 206	CA N = 109	TDM N = 109
Overview				
TEAE	185 (60.1)	133 (64.6)	77 (70.6)	76 (69.7)
Serious AE	14 (4.5)	10 (4.9)	5 (4.6)	7 (6.4)
AE leading to discontinuation of study drug	13 (4.2)	8 (3.9)	8 (7.3)	9 (8.3)
Severe TEAE	17 (5.5)	13 (6.3)	7 (6.4)	6 (5.5)
TEAE possibly related to study drug[a]	75 (24.4)	54 (26.2)	29 (26.6)	33 (30.3)
Death	0	0	0	0
TEAEs reported in ≥5% of patients				
Crohn's disease	17 (5.5)	15 (7.3)	18 (16.5)	16 (14.7)
Nasopharyngitis	19 (6.2)	9 (4.4)	15 (13.8)	10 (9.2)
Headache	17 (5.5)	18 (8.7)	9 (8.3)	8 (7.3)
Arthralgia	11 (3.6)	16 (7.8)	8 (7.3)	4 (3.7)
Nausea	9 (2.9)	15 (7.3)	5 (4.6)	3 (2.8)
Diarrhea	2 (0.6)	3 (1.5)	6 (5.5)	4 (3.7)
Dizziness	2 (0.6)	11 (5.3)	0	0
AESIs				
Infection	69 (22.4)	49 (23.8)	37 (33.9)	38 (34.9)
Serious infection[b]	2 (0.6)	2 (1.0)	0	3 (2.8)
Opportunistic infection[c]	1 (0.3)	2 (1.0)	0	0
Oral candidiasis	1 (0.3)	2 (1.0)	1 (0.9)	0
Tuberculosis (active or latent)[d]	0	0	0	0
Parasitic infection	0	0	1 (0.9)	1 (0.9)

	ADA	Induction		Maintenance	
		HIR N = 308	SIR N = 206	CA N = 109	TDM N = 109
Malignancy		1 (0.3)[e]	0	0	0
Allergic reaction[f]		8 (2.6)	10 (4.9)	1 (0.9)	3 (2.8)
Vasculitis		0	0	0	0
Myocardial infarction		0	0	0	0
Congestive heart failure		1 (0.3)	0	0	0
Cerebrovascular accident		1 (0.3)	0	0	0
Pulmonary embolism		0	0	0	0
Pancreatitis		0	0	0	0
Worsening/new onset of psoriasis		0	1 (0.5)	1 (0.9)	2 (1.8)
Demyelinating disorder		0	0	0	0
Hematologic disorder[g]		11 (3.6)	10 (4.9)	0	0
Liver failure and other liver event		0	0	0	0
Injection site reaction		26 (8.4)	17 (8.3)	6 (5.5)	2 (1.8)
Laboratory parameters (CTC criteria ≥ grade 3), n/N (%)					
Hemoglobin		2/304 (0.7)	1/204 (0.5)	0/103	0/107
Platelets		0/307	0/206	0/104	0/107
Neutrophils		3/306 (1.0)	3/206 (1.5)	1/104 (1.0)	0/107
Lymphocytes		4/302 (1.3)	2/200 (1.0)	1/101 (1.0)	0/107
ALT		0/308	0/206	0/105	0/107
AST		1/308 (0.3)	0/206	0/105	1/107 (0.9)

NOTE. Data are presented as n (%), unless otherwise noted.

ADA, adalimumab; AE, adverse event; AESI, adverse event of special interest; ALT, alanine transaminase; AST, aspartate transaminase; CA, clinically adjusted; CD, Crohn's disease; CTC, Common Terminology Criteria; HIR, higher induction regimen; MeDRA, Medical Dictionary for Regulatory Activities; SIR, standard induction regimen; TB, tuberculosis; TDM, therapeutic drug monitoring; TEAE, treatment-emergent AE.

[a]As assessed by the investigator. All relatedness described below was per investigator assessment.

[b]HIR: 1 patient with pyelonephritis and urinary tract infection (not related, resolved with antibiotic therapy, study drug not discontinued); 1 patient with AIDS and *Pneumocystis jirovecii pneumonia* (not related, study drug discontinued). SIR: 1 patient with cellulitis of the leg (resolved with antibiotic therapy, study drug not discontinued); 1 patient with

worsening of CD with abdominal abscess (not related, study drug discontinued). TDM: 1 patient with urinary tract infection (not related, study drug not discontinued, patient improved with antibiotic therapy); 1 patient with varicella following contact with a child with chicken pox (possibly related, study drug discontinued); 1 patient with mononucleosis and sepsis (possibly related, resolved with treatment, study drug not discontinued).

[c]Excluding oral candidiasis and tuberculosis. HIR: 1 patient with *Pneumocystis jirovecii* pneumonia (not related) with subsequent diagnosis of AIDS. SIR: 1 patient each with esophageal candidiasis and systemic *Candida* (not related).

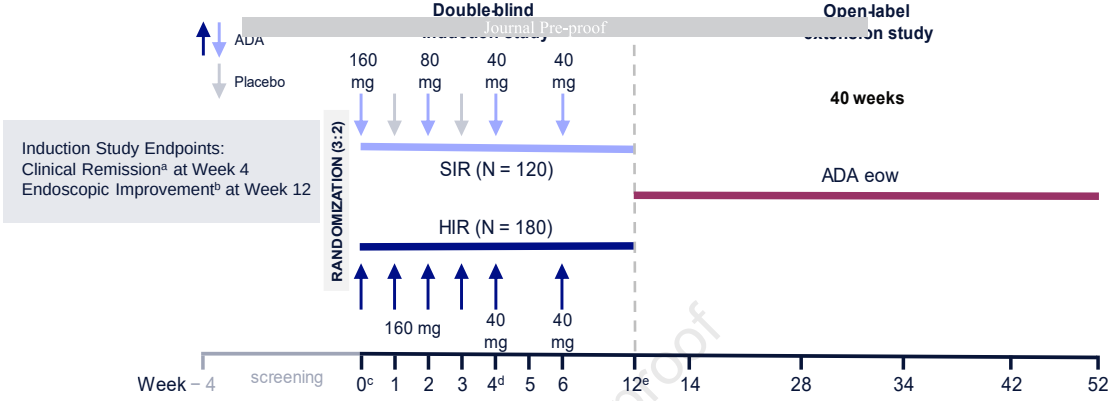
[d]No cases of active or latent pulmonary tuberculosis; Lower MeDRA Query coding for AESI of active or latent TB does not include intestinal TB (captured under serious AEs). 1 patient (SIR) with intestinal tuberculosis found on histology of ileal resection (possibly related; study drug discontinued; patient received antimycobacterial treatment).

[e]1 patient with papillary renal cell carcinoma (incidentaloma, resolved after partial nephrectomy; not related).

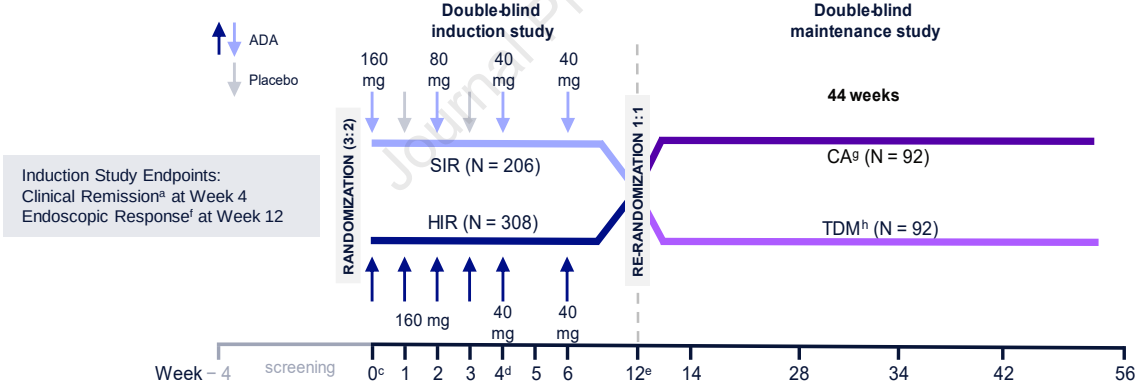
[f]No cases of angioedema/anaphylaxis occurred.

[g]No cases of pancytopenia occurred.

Initial Study Design



Revised Study Design



[a]CDAI <150.
[b]SES-CD ≤4 with no ulcerated surface subscore >1 in any segment.
[c]Stratification factors for randomization: hs-CRP (levels <10 and ≥10 mg/L) at baseline, prior infliximab use, and CD activity (CDAI ≤300, >300) at baseline.
[d]Mandatory corticosteroid taper was initiated at week 4.
[e]Stratification factors for rerandomization at week 12: induction treatment regimen, clinical response (≥70% reduction from baseline in CDAI) at week 12 and decrease in SES-CD >50% from baseline at week 12.
[f]SES-CD >50% decrease from baseline (or for a baseline SES-CD of 4, ≥2-point reduction from baseline).
[g]Patients in the CA group may have had their ADA dose adjusted to ew during unscheduled visits at weeks 16, 18, 22, 24, 30, 32, 36, 38, 44, 46, 50, 52, or 54.
[h]Patients in the TDM group may have had their ADA dose adjusted to ew at weeks 14, 28, or 42 based on protocol-specified dose-adjustment criteria.

A. Induction Study

Randomization

N = 514

Allocation

ADA HIR	ADA SIR
N = 308	N = 206

Follow-up

Primary reason for discontinuation, n (%)		
Adverse event	12 (3.9)	5 (2.4)
Withdrew consent	3 (1.0)	2 (1.0)
Lost to follow-up	1 (0.3)	1 (0.5)
Other	5 (1.6)	6 (2.9)

Analysis

Completed, n (%)	Completed, n (%)
287 (93.2)	192 (93.2)

Completed Week 12
N = 479

B. Maintenance Study

Completed Week 12
N = 479

Randomization

Chose to Continue
N = 470

initial design | revised design

Allocation

Open Label Extension	Maintenance (Rerandomized)
N = 252	N = 218

Clinical response at week 12 (mITT)
n (%) = 184 (84%)

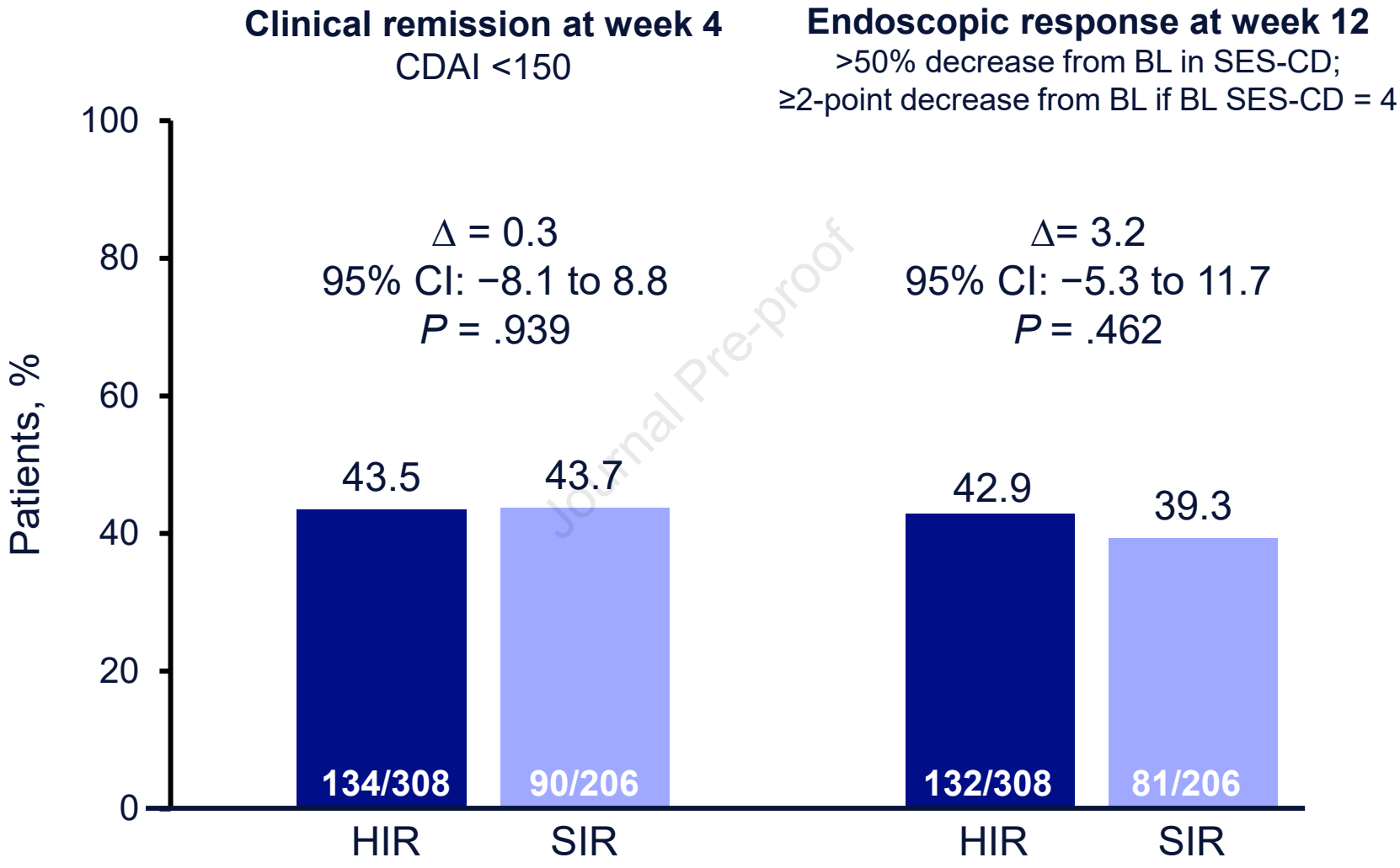
CA	TDM
N = 92	N = 92

Follow-up

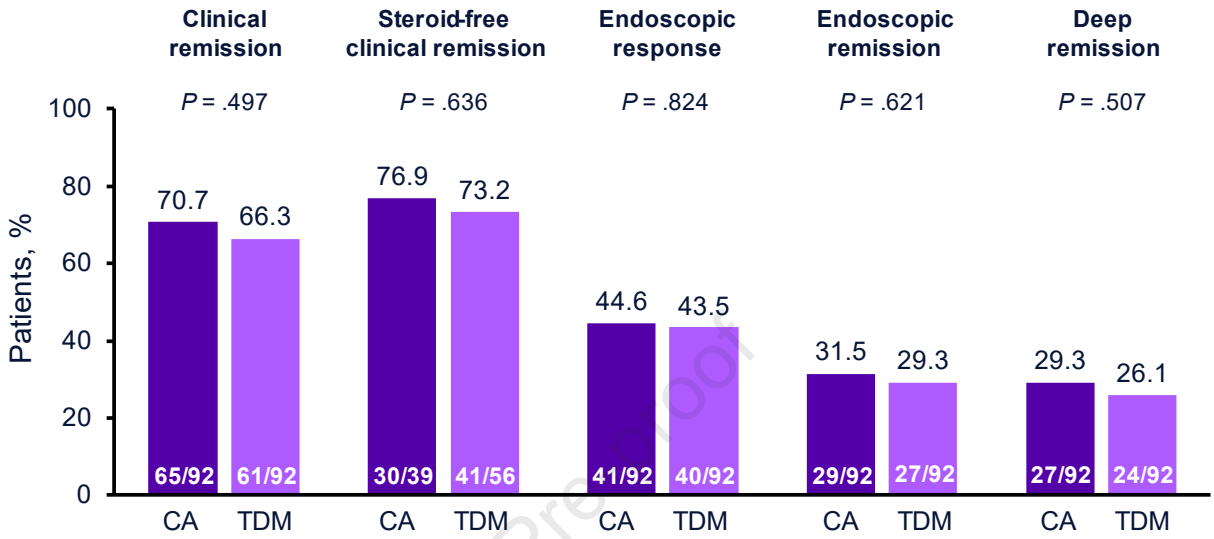
Primary reason for discontinuation, n (%)			
Adverse event	18 (7.1)	6 (6.5)	6 (6.5)
Withdrew consent	8 (3.2)	1 (1.1)	4 (4.3)
Lost to follow-up	4 (1.6)	2 (2.2)	1 (1.1)
Other	24 (9.5)	7 (7.6)	2 (2.2)

Analysis

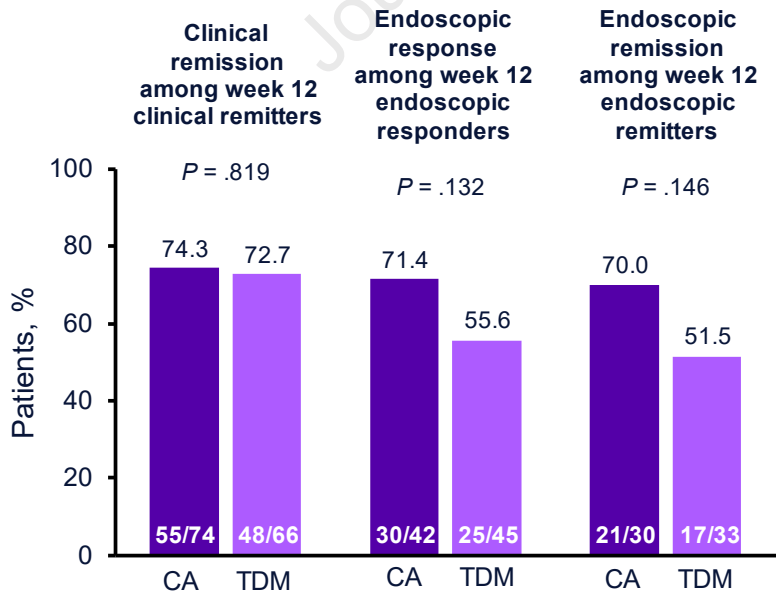
Completed, n (%)	Completed, n (%)	Completed, n (%)
198 (78.6)	76 (82.6)	79 (85.9)



A. Achievement of Key Efficacy Endpoints at Week 56



B. Sustained Efficacy at Week 56 Among Patients Who Achieved Key Efficacy Endpoints at Week 12



WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Adalimumab is approved for moderate-to-severe Crohn's disease in adults with inadequate response to conventional therapy. SERENE CD evaluated higher vs standard induction and clinically-adjusted vs therapeutic dose monitoring maintenance strategies.

NEW FINDINGS

Higher induction dosing was similar in efficacy and safety to the approved standard induction dosing. Maintenance-dose adjustment primarily by serum adalimumab levels was not more efficacious than clinically adjusted dosing.

LIMITATIONS

All maintenance-study endpoints were exploratory. Placebo-adjusted effects were not evaluated.

IMPACT

SERENE CD confirms the appropriateness of the approved adalimumab induction dose regimen. Although exploratory, no clinical advantage for therapeutic drug monitoring over clinical adjustment during maintenance therapy was observed.

LAY SUMMARY

SERENE CD study results demonstrate no additional benefit of higher adalimumab induction dosing vs the approved standard induction dosing for treating patients with moderately to severely active Crohn's disease.

SUPPLEMENTARY MATERIALS

Higher vs Standard Adalimumab Induction Dosing Regimens and 2 Maintenance Strategies: Randomized SERENE CD Trial Results

Geert R. D'Haens,[1] William J. Sandborn,[2] Edward V. Loftus, Jr,[3] Stephen B. Hanauer,[4] Stefan Schreiber,[5] Laurent Peyrin-Biroulet,[6] Remo Panaccione,[7] Julian Panés,[8] Filip Baert,[9] Jean-Frederic Colombel,[10] Marc Ferrante,[11] Edouard Louis,[12] Alessandro Armuzzi,[13] Qian Zhou,[14] Venkata S. Goteti,[14] Nael M. Mostafa,[14] Thao T. Doan,[14] Joel Petersson,[14] Tricia Finney-Hayward,[15] Alexandra P. Song,[14] Anne M. Robinson,[14] and Silvio Danese[16]

[1]Amsterdam Gastroenterology Endocrinology Metabolism and Gastroenterology and Hepatology Departments, Amsterdam University Medical Centers, Amsterdam, The Netherlands; [2]Gastroenterology Department, University of California San Diego, La Jolla, California; [3]Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; [4]Department of Medicine (Gastroenterology and Hepatology), Northwestern University, Chicago, Illinois; [5]Department of Internal Medicine, University Hospital Schleswig-Holstein, Kiel, Germany; [6]Department of Gastroenterology, University Hospital of Nancy, Lorraine University, Vandoeuvre, France; [7]Department of Medicine, University of Calgary, Calgary, AB, Canada; [8]Department of Gastroenterology, Hospital Clinic Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain; [9]Department of Gastroenterology, AZ Delta, Roeselare-Menen, Belgium; [10]Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; [11]Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium; [12]Department of Gastroenterology, University Hospital CHU of Liège, Liège, Belgium; [13]CEMAD-IBD Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [14]AbbVie Inc.,

North Chicago, Illinois; [15]AbbVie Ltd, Maidenhead, United Kingdom; and [16]Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milan, Italy

SUPPLEMENTARY METHODS

Sample Size Calculations

A sample size of 500 patients (300 in the HIR group and 200 in the SIR group) was predicted to provide 99% power to detect a ≥20% difference between HIR and SIR in clinical remission rates at week 4 and a ≥22% difference in endoscopic response rates at week 12 using Fischer's exact test with a .05 (2-sided) significance level. Additional secondary endpoints were also considered for the determination of the study sample size. A sample size of 500 patients provided 72% power to detect a ≥10% difference between HIR and SIR in SES-CD ≤2 rates at week 12 using Fischer's exact test with a .05 (2-sided) significance level. All analyses were performed using SAS software (SAS Institute Inc., Cary, NC). All statistical tests were 2-sided with a 0.05 significance level. There was no sample size calculation for the maintenance study, as it was exploratory.

Randomization Procedure

Block randomization was implemented in this study within each of the stratification variable combinations. Patients were assigned to treatment arms following randomization schedules and this process was implemented by an independent organization external to the sponsor via an Interactive Voice/Web Response System ensuring patient randomization blinding is preserved throughout the study.

Selected Additional Induction Study Endpoints

Selected other endpoints included: (1) change from baseline in CDAI at weeks 2, 4, 6, 8, and 12; (2) clinical remission at weeks 2, 4, 6, 8, and 12; (3) enhanced clinical response (≥100-point

decrease from baseline in CDAI) at week 12; (4) symptomatic remission (average daily stool frequency ≤2.8 and no worse than baseline and average daily abdominal pain ≤1.0 and no worse than baseline) at week 12; (5) symptomatic response (≥30% reduction from baseline in average daily stool frequency and average daily abdominal pain no worse than baseline, or ≥30% reduction from baseline in average daily abdominal pain and average daily stool frequency no worse than baseline) at week 12 among patients with baseline SF ≥ 4.0 and/or AP ≥ 2.0; (6) IBDQ remission (IBDQ total score ≥170 points) at week 12; and (7) IBDQ response (≥16-point increase from baseline in IBDQ total score) at week 12.

Complete Patient Eligibility

Inclusion Criteria

1. Men and women aged 18–75 years at baseline
2. Diagnosis of colonic, ileocolonic, or ileal Crohn's disease (CD) ≥ 3 months before baseline and confirmed by endoscopy during screening period or ≤ 45 days before baseline
3. Simple Endoscopic Score for CD (SES-CD) ≥ 6 for ileocolonic or colonic disease (or ≥ 4 for ileal disease only), excluding the presence of narrowing component, confirmed by a central reader
4. Crohn's Disease Activity Index (CDAI) 220–450 despite concurrent or previous treatment with oral corticosteroids and/or immunosuppressants as defined below:

- Oral corticosteroids:
    - Dose ≤ 40 mg/day (prednisone or equivalent) or ≤ 9 mg/day (budesonide)
    - Current steroid course started ≥ 14 days before baseline
    - Stable dose for ≥ 7 days (≥ 10 days for prednisone/equivalent doses ≤ 10 mg/day and budesonide doses < 6 mg/day)

- A consecutive course (≥ 42 days) of azathioprine, mercaptopurine (6-MP), or injectable methotrexate
    - Stable dose for ≥ 28 days before baseline
    - Azathioprine ≥ 1.5 mg/kg/day, 6-MP ≥ 1 mg/kg/day, or 6-thioguanine nucleotide (6-TGN) levels ≥ 230 pmol/8 × 10^8 red blood cells
    - Methotrexate ≥ 15 mg/week (or highest tolerated dose)
- Concurrent therapy was not required for patients who failed to respond to treatment in the past year or were intolerant to treatment in the past 5 years

5. Previous treatment with infliximab was allowed if it was discontinued due to loss of response or lack of tolerability

6. Negative tuberculosis (TB) screening assessment and negative findings on chest x-ray at screening. Patients with evidence of latent TB infection were required to complete ≥ 2 weeks of TB prophylaxis before baseline

7. For female patients, either not of childbearing potential or currently practicing an approved method of birth control (eg, implants, injectables, some intrauterine devices, intrauterine hormone-releasing systems, abstinence, vasectomized partner, or hormonal contraceptives other than low-dose progestin for ≥ 90 days) throughout the study and for 150 days after last dose of study drug

8. Willing to give written informed consent and to comply with the requirements of the study protocol

9. In otherwise good health, as determined by the investigator

10. Willing and able to self-administer subcutaneous injections or have a qualified person available to administer subcutaneous injections.

Exclusion Criteria

1. Current diagnosis of ulcerative colitis or indeterminate colitis
2. Concurrent immunosuppressant treatment not meeting inclusion criteria, or discontinued use of immunosuppressants ≤ 14 days of baseline
3. Concurrent oral aminosalicylate use, if not at a stable dose for ≥ 28 days before baseline, or discontinued use of aminosalicylates ≤ 14 days of baseline
4. Concurrent treatment with oral corticosteroids not meeting inclusion criteria, or concurrent use of both oral budesonide and prednisone (or equivalent), except inhalers
5. Intravenous corticosteroid use ≤ 14 days before or during screening
6. Bowel resection ≤ 6 months before or planned during the study
7. Symptomatic bowel stricture
8. Abdominal or peri-anal abscess
9. Any ostomy or ileoanal pouch
10. Short bowel syndrome
11. Therapeutic enema or suppository use, other than required for endoscopy, ≤ 14 days before or during screening
12. Previous exposure to medications that have a potential or known association with progressive multifocal leukoencephalopathy, including participation in a clinical trial of investigational agents targeting white cell trafficking
13. Any investigational agent use or procedure ≤ 30 days or 5 half-lives before baseline, whichever is longer
14. Previous treatment with adalimumab or participation in an adalimumab clinical study
15. Use of cyclosporine, tacrolimus, or mycophenolate mofetil ≤ 60 days before baseline
16. Previous stem cell transplantation
17. Previous fecal microbial transplantation

18. Nonsteroidal anti-inflammatory drug use ≤ 14 days before or during the study, except low-dose aspirin or topical nonsteroidal anti-inflammatory drugs

19. Infection(s) requiring treatment with intravenous anti-infectives ≤ 30 days before baseline, or use of oral anti-infectives for non-CD-related infections ≤ 14 days before baseline

20. Treatment with CD-related antibiotics, if doses have not been stable for ≥ 4 weeks before baseline, or discontinued use of CD-related antibiotics ≤ 4 weeks of baseline

21. Current or planned total parenteral nutrition

22. Stool assay positive for *Clostridium difficile* toxin during screening

23. Any following abnormal finding:

- Aspartate transaminase or alanine transaminase > 1.75 × upper limit of the reference range
- White blood cell count < 3.0×10^9/L
- Electrocardiogram with clinically significant abnormalities
- Total bilirubin ≥ 3 mg/dL, except for isolated elevation of indirect bilirubin relating to Gilbert syndrome
- Serum creatinine > 1.6 mg/dL

24. Known hypersensitivity to adalimumab or its excipients

25. Primary nonresponse to infliximab, or infliximab use ≤ 56 days before baseline

26. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease

27. History of invasive infection (eg, listeriosis and histoplasmosis) or human immunodeficiency syndrome

28. Active systemic viral infection

29. Hepatitis B positivity

30. Chronic recurring infections

31. Active TB

32. Latent TB, unless patient completed a full course or ≥ 2 weeks of ongoing TB prophylaxis

33. Moderate-to-severe congestive heart failure or recent cerebrovascular accident

34. History of gastrointestinal tract dysplasia

35. Positive pregnancy test at screening or baseline

36. Breastfeeding or considering becoming pregnant during the study

37. Clinically significant drug or alcohol abuse ≤ 12 months

38. Clinically significant abnormal screening laboratory results as evaluated by the investigator

39. Current evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix

40. Considered by the investigator, for any reason, to be an unsuitable candidate for the study

Protocol Amendments

The original protocol (dated October 25, 2013; 10 patients enrolled) had 6 global amendments. The key changes made and the number of patients enrolled under each amendment are summarized below.

Amendment 1 (May 21, 2014; 122 patients):

- Inclusion criteria updated with additional biologic medications to which patients could not have been previously exposed

Amendment 2 (May 21, 2015; 156 patients):

- Expanded SES-CD inclusion criteria and removed the requirement for ulcerated subscore of 2 or 3

- Modified the definition of endoscopic remission (coprimary endpoint) based on the revised inclusion criterion (added requirement for ≥ 2-point reduction from baseline; clarified no subscore > 1 in any individual variable)

Amendment 3 (December 14, 2015; 18 patients)

- Clarifications only

Amendment 4 (March 28, 2016; 113 patients)

- Added the 44-week, 2-arm, double-blind maintenance study and removed reference to open-label extension study
- Added new ranked secondary endpoint (SES-CD ≤ 2 at week 12)
- Added 300 patients to the sample size based on adequacy of power assumed for new ranked secondary endpoint

Amendment 5 (March 20, 2017; 99 patients)

- Clarifications only

Amendment 6 (November 27, 2018; 0 patients)

- Updated endoscopic coprimary endpoint from endoscopic remission to endoscopic response
    - Decreased sample size based on adequacy of power assumed for updated endoscopic coprimary endpoint
    - Updated secondary and exploratory maintenance endpoints to reflect change in coprimary endoscopic endpoint
- Modified ranked secondary endpoints No. 13 and No. 14 to focus on evaluation of bowel symptom domain of Inflammatory Bowel Disease Questionnaire (IBDQ)
- Added ranked secondary endpoint No. 15 (IBDQ fatigue item)

- Added and modified nonranked endpoints, including adding endpoints to assess the effect of dose escalation

Corticosteroid Tapering

Prednisone dose tapering started with a weekly decrease by 5 mg/day prednisone (or equivalent) for doses > 10 mg/day of prednisone (or equivalent) until a 10 mg/day (or equivalent) dose was reached, then a weekly decrease by 2.5 mg/day (or equivalent) until discontinuation. Budesonide dose tapering started with a weekly decrease by 3 mg/day budesonide until discontinuation.

OLE Study Design and Treatment

The phase 3, multicenter open-label extension (OLE) study was designed to evaluate the long-term efficacy and safety of adalimumab. Patients who successfully completed the induction study through protocol amendment 3 were eligible for inclusion in the OLE.

The duration of the OLE study was up to 40 weeks, with study visits at 0 (ie, week 12 of the induction study), 8, 16, 24, 32, and 40 weeks/premature discontinuation. A follow-up phone call approximately 70 days after the last administration of the study drug was required unless patients initiated commercial adalimumab therapy.

All patients received open-label adalimumab 40 mg every other week (eow) beginning at week 0. Patients meeting the criteria for inadequate response (Crohn's disease Activity Index [CDAI] ≥ 200 and ≥ 1 mg/L increase in high-sensitivity C-reactive protein [hs-CRP] from baseline and/or an hs-CRP level ≥ 5 mg/L) could be escalated to adalimumab 40 mg every week (ew) at or after week 1 of the OLE. The dose for patients for whom the dose was escalated to adalimumab 40

mg ew could de-escalate once to adalimumab 40 mg eow if the patient's CDAI was < 200 and their hs-CRP concentration was no higher than at dose escalation. Patients who experienced inadequate response after dose de-escalation could re-escalate to 40 mg ew.

Efficacy Assessments

The primary efficacy endpoint for the OLE study was the proportions of patients who achieved endoscopic improvement (ie, endoscopic remission), defined as a Simple Endoscopic Score for Crohn's disease (SES-CD) ≤ 4, ≥ 2-point reduction from induction study baseline in SES-CD, and no subscore > 1 in any individual variable at week 40 among subjects with endoscopic remission at week 0. Patients who underwent dose escalation were considered nonresponders at week 40.

Additional efficacy endpoints included the proportions of patients who achieved the following endpoints at week 40: (1) endoscopic response (> 50% decrease from induction study baseline in SES-CD); (2) SES-CD ≤ 2; (3) clinical response (≥ 70-point decrease in CDAI from induction study baseline); (4) enhanced clinical response (≥ 100-point decrease in CDAI from induction study baseline); (5) clinical remission (CDAI < 150); (6) clinical remission and endoscopic remission; (7) steroid-free clinical remission; (8) clinical remission, hs-CRP levels < 5 mg/L, and fecal calprotectin < 250 μg/g; (9) clinical remission, hs-CRP levels < 5 mg/L, endoscopic remission, and fecal calprotectin < 250 μg/g; (10) stool (liquid/soft) frequency + abdominal pain score (SFPS) remission, defined as SFPS < 50; (11) hs-CRP levels < 5 mg/L and fecal calprotectin < 250 μg/g; (12) Inflammatory Bowel Disease Questionnaire (IBDQ) remission; (13) IBDQ response; and (14) modified symptomatic remission (average daily stool frequency ≤ 2.8 [and not worse than induction baseline], and average daily abdominal pain ≤ 1.0 [and not worse than induction baseline]).

Safety Assessments

Adverse events, vital signs, and laboratory parameters were assessed throughout the induction and maintenance studies. Except for those who continued commercially available adalimumab after the end of study, patients were contacted 70 days after their last dose of study drug for assessment of any new or ongoing AEs.

Patient-reported outcomes (PROs)

Changes from baseline in IBDQ total score and 5-level European Quality of Life 5 Dimensions (EQ-5D-5L) index score were evaluated at weeks 16, 32, and 40. Changes from baseline in Work Productivity and Impairment Questionnaire (WPAI) scores were evaluated at week 40.

Statistics

The intent-to-treat population, which included all subjects who enrolled in the OLE and received ≥ 1 dose of study drug, was used for both the efficacy and safety analyses. Missing data were imputed using nonresponder imputation. Data were summarized using descriptive statistics.

Key OLE protocol differences from the CA/TDM

Patients randomized to the CA regimen had their adalimumab dose escalated from 40 mg eow to 40 mg ew as early as week 14 (dose escalation could occur at weeks 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, or 54) if their CDAI was ≥ 220 (measured at weeks 12, 26, and 40, and unscheduled visits) or hs-CRP was ≥ 10 mg/L (based on measured hematocrit and hs-CRP levels from the previous or current study visit). Patients randomized to the TDM regimen had their adalimumab dose escalated at weeks 14, 28, and 42 if they met the dose adjustment criteria (**Supplemental Figure 2**). In the OLE, patients had their adalimumab dose escalated as early as week 1 from 40 mg eow to 40 mg ew if their CDAI was

≥ 200 (measured at weeks 0, 8, 16, 24, 32, and 40) or hs-CRP increased ≥ 1 mg/L from baseline and/or hs-CRP level was ≥ 5 mg/L (measured at weeks 0, 8, 16, 24, 32, 40, and unscheduled visits) rather than ≥ 10 mg/L. Patients who underwent dose escalation were considered nonresponders at week 40, a key difference in the OLE.

SUPPLEMENTAL TABLES

Supplementary Table 1. Nonranked Efficacy Endpoints at Week 12 (Induction Study)

Patients, n (%)	ADA	HIR N = 308	SIR N = 206	Nominal *P* value
Enhanced clinical response		233 (75.6)	135 (65.5)	.011
Symptomatic remission[a]		124 (49.4)	70 (40.2)	.054
Symptomatic response[a]		207 (82.5)	125 (71.8)	.011
IBDQ remission		155 (50.3)	90 (43.7)	.115
IBDQ response		249 (80.8)	151 (73.3)	.044

NOTE. Clinical remission: CDAI <150.
Enhanced clinical response: ≥100-point decrease in CDAI.
Symptomatic remission: average daily SF ≤2.8 (and not worse than baseline), and average daily AP ≤1.0 (and not worse than baseline) among patients with baseline SF ≥4.0 and/or AP ≥2.0 (HIR, N = 251; SIR, N = 174).
Symptomatic response: ≥30% reduction from baseline in average daily SF and average daily AP not worse than baseline, or ≥30% reduction from baseline in AP and average daily stool frequency not worse than baseline among patients with baseline SF ≥4.0 and/or AP ≥2.0 (HIR, N = 251; SIR, N = 174).
IBDQ remission: IBDQ score ≥170.
IBDQ response: ≥16-point increase in IBDQ score from baseline.
IBDQ fatigue item response: ≥1-point increase in IBDQ fatigue item score.
ADA, adalimumab; AP, abdominal pain; CDAI, Clinical Disease Activity Index; HIR, higher induction regimen; IBDQ, Inflammatory Bowel Disease Questionnaire; SIR, standard induction regimen; SF, stool frequency.
[a]HIR group: N = 251; SIR group: N = 174.

Supplementary Table 2. Primary Efficacy Endpoints at Week 12 in the Stratified Groups (Induction Study)

Patients, n (%)		ADA	HIR N = 308	SIR N = 206	Nominal *P* value
Clinical Remission					
Baseline hs-CRP	< 10 mg/L		N = 175 67 (38.3)	N = 113 43 (38.1)	0.968
	≥ 10 mg/L		N = 133 67 (50.4)	N = 93 47 (50.5)	0.981
Baseline CD severity	CDAI ≤ 300		N = 179 95 (53.1)	N = 119 61 (51.3)	0.759
	CDAI > 300		N = 129 39 (30.2)	N = 87 29 (33.3)	0.630
Prior infliximab use	Yes		N = 53 23 (43.4)	N = 36 16 (44.4)	0.922
	No		N = 255 111 (43.5)	N = 170 74 (43.5)	1.000
Endoscopic Response					
Baseline hs-CRP	< 10 mg/L		N = 175 79 (45.1)	N = 113 51 (45.1)	0.999
	≥ 10 mg/L		N = 133 53 (39.8)	N = 93 30 (32.3)	0.244
Baseline CD severity	CDAI ≤ 300		N = 179 76 (42.5)	N = 119 54 (45.4)	0.619
	CDAI > 300		N = 129 56 (43.4)	N = 87 27 (31.0)	0.067
Prior infliximab use	Yes		N = 53 18 (34.0)	N = 36 10 (27.8)	0.537
	No		N = 255 114 (44.7)	N = 170 71 (41.8)	0.549

Clinical remission: CDAI < 150.
Endoscopic response: >50% decrease from baseline in SES CD [or a ≥2-point reduction in patients with a baseline SES-CD of 4.
ADA, adalimumab; CD, Crohn's disease; CDAI, Clinical Disease Activity Index; HIR, higher induction regimen; hs-CRP, high-sensitivity C-reactive protein; SIR, standard induction regimen.

Supplementary Table 3. Additional Efficacy Endpoints (Maintenance Study Week 56) (mITT Population)

Efficacy Endpoints	CA N = 92	TDM N = 92	Nominal *P* value
Change from induction baseline in fecal calprotectin concentration, ***µg/g***, mean (SD)	−1017.2 (2113.5)	−961.0 (2348.9)	.913
hs-CRP level <5 mg/L and fecal calprotectin <250 µg/g	33 (35.9)	31 (33.7)	.744
Clinical remission, hs-CRP level <5 mg/L, and fecal calprotectin <250 µg/g	29 (31.5)	26 (28.3)	.585
Clinical remission, hs-CRP level <5 mg/L, endoscopic remission, and fecal calprotectin <250 µg/g	15 (16.3)	14 (15.2)	.831
SES-CD ≤2	27 (29.3)	24 (26.1)	.528
CDAI, change from baseline, mean (SD)	−205.3 (90.1)	−206.6 (80.5)	.663
Clinical response	71 (77.2)	74 (80.4)	.573
IBDQ bowel symptom response	61 (66.3)	65 (70.7)	.469
IBDQ fatigue item response	63 (68.5)	63 (68.5)	.959
Enhanced clinical response	68 (73.9)	69 (75.0)	.829
Symptomatic remission[a]	39 (55.7)	46 (56.1)	.982
Symptomatic response[a]	51 (72.9)	59 (72.0)	.930
IBDQ response	65 (70.7)	70 (76.1)	.345
IBDQ remission	54 (58.7)	53 (57.6)	.789

NOTE. Data are presented as n (%), unless otherwise noted.
Clinical response: ≥70-point decrease in CDAI.
Enhanced clinical response: ≥100-point decrease in CDAI.
Symptomatic remission: average daily SF ≤2.8 (and not worse than baseline), and average daily AP ≤1.0 (and not worse than baseline) among subjects with baseline SF ≥4.0 and/or AP ≥2.0.
Symptomatic response: ≥30% reduction from baseline in average daily SF and average daily AP not worse than baseline, or ≥30% reduction from baseline in AP and average daily stool frequency not worse than baseline among subjects with baseline SF ≥4.0 and/or AP ≥2.0.
IBDQ remission: IBDQ score ≥170.
IBDQ response: ≥16-point increase in IBDQ score from baseline.

Nonresponder imputation was used for binary outcomes, and last observation carried forward was used for continuous outcomes.
ADA, adalimumab; AP, abdominal pain; CA, clinically adjusted; CDAI, Clinical Disease Activity Index; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; SES-CD, Simple Endoscopic Score for Crohn's Disease; SIR, standard induction regimen; SF, stool frequency; TDM, therapeutic drug monitoring.

[a]CA group: N = 70; TDM group: N = 82.

Supplementary Table 4. OLE Demographics and Baseline Characteristics at OLE Study Entry

Characteristic	OLE N = 252
Female, n (%)	139 (55.2)
Race, n (%)	
White	229 (90.9)
Black/African American	12 (4.8)
Asian	10 (4.0)
Multirace	1 (0.4)
Ethnicity, not Hispanic/Latino, n (%)	245 (97.2)
Age, y, median (range)	36 (18–68)
Disease duration, y, mean (SD)	8.3 (9.2)
Weight, *kg*, mean (SD)	74.1 (19.3)
SES-CD, mean (SD)	14.2 (6.7)
IBDQ total score, mean (SD)	113.1 (31.3)
Daily AP, mean (SD)	5.6 (2.0)
SFPS, mean (SD)	131.5 (42.8)
Fecal calprotectin, *μg/g*, median (range)	1162 (26–9600)
hs-CRP levels, *mg/L*, n (%)	
<10	147 (58.3)
≥10	105 (41.7)
Mean (SD)	19.5 (32.8)
Corticosteroid use, n (%)	119 (47.2)
Immunosuppressant use, n (%)	64 (25.4)
CDAI	
≤300, n (%)	151 (59.9)

Characteristic	OLE N = 252
>300, n (%)	101 (40.1)
Mean (SD)	294.4 (50.9)
Disease location per SES-CD, n (%)	
Illeal only	53 (21.0)
Colonic only	88 (34.9)
Ileocolonic	111 (44.0)

AP, abdominal pain; CDAI, Crohn's Disease Activity Index; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; OLE, open-label extension; SES-CD, Simple Endoscopic Score for Crohn's Disease; SFPS, stool (liquid/soft) frequency + AP score (CDAI components).

Supplementary Table 5. OLE Efficacy Endpoints (ITT Population)

	Week 40
Primary Efficacy Endpoint	
Endoscopic remission	24/76 (31.6)
Additional Efficacy Endpoints	
Clinical remission	105/154 (68.2)
Endoscopic response	54/119 (45.4)
SES-CD ≤2	17/50 (34.0)
Clinical remission and endoscopic remission	18/49 (36.7)
Steroid-free clinical remission[a]	59/119 (49.6)
Fecal calprotectin change from induction baseline, *µg/g*, mean (SD)	−919.8 (1918.7)
hs-CRP level <5 mg/L and fecal calprotectin <250 µg/g	35/85 (41.2)
Clinical remission, hs-CRP level <5 mg/L, and fecal calprotectin <250 µg/g	20/55 (36.4)
Clinical remission, hs-CRP level <5 mg/L, endoscopic remission, and fecal calprotectin <250 µg/g	6/25 (24.0)
Change from induction baseline in CDAI, mean (SD)	−134.0 (114.2)
Clinical response	139/219 (63.5)
Enhanced clinical response	126/196 (64.3)
Modified symptomatic remission[b]	88/205 (42.9)
Symptomatic response	137/252 (54.4)
IBDQ remission	79/120 (65.8)
IBDQ response	126/203 (62.1)

NOTE. Data are presented as n/N (%), unless otherwise noted.
All proportions are among patients who achieved the same endpoint at OLE week 0.

Endoscopic remission (eg, endoscopic improvement): SES-CD ≤4 with no ulcerated surface, ≥2-point reduction from induction baseline, and no subscore >1 in any individual variable.
Endoscopic response: >50% decrease from induction baseline in SES-CD.
Clinical response: ≥70-point reduction from induction baseline in CDAI.
Clinical remission: CDAI <150.
Modified symptomatic remission: average daily SF ≤2.8 (and not worse than induction baseline), and average daily AP ≤1.0 (and not worse than induction baseline).
Symptomatic response: average daily SF ≥30% reduced from induction baseline and average daily AP not worse than induction baseline, or average daily AP ≥30% reduced from induction baseline and average daily SF not worse than induction baseline.
IBDQ remission: IBDQ score ≥170.
IBDQ response: ≥16-point increase from induction baseline in IBDQ score.
Nonresponder imputation.
AP, abdominal pain; CDAI, Clinical Disease Activity Index; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; OLE, open-label extension; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency.
[a]Among patients who were using corticosteroids at induction baseline.
[b]Among patients with average daily SF ≥4.0 or average daily AP ≥2.0 at induction baseline.

Supplementary Table 6. OLE Safety Results

	OLE N = 252
Overview	
TEAE	182 (72.2)
Serious AE	27 (10.7)
TEAE leading to discontinuation of study drug	22 (8.7)
Severe TEAE	28 (11.1)
TEAE possibly related to study drug[a]	62 (24.6)
Deaths	0
TEAEs reported in ≥5% of patients	
Crohn's disease	46 (18.3)
Arthralgia	18 (7.1)
Nausea	15 (6.0)
Upper respiratory tract infection	13 (5.2)
AESIs	
Infection	82 (32.5)
Serious infection[b]	3 (1.2)
Opportunistic infection	0
Oral candidiasis	1 (0.4)
Tuberculosis (active or latent)	0
Parasitic infection	0
Malignancy	0
Allergic reaction[c]	3 (1.2)
Vasculitis (including cutaneous and noncutaneous)	0
Myocardial infarction	0

	OLE N = 252
Congestive heart failure	0
Cerebrovascular accident	0
Pulmonary embolism	0
Pancreatitis	0
Intestinal perforation	0
Intestinal stricture	10 (4.0)
Worsening/new onset of psoriasis	3 (1.2)
Demyelinating disorder	0
Hematologic disorders[d]	6 (2.4)
Liver failure and other liver event[e]	1 (0.4)
Injection-site reaction	4 (1.6)
Laboratory parameters (CTC criteria ≥ grade 3), n/N (%)	
Hemoglobin	2/249 (0.8)
Platelets	0/252
Neutrophils	2/252 (0.8)
Lymphocytes	2/245 (0.8)
ALT	2/252 (0.8)
AST	2/252 (0.8)

NOTE. Data are presented as n (%), unless otherwise noted.

AE, adverse event; AESI, adverse event of special interest; ALT, alanine transaminase; AST, aspartate transaminase; CTC, Common Terminology Criteria; OLE, open-label extension; SAE, serious AE; TEAE, treatment-emergent adverse event.

[a]As assessed by investigator.

[b]All were anal abscesses.

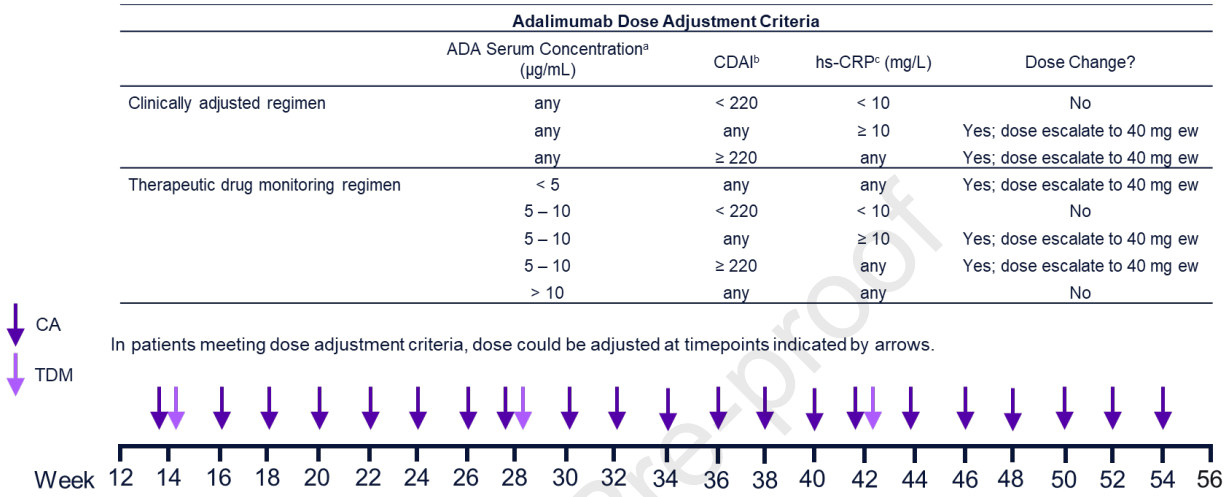
[c]All events were nonserious and mild.

[d]All events were nonserious, mild or moderate, and not considered to be related to the study drug.

[e]Moderate hepatic steatosis (nonserious, did not result in discontinuation of the study drug).

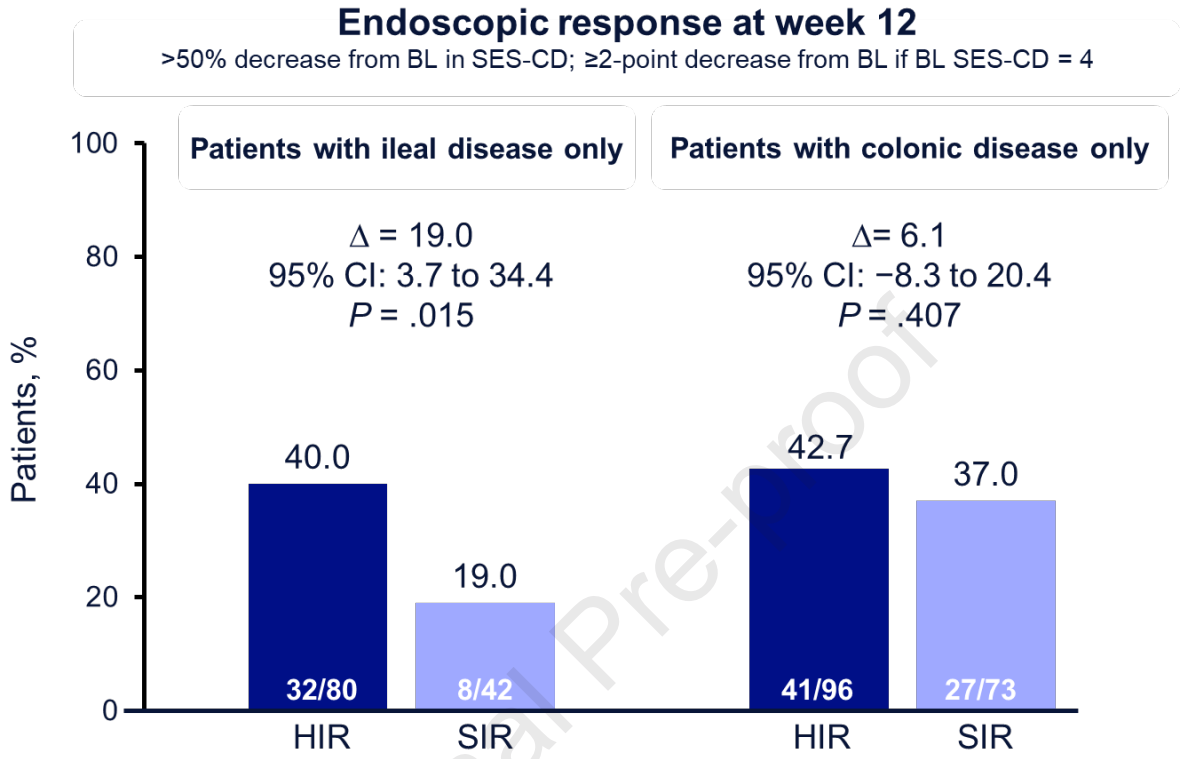
SUPPLEMENTAL FIGURES

Supplementary Figure 1. Dose Escalation Schematic for Maintenance Study



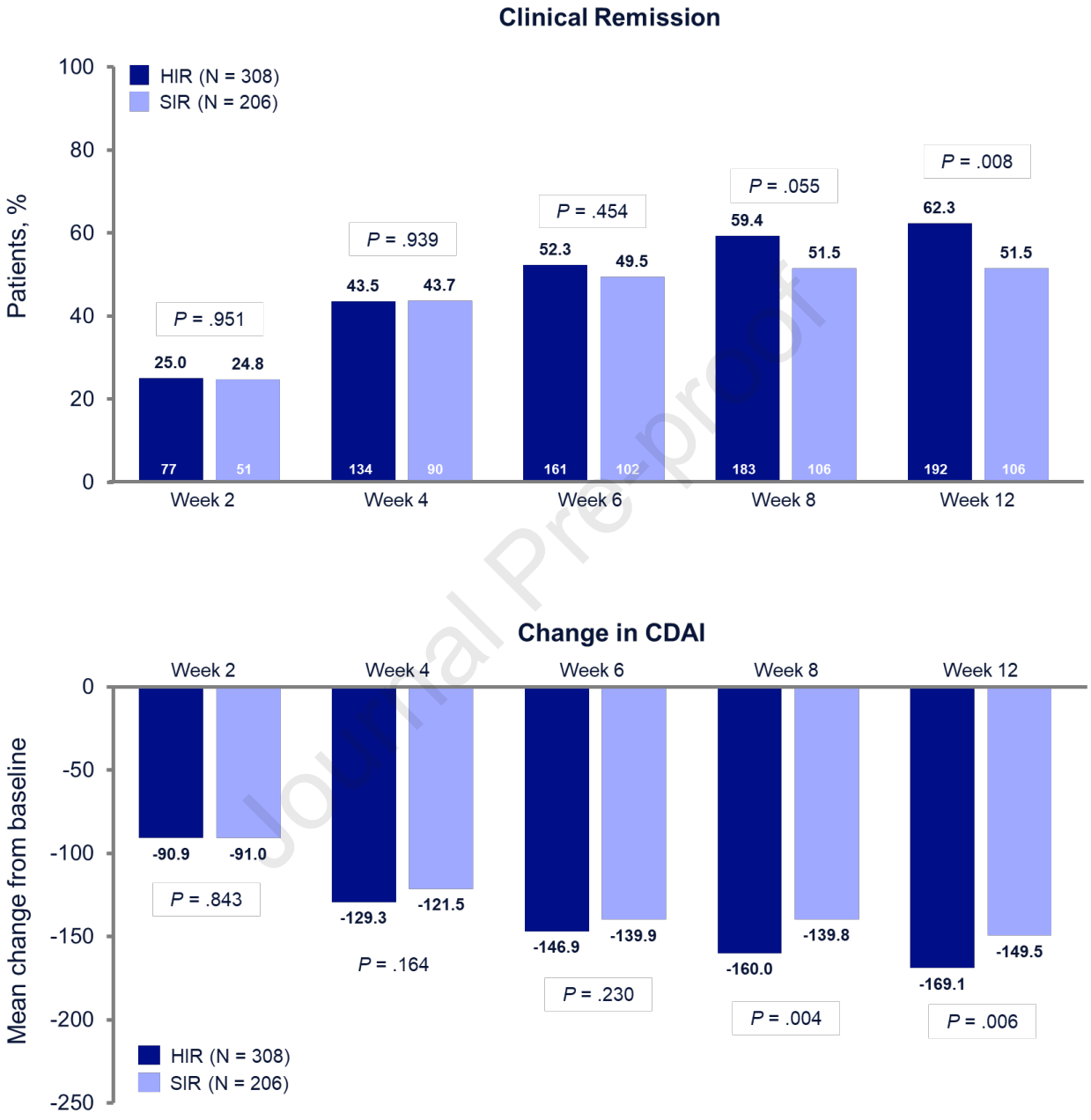
NOTE. After dose escalation to 40 mg ew, patients remained at 40 mg ew.
ADA, adalimumab; CDAI, Clinical Disease Activity Index; ew, every week; hs-CRP, high-sensitivity C-reactive protein.
[a]Based on serum concentration from the previous study visit.
[b]Based on hematocrit from the previous study visit.
[c]Based on hs-CRP from the previous or current study visit.

Supplementary Figure 2. Endoscopic Response –Induction Study (ITT Population)



Endoscopic response at week 12 (coprimary efficacy endpoint–induction study; ITT population). Delta adjusted by stratification factors. Central reviewer scoring of endoscopy results was used for all efficacy assessments. Missing data were handled by nonresponder imputation.
BL, baseline; CDAI, Clinical Disease Activity Index; ITT, intent to treat; HIR, higher induction regimen; SES-CD, Simple Endoscopic Score for Crohn's Disease; SIR, standard induction regimen.

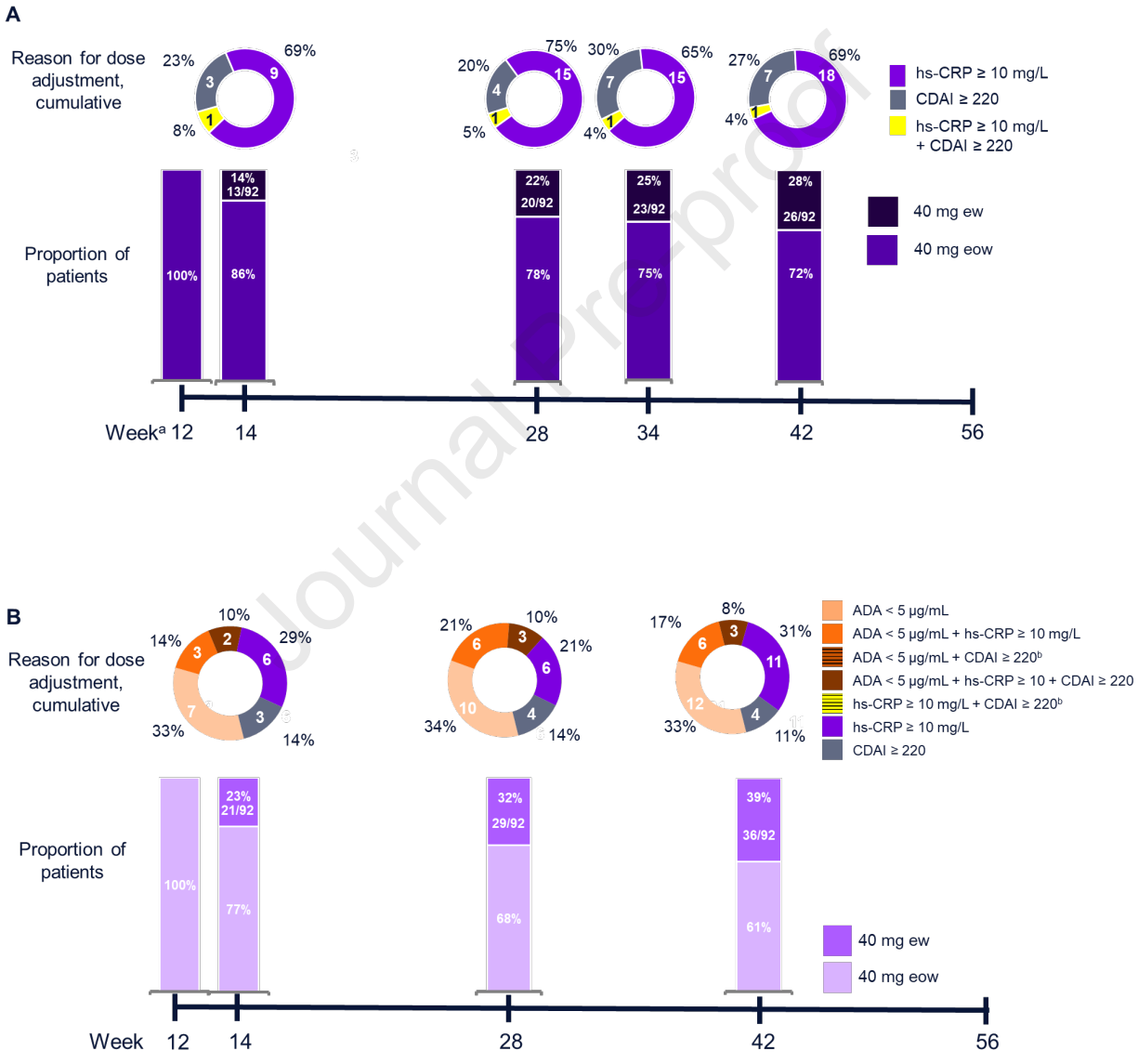
Supplementary Figure 3. Induction Study Other Endpoints (Responses Over Time)



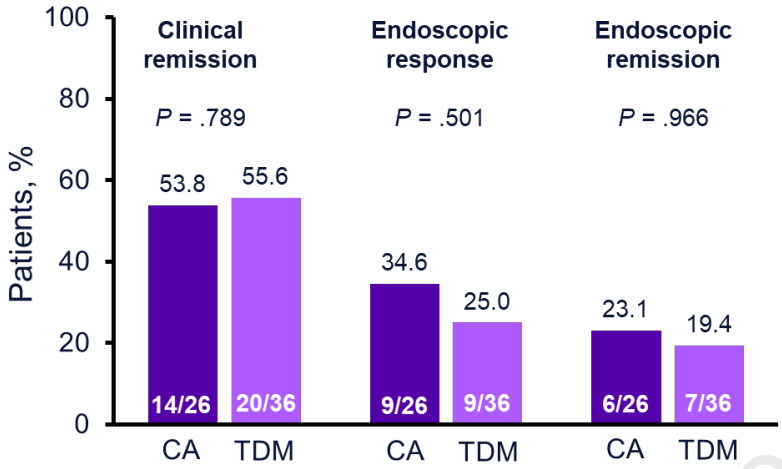
Numbers in bars are n's.
Clinical remission: CDAI < 150.
CDAI, Crohn's Disease Activity Index. HIR, higher induction regimen; SIR, standard induction regimen.

Supplementary Figure 4. Dose Adjustment (Maintenance Study).

(*A*) Timepoints and reasons for dose escalation for the clinically adjusted strategy. (*B*) Timepoints and reasons for dose escalation for the therapeutic drug monitoring strategy. (*C*) Efficacy at week 56 among patients who underwent dose escalation.

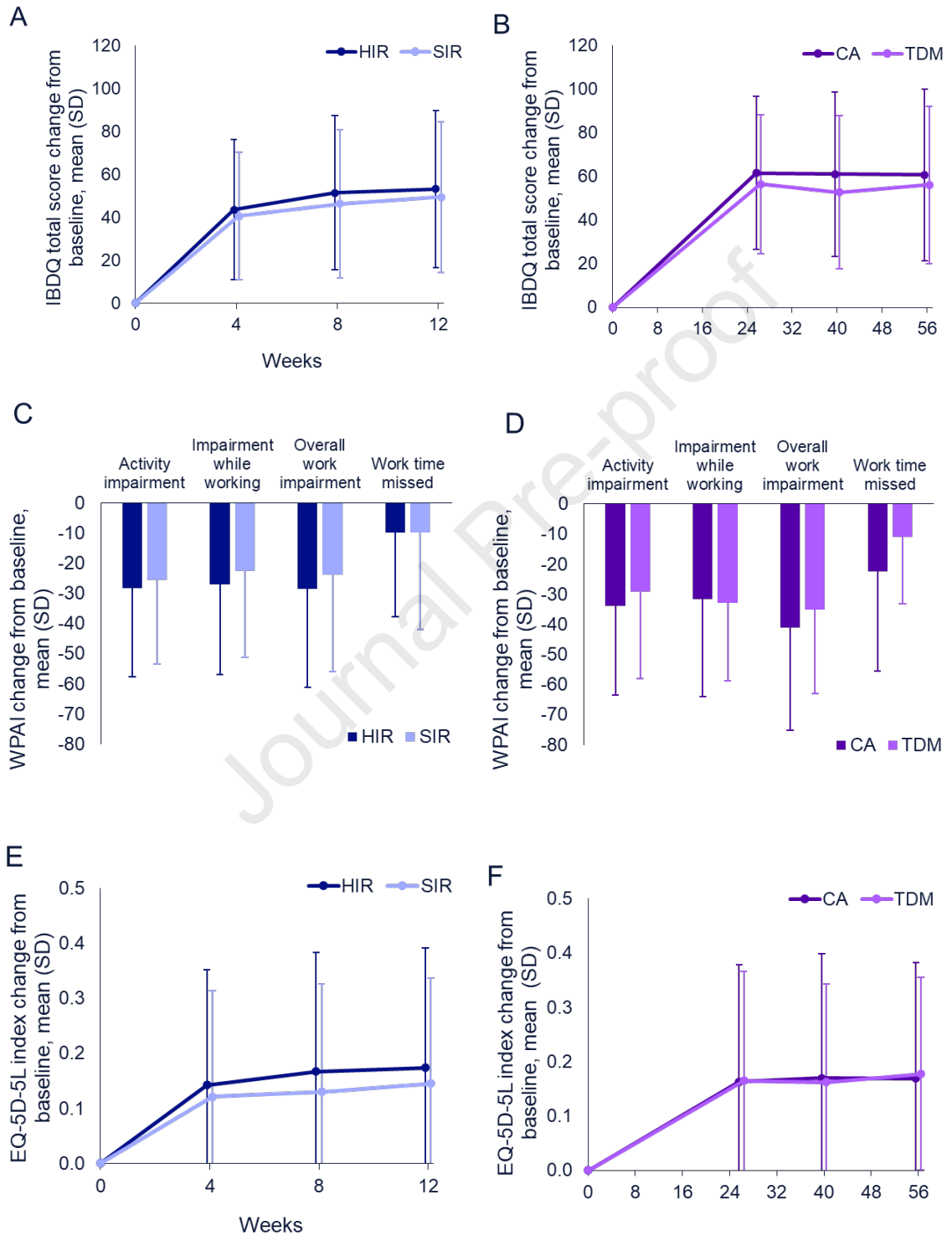


C



ADA, adalimumab; CA, clinically adjusted; CDAI, Crohn's Disease Activity Index; hs-CRP, high-sensitivity C-reactive protein; SES-CD, Simple Endoscopic Score for Crohn's disease; TDM, therapeutic drug monitoring.
[a]Though CA dose escalation could occur at scheduled and unscheduled visits throughout the study, dose escalation only occurred at weeks 14, 28, 34, and 42.
[b]In the TDM group, no patients dose escalated with ADA <5 µg/mL + CDAI ≥220 or with hs-CRP ≥10 mg/L + CDAI ≥220.
Clinical remission: CDAI <150.
Endoscopic response: SES-CD >50% decrease from induction baseline (or for induction baseline SES-CD of 4, ≥ 2-point reduction from induction baseline).

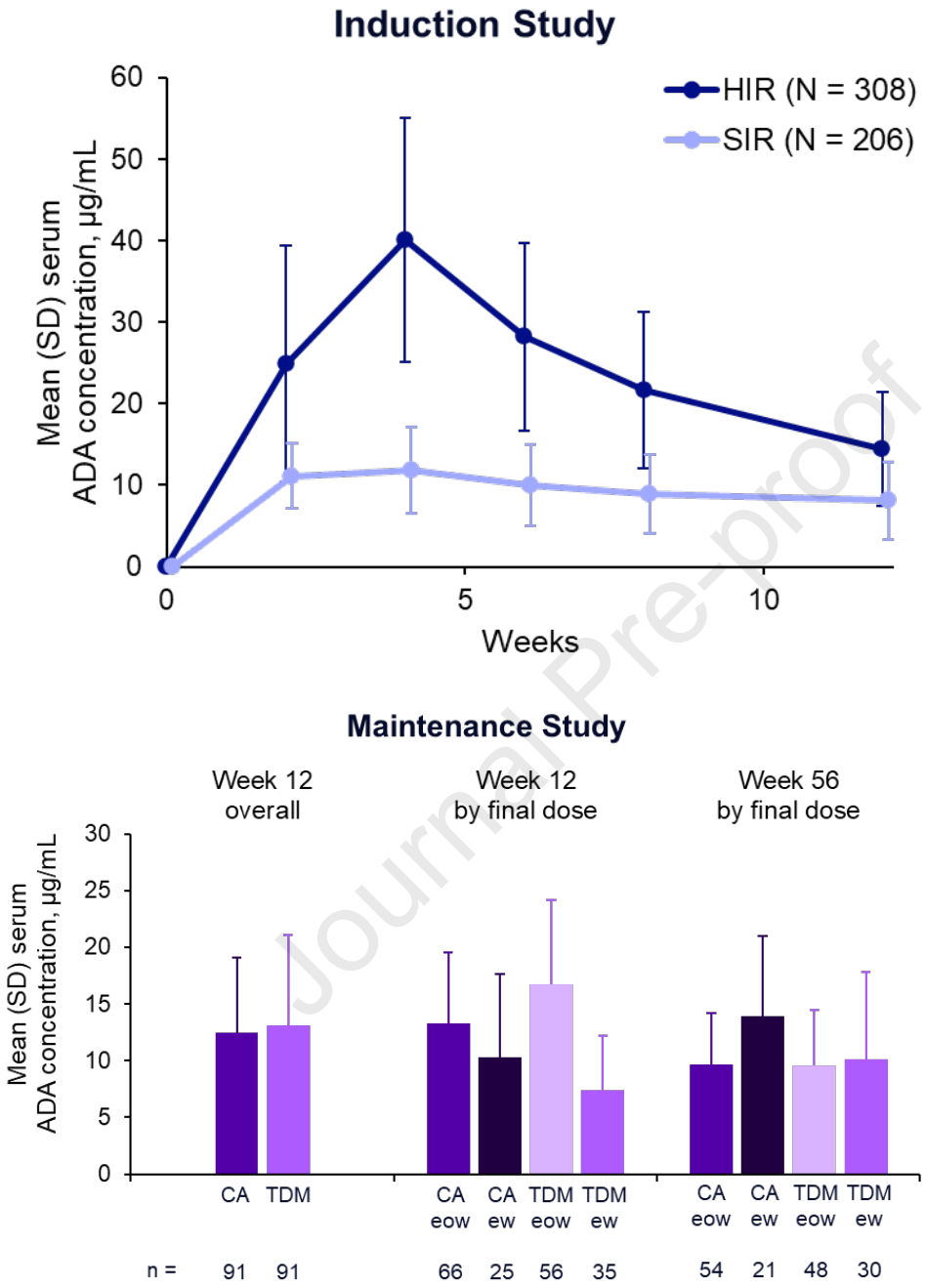
Supplementary Figure 5. Patient-Reported Outcomes



NOTE. Changes from baseline in WPAI were assessed at week 12 (induction study) and week 56 (maintenance study).

CA, clinically adjusted; EQ-5D-5L, 5-level European Quality of Life 5 Dimensions; HIR, higher induction regimen; IBDQ, Inflammatory Bowel Disease Questionnaire; SIR, standard induction regimen; TDM, therapeutic drug monitoring; WPAI, work productivity activity index.

Supplementary Figure 6. Pharmacokinetics and immunogenicity.



(A) Mean (SD) serum adalimumab concentration (µg/mL) over time by induction dose (HIR vs SIR) in the induction study. (B) Mean (SD) serum adalimumab concentration (µg/mL) by maintenance strategy (CA vs TDM) and dose (eow vs ew) in the maintenance study. All week 12 concentrations were measured prior to dose escalation. ADA, adalimumab; CA, clinically adjusted; eow, every other week; ew, every week; HIR, higher induction dose regimen; SIR, standard induction dose regimen; TDM, therapeutic drug monitoring.