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Histologic Outcomes With Vedolizumab Versus Adalimumab in Ulcerative Colitis: Results From VARSITY

Short Title (limit: 45 characters, incl spaces) = Histologic Outcomes in VARSITY

Laurent Peyrin-Biroulet,¹ Edward V. Loftus Jr.,² Jean-Frédéric Colombel,³ Silvio Danese,⁴ Raquel Rogers,⁵ Jeffrey D. Bornstein,⁶ Jingjing Chen,⁷ Stefan Schreiber,⁸ Bruce E. Sands,³ Richard A. Lirio⁹

¹Department of Gastroenterology, Nancy University Hospital, and Inserm U1256 NGERE, Lorraine University, Vandoeuvre-les-Nancy, France; ²Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA; ³Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ⁴Department of Biomedical Sciences, Humanitas Clinical and Research Center – IRCCS, Humanitas University, Milan, Italy; ⁵ Pharmacovigilance, Takeda Development Center Americas Inc, Cambridge, MA, USA; ⁶ Clinical Science, Takeda Development Center Americas Inc, Cambridge, MA, USA; ⁷Statistics and Quantitative Sciences, Takeda Development Center Americas Inc, Cambridge, MA, USA; ⁸Department of Medicine I, University Hospital Schleswig-Holstein, Kiel, Germany; ⁹ Clinical Science, Takeda Development Center Americas Inc, Cambridge, MA, USA

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Abbreviations: CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; RHI, Roberts Histopathology Index; SC, subcutaneous; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis.

Correspondence

Laurent Peyrin-Biroulet, MD, PhD
Department of Gastroenterology
Nancy University Hospital, France
Phone: 33383153661
Email: peyrinbiroulet@gmail.com

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Laurent Peyrin-Biroulet peyrinbiroulet@gmail.com	Personal fees: AbbVie, Janssen, Genentech, Ferring, Tillotts, Pharmacosmos, Celltrion, Takeda, Boehringer Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma,

Author	Conflict(s) of interest
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<p>Edward V. Loftus, Jr. loftus.edward@mayo.edu</p>	<p>Financial support for research: AbbVie, Takeda, Janssen, UCB, Amgen, Pfizer, Genentech, Celgene, Receptos, Gilead, Bristol-Myers Squibb, Robarts Clinical Trials, Theravance; Consultancy: AbbVie, Takeda, Janssen, UCB, Amgen, Pfizer, Eli Lilly, Celltrion Healthcare, Allergan, Bristol-Myers Squibb, Celgene, Gilead, Genentech, Boehringer Ingelheim, Calibr, Iterative Scopes, Ono Pharma, Sun Pharma, Arena.</p>
<p>Jean-Frédéric Colombel jean-frederic.colombel@mssm.edu</p>	<p>Research grants: AbbVie, Janssen Pharmaceuticals, Takeda; Lecture fees: AbbVie, Amgen, Allergan, Inc., Ferring Pharmaceuticals, Shire, Takeda; Consulting fees: AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Geneva, Genentech, Janssen Pharmaceuticals, Immunic, Landos, Ipsen,</p>

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Silvio Danese sdanese@hotmail.com	Lecture fees: AbbVie, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer Inc, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz, Boehringer Ingelheim; Consultancy: AbbVie, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer Inc, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz, Boehringer Ingelheim.
Raquel Rogers Raquel.Rogers@takeda.com	Employee of Takeda; holds Takeda stock or stock options.
Jeffrey D. Bornstein Jeffrey.Bornstein@takeda.com	Employee of Takeda; holds Takeda stock or stock options.
Jingjing Chen Jingjing.Chen@takeda.com	Employee of Takeda; holds Takeda stock or stock options.
Stefan Schreiber s.schreiber@mucosa.de	Consultancy fees: AbbVie, Celltrion, Janssen, Merck, Pfizer, Roche, Takeda.
Bruce E. Sands bruce.sands@mssm.edu	Consultancy: 4D Pharma, AbbVie, Allergan, Amgen, Arena Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Capella Bioscience, Celgene, Celltrion Healthcare, Eli Lilly and Company, EnGene, F. Hoffmann-La Roche, Ferring, Gilead Sciences,

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Richard A. Lirio Richard.Lirio@takeda.com	Employee of Takeda; holds Takeda stock or stock options.

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ABSTRACT

Background and Aims: VARSITY showed superior clinical remission and endoscopic improvement in ulcerative colitis with vedolizumab versus adalimumab. This analysis compared histologic outcomes.

Methods: Patients in VARSITY were randomized 1:1 to vedolizumab 300-mg intravenous infusions or adalimumab 40-mg subcutaneous injections. Geboes and Robarts Histopathology Index (RHI) scores were used to assess prespecified histologic exploratory endpoints (histologic remission [Geboes <2 or RHI ≤2] and minimal histologic disease activity [Geboes ≤3.1 or RHI ≤4]) at Weeks 14 and 52.

Results: In total 769 patients received vedolizumab (n=383) or adalimumab (n=386). Mean baseline histologic disease activity was similar between vedolizumab and adalimumab groups. Vedolizumab induced greater histologic remission than adalimumab at Weeks 14 (Geboes: 16.7% vs 7.3%, Δ9.4%, 95% CI, 4.9 to 13.9, $P < .0001$; RHI: 25.6% vs 16.1%, Δ9.5%, 95% CI, 3.8 to 15.2, $P = .0011$) and 52 (Geboes: 29.2% vs 8.3% Δ20.9%, 95% CI, 15.6 to 26.2, $P < .0001$; RHI: 37.6% vs 19.9%, Δ17.6%, 95% CI, 11.3 to 23.8, $P < .0001$) overall and in both anti-tumor necrosis factor (TNF)–naïve and –failure subgroups. Results were similar for minimal histologic disease activity. Histologic outcomes were generally better in anti-TNF–naïve versus –failure patients. At Week 52, rates of mucosal healing (composite endpoint of histologic plus endoscopic improvement) were also higher with vedolizumab than adalimumab (Geboes: 25.6% vs 6.7%; RHI: 30.5% vs 14.5%).

Conclusion: Higher rates of histologic remission, minimal histologic disease activity, and combined histologic plus endoscopic outcomes were observed with vedolizumab versus adalimumab in ulcerative colitis in both anti-TNF–naïve and –failure subgroups.

Registration: NCT02497469; EudraCT 2015-000939-33

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INTRODUCTION

Ulcerative colitis (UC) is a chronic and disabling inflammatory bowel disease, characterized by relapsing and remitting mucosal inflammation. The ultimate goals of treatment are to induce and maintain clinical remission and improve quality of life.¹ Conventional treatments for UC include aminosalicylates, thiopurines, oral immunomodulators, and corticosteroids. When these agents fail, biologic agents, such as anti-tumor necrosis factor (TNF; e.g., infliximab, adalimumab, and golimumab) and anti-integrin (vedolizumab) therapies, are commonly and widely used.^{2, 3}

VARITY (NCT02497469; EudraCT 2015-000939-33) is the first head-to-head comparison of the efficacy and safety of 2 biologic agents in UC.⁴ Vedolizumab and adalimumab are both approved for use in patients with moderately to severely active UC and Crohn's disease refractory to conventional therapies.^{5, 6} The study showed superior clinical remission and endoscopic improvement at Week 52 with vedolizumab versus adalimumab. Both vedolizumab and adalimumab were generally safe and well tolerated.⁴

There is general consensus that, aside from resolution of symptoms, endoscopic improvement is the ultimate endpoint marking successful maintenance therapy for patients with UC in clinical practice and trials.⁷⁻¹⁰ However, endoscopic changes do not necessarily reflect quiescent microscopic disease, and complete resolution of mucosal inflammation can only be confirmed by histologic assessment.^{9, 10} Thus, including histologic outcomes as treatment targets should be considered. Histologic outcomes can also be useful for assessing disease activity or treatment response.^{7, 11}

Histologic outcomes are not currently recommended as a therapeutic goal for UC in clinical practice. This is possibly because of the current lack of sufficient evidence to support consensus on standardized and validated scoring systems that could be implemented routinely.^{1, 12-14} The recently published STRIDE II guidelines affirms that histological healing is

not a formal treatment target but could be assessed as a measure of the depth of clinical remission.¹ Microscopic evaluation of biopsy samples are prone to sampling error and inter- and intra-observer variability.¹⁴⁻¹⁶ Despite these limitations, histologic outcomes in addition to endoscopic improvement may be associated with superior long-term clinical outcomes in UC^{7, 17} and may predict future UC relapse and complications.^{18, 19} These outcomes are also predictive of future hospitalization, corticosteroid use, exacerbation of UC, and progression to advanced colorectal neoplasia.²⁰⁻²²

In many clinical trials, endoscopic improvement (based on the Mayo endoscopic subscore) has been included as a secondary endpoint. However, according to the most recent US Food and Drug Administration guidance on UC clinical trial endpoints, the determination of mucosal healing must be supported by both endoscopic appearance of the mucosa and histologic assessment of the mucosa.²³ Validated histologic scoring systems in UC include the Geboes score, the Robarts Histopathology Index (RHI), and the Nancy Index.¹¹ Data on mucosal healing assessed histologically with vedolizumab and adalimumab are currently limited.

Here, we report further results from the VARSITY trial that more fully explore the histologic endpoints of histologic remission and minimal histologic disease activity associated with vedolizumab versus adalimumab treatment of UC as assessed using both Geboes and RHI histologic scoring systems, including a composite endoscopic-histologic outcome endpoint.

PATIENTS AND METHODS

Study Design

VARSITY was a phase 3b, randomized, double-blind, double-dummy, multicenter, active-controlled study that evaluated the efficacy and safety of vedolizumab compared with adalimumab among adult patients with moderately to severely active UC over a 52-week

treatment period and a subsequent 18-week follow-up period following last dose. The trial was conducted from July 2015 through January 2019 at 245 sites in 34 countries. A comprehensive description of the VARSITY trial, the study protocol, and institutional review board approvals was published with the primary efficacy and safety results.⁴

Patient Eligibility

Eligible patients were adults 18 to 85 years of age with moderately to severely active UC, defined as a complete Mayo score of 6 to 12 and an endoscopic subscore of ≥ 2 , colonic involvement of ≥ 15 cm, and a confirmed diagnosis of UC for ≥ 3 months prior to screening. Anti-TNF-experienced patients (except adalimumab) who discontinued treatment due to documented reasons other than safety were eligible, with enrollment capped at 25%. Anti-TNF-naïve patients who were unresponsive to or had lost response to conventional treatments were also eligible. Patients on corticosteroids at baseline continued on the same dose until week 6, after which the dose was tapered based on physician's clinical judgement (no forced tapering) if the patient exhibited a treatment response. Patients for whom corticosteroid tapering was not possible were withdrawn from the study and recorded as treatment failures.⁴

The main criteria for patient exclusion included the following: extensive colonic resection, colectomy, evidence of active infection, and prior exposure to vedolizumab, natalizumab, efalizumab, adalimumab, etrolizumab, rituximab, or anti-mucosal addressin cell adhesion molecule-1 antibodies. No topical treatment was allowed at baseline or during the study.

Randomization and Treatment

Patients were randomized 1:1 to vedolizumab or adalimumab. Patients in the vedolizumab treatment group received a 300-mg intravenous (IV) infusion on Day 1 and again at Weeks 2, 6, 14, 22, 30, 38, and 46, plus placebo subcutaneous (SC) injections on Day 1 (4 injections), Week 2 (2 injections), and a single injection every 2 weeks thereafter until Week 50.

Patients assigned to adalimumab received multiple SC injections on Days 1-2 (4 injections of 40 mg each on 1 day or two 40-mg injections per day for 2 consecutive days, totaling 160 mg), Week 2 (two 40-mg injections on one day, totaling 80 mg), and single 40-mg injections every 2 weeks thereafter until Week 50, as well as placebo IV infusions at Day 1 and Weeks 2, 6, 14, 22, 30, 38, and 46. Both vedolizumab and adalimumab were administered according to their US prescribing guidelines.^{5, 6}

Randomization was performed centrally using computer-generated randomization schedules and stratified by prior use of anti-TNF and concomitant use of oral corticosteroids. Patients who did not respond to treatment based on the investigator's discretion were withdrawn and treated with the local standard of care. No dose escalation was permitted for either treatment group.

Assessment and Outcomes

Flexible sigmoidoscopy was performed at screening, at Weeks 14 and 52, or at early termination. Procedure videos were sent to and read by a central reader blinded to patient details, study visit, and treatment. One recto-sigmoid biopsy was obtained from the most severely affected area of inflammation from each patient to evaluate histology. Biopsies were read by a single central reader blinded to patient details, study visit, and treatment. Regular study visits occurred through Week 52, with a final safety follow-up visit at Week 68.

Prespecified histologic exploratory endpoints included histologic remission and minimal histologic disease activity based on the Geboes and RHI scoring systems at study Week 14 and Week 52. Histologic outcomes were assessed in the overall population and in patient subgroups with or without prior anti-TNF use. The thresholds for histologic remission and minimal disease activity on the two scores were each pre-defined individually based on available literature on each system at the time of the study design, prior to the establishment of new standards and guidance. Histologic remission was defined as Geboes grade <2 (with no neutrophils or

eosinophils) and minimal histologic disease activity as Geboes grade ≤ 3.1 . The Geboes Index is a validated and reproducible histologic scoring system, with particular focus/interest for pathologists. It includes 6 grades: structural changes (0), chronic inflammatory infiltrates (1), neutrophils and eosinophils in lamina propria (2), neutrophils in epithelium (3), crypt destruction (4), and erosion or ulceration (5), each subdivided into four to five subgrades. The grades and subgrades can be assigned numerical values to produce a continuous Geboes score between 0 and 22 (as used for baseline histologic disease assessment).²⁴ Geboes subgrade 2B.0 is defined as having no neutrophils and subgrade 2A.0 as no increase in eosinophils within the lamina propria, whereas Geboes grade 3.1 is defined as having neutrophils in the epithelium with $<5\%$ crypts involved (see supplemental Table 1).²⁴

Histologic remission was also defined as RHI score ≤ 2 and minimal histologic disease activity as RHI score ≤ 4 . The RHI is also a valid and reproducible scoring system developed after a model-building process. Scores range from 0-33 based on 4 main parameters: chronic inflammatory infiltrates, lamina propria neutrophils, neutrophils in the epithelium, and surface epithelial injury.²⁶ An RHI score of ≤ 2 denotes histologic remission as long as there are no neutrophils in the lamina propria and in the epithelium; while an RHI score of ≤ 4 can involve some chronic inflammatory infiltrate plus some increase in neutrophils in the lamina propria or epithelium.²⁶ Full details of the RHI are shown in supplemental Table 2.

Post hoc exploratory endpoints included assessment of mucosal healing based on composite outcomes of histologic remission or minimal histologic disease activity and endoscopic improvement (defined as a Mayo endoscopic subscore ≤ 1 point) at Week 52, and evaluation of potential statistical associations between histologic outcomes and endoscopic improvement at Weeks 14 and 52.

Statistical Analysis

Efficacy was analyzed in the full analysis set (all randomized patients who received ≥ 1 dose of study drug, according to treatment allocation). All statistical inference was 2-sided at a 0.05 level of significance. All proportion-based efficacy endpoints were analyzed using the Cochran-Mantel-Haenszel tests adjusting for randomization stratification factors, producing nominal p values and point estimates of treatment difference along with 95% confidence intervals (CIs). All patients with missing data for determination of endpoint status were considered treatment failures (e.g., nonresponders) in the analyses.

The associations between histologic outcomes and endoscopic improvement were explored in a post hoc fashion based on observed data. To assess the degree of agreement (e.g., concordance) between histologic and endoscopic measurements, Cohen's kappa coefficient statistics were generated for binary histologic outcomes and endoscopic improvement using pooled data for both treatment arms at Week 14 and Week 52. Kappa values were interpreted as follows: <0 , disagreement; 0-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; 0.81-1.00, almost perfect agreement.²⁷ To evaluate potential correlations between endoscopy and the 2 histologic scoring systems, Spearman correlation coefficients (ρ) were determined for binary histologic outcomes, endoscopic improvement, and numeric histologic scores and Mayo endoscopic subscores using pooled data for both treatment arms at Week 14 and Week 52. Spearman correlation values were interpreted as follows: 0-0.30, negligible positive correlation; 0.30-0.50, low/weak positive correlation; 0.50-0.70, moderate positive correlation; 0.70-0.90; high/strong positive correlation; 0.90-1.00, very high/strong positive correlation.²⁸

All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Patient Characteristics

There were 1,285 patients screened for eligibility, 771 patients were enrolled, and 769 patients were randomized and received ≥ 1 dose of adalimumab SC (N = 386) or vedolizumab IV (N = 383). Patient characteristics were generally comparable between treatment groups (**Table 1**). Discontinuation of treatment due to lack of efficacy occurred in 82 patients on adalimumab and 41 on vedolizumab.

Median duration of exposure was 477 days (range, 127-630 days) for vedolizumab (calculated as the date of last dose – date of first dose + 1 + 126 [5 half-lives after the last dose of vedolizumab]⁶) and 420 days (range, 71-454 days) for adalimumab (calculated as the date of last dose – date of first dose + 1 + 70 [5 half-lives after the last dose of adalimumab]⁵). Mean baseline histologic disease activity was similar between groups (**Table 1**; mean [standard deviation] Geboes continuous score: vedolizumab 15.0 [4.9], adalimumab 15.1 [5.0]; RHI: vedolizumab 19.5 [8.7], adalimumab 19.6 [8.9]).

Geboes Grade

Histologic Remission

Histologic remission at Week 14 (Geboes grade < 2) was observed in 16.7% of patients in the vedolizumab group and in 7.3% in the adalimumab group (difference, 9.4%; 95% CI, 4.9 to 13.9; $P < .0001$) (**Figure 1A**). Overall, histologic remission at Week 52 was 29.2% (112 of 383) with vedolizumab versus 8.3% (32 of 386) with adalimumab (difference, 20.9%; 95% CI, 15.6 to 26.2; $P < .0001$) (**Figure 1B**). Histologic remission at Week 52 was greater with vedolizumab than with adalimumab in the anti-TNF-naïve patient subgroup (32.2% versus 9.5%; difference, 22.7%; 95% CI, 16.5 to 29.0; $P < .0001$) and in the Anti-TNF exposure/failure subgroup (17.7% versus 3.7%; difference, 14.0%; 95% CI, -1.2 to 29.4; $P = .0045$).

Minimal Histologic Disease Activity

Minimal histologic disease activity at Week 14, defined as Geboes grade ≤ 3.1 , occurred in 45.2% of patients on vedolizumab and in 30.6% on adalimumab (difference, 14.5%; 95% CI, 7.8 to 21.2; $P < .0001$) (**Figure 2A**). Vedolizumab outperformed adalimumab in achieving minimal histologic disease activity at Week 52 (45.7% versus 30.8%; difference, 14.8%; 95% CI, 8.0 to 21.5; $P < .0001$) (**Figure 2B**). More patients achieved minimal histologic disease activity with vedolizumab than with adalimumab at Week 52 in both anti-TNF-naïve (48.0% versus 34.1%; difference, 13.9%; 95% CI, 6.2 to 21.7; $P = .0005$) and anti-TNF-failure (36.7% versus 18.5%; difference, 18.0%; 95% CI, 4.5 to 31.5; $P = .0107$) cohorts.

Histologic Improvement

Mean (SD) change from baseline in continuous Geboes score was -3.4 (7.38) at Week 14 and -5.4 (7.65) at Week 52 in the adalimumab group compared with -5.2 (7.26) at Week 14 and -7.8 (7.01) at Week 52 in the vedolizumab group.

RHI Score

Histologic Remission

RHI scores showed a differentiation between treatment arms in patients achieving histologic remission at Week 14 (25.6% with vedolizumab and 16.1% with adalimumab; difference, 9.5%; 95% CI, 3.8 to 15.2; $P = .0011$) (**Figure 3A**). Similar treatment differentiation was observed at Week 52 with histologic remission defined as RHI score ≤ 2 (37.6% with vedolizumab and 19.9% with adalimumab; difference, 17.6%; 95% CI, 11.3 to 23.8, $P < .0001$) (**Figure 3B**) and in the anti-TNF-naïve (39.8% versus 22.6%; difference, 17.2%; 95% CI, 9.9 to 24.4; $P < .0001$) and anti-TNF-failure (29.1% versus 9.9%; difference, 19.0%; 95% CI, 7.1 to 31.0; $P = .0022$) patient subgroups.

Minimal Histologic Disease Activity

Minimal histologic disease activity at Week 14 (RHI score ≤ 4) favored vedolizumab (37.3%) over adalimumab (24.4%) (difference, 12.9%; 95% CI, 6.5 to 19.4; $P < .0001$) (**Figure 4A**). Week 52 rates of minimal histologic disease activity were 42.3% with vedolizumab versus 25.6% with adalimumab (difference, 16.6%; 95% CI, 10.0 to 23.1; $P < .0001$) (**Figure 4B**). Vedolizumab was superior to adalimumab in achieving minimal histologic disease activity at Week 52 among both anti-TNF-naïve (45.1% versus 27.9%; difference, 17.2%; 95% CI, 9.6 to 24.7; $P < .0001$) and anti-TNF-failure (31.6% versus 17.3%; difference, 14.1%; 95% CI, 1.1 to 27.2; $P = .0364$) subgroups.

Histologic Improvement

Mean (SD) change from baseline in RHI was -5.0 (12.19) at Week 14 and -8.1 (13.08) at Week 52 in the adalimumab group compared with -7.5 (11.75) at Week 14 and -10.9 (11.04) at Week 52 in the vedolizumab group.

Post Hoc Analysis of Mucosal Healing (Composite Histologic and Endoscopic Outcomes)

Patients who achieved histologic remission or minimal histologic disease activity (Geboes or RHI) plus endoscopic improvement rates at Week 52 are shown in **Figures 5 and 6**. More vedolizumab patients achieved histologic remission plus endoscopic improvement than those treated with adalimumab (vedolizumab: 30.5% [RHI] and 25.6% [Geboes]; adalimumab: 14.5% [RHI] and 6.7% [Geboes]). This pattern was the same for minimal histologic disease activity plus endoscopic improvement (vedolizumab: 33.7% [RHI] and 35.0% [Geboes]; adalimumab: 18.1% [RHI] and 20.2% [Geboes]).

Subgroup analysis by use of baseline corticosteroids or immunomodulators

Subgroup data on patients who were on corticosteroids or immunomodulators at baseline showed a consistent treatment effect for all histologic endpoints, although the data are not sufficiently powered to draw any conclusions (Supplementary Figure S1).

Post Hoc Analysis of Associations Between Histologic and Endoscopic Outcomes

Kappa statistics were used to assess the agreement between histologic remission or minimal histologic disease activity and endoscopic improvement in UC using both the RHI and Geboes scoring systems. When Week 14 and Week 52 time points and both treatment arms were pooled, both RHI and Geboes scores showed moderate agreement between minimal histologic disease activity and endoscopic improvement (RHI: $\kappa=0.53$; 95% CI, 0.48 to 0.58; Geboes: $\kappa=0.55$; 95% CI, 0.51 to 0.60). The RHI scores also showed moderate agreement between histologic remission and endoscopic improvement ($\kappa=0.47$; 95% CI, 0.42 to 0.52), as did Geboes grades ($\kappa=0.36$; 95% CI, 0.31 to 0.41).

Using pooled data for both treatment arms at Week 14 and Week 52, Spearman correlation coefficients between histologic remission and endoscopic improvement were as follows: Spearman's $\rho=0.48$, $P < .0001$ (RHI) and Spearman's $\rho=0.63$, $P < .0001$ (Geboes). Correlations between minimal histologic disease activity and endoscopic improvement were moderate using both scoring systems: Spearman's $\rho=0.53$, $P < .0001$ for RHI and Spearman's $\rho=0.56$, $P < .0001$ for Geboes. Correlations were also moderate both between numeric RHI scores and Mayo endoscopic subscores ($\rho=0.63$, $P < .0001$) and between numeric continuous Geboes scores and Mayo endoscopic subscores ($\rho=0.64$, $P < .0001$).

DISCUSSION

VARITY data analyses suggest superior treatment effects of vedolizumab versus adalimumab in achieving all histologic outcomes in patients with moderate to severe UC. This finding is consistent with the superior clinical and endoscopic efficacy outcomes with vedolizumab versus adalimumab already reported from the VARSITY trial.⁴ Patients achieved higher rates of histologic remission and minimal histologic disease activity at Weeks 14 and 52 on vedolizumab than on adalimumab. Anti-TNF-naïve patients generally had superior histologic outcomes relative to patients with prior anti-TNF exposure, which was similar to the previously reported finding that clinical remission was higher among anti-TNF-naïve than -exposed patients for both vedolizumab and adalimumab.⁴ Vedolizumab was superior to adalimumab in achieving histologic remission and minimal histologic disease activity in nearly all anti-TNF-naïve and prior anti-TNF-exposure/failure subgroup comparisons. In addition, subgroup data on baseline corticosteroid or immunomodulator use showed a consistent treatment effect of vedolizumab with or without baseline corticosteroid or immunomodulator use; however, caution should be exercised when interpreting this data as the study was not designed for such analysis.

Histologic outcomes may be important treatment targets for patients with UC. However, a standard histologic scoring system is still lacking. This study used common scoring system definitions reported in the current literature. With both Geboes and RHI scores, vedolizumab outperformed adalimumab in achieving histologic outcomes. More patients had mucosal healing (histologic outcomes and endoscopic improvement) at Week 52 with vedolizumab than with adalimumab. When comparing treatment outcomes in clinical trials, the RHI score is likely more appropriate than the Geboes score due to its reproducibility, its sensitivity to change, and its relative ease of interpretation.¹¹

Despite the importance of microscopic activity for disease assessment, histologic remission has yet to be recommended as a therapeutic goal for UC in clinical practice or in clinical trials.^{1, 12, 23} Multiple studies were conducted to assess the use of histologic outcome as a measure of disease activity or clinical outcomes and its association with achieving endoscopic remission.^{20-22, 29} One study found a statistically significant overall association between the histologic (using the Geboes and RHI scores) and endoscopic (using the Mayo endoscopic subscore) scores, with Kendall's $\tau=0.482$ ($P < .0001$) showing the best correlation.³⁰ Another study showed a good agreement between the Geboes histologic score and the Mayo endoscopic subscore (Spearman's $\rho=0.65$, $P < .001$).²⁹ In a cohort study of 34 patients with UC who received vedolizumab for more than a year, a statistically significant association between histologic and endoscopic improvement was observed (r^2 0.61, $P < .001$). The majority of patients with endoscopic improvement also had histologically quiescent disease.³¹

This study was the first head-to-head study of biologics in IBD, and its multiple outcomes and assessments allow treatment effects across a range of outcomes to be explored, including histology using two well-known, robust scoring systems: the Geboes score, which is commonly used, and RHI, which has advantages for use in the clinical trial setting. This study had several limitations. First, only 2 histologic scoring systems (Geboes grade and RHI) were used in this study despite the availability of other validated scoring systems for UC, such as the Nancy Index.^{7, 11} Second, only 1 recto-sigmoid biopsy sample was taken for each patient. Because UC presents with diffuse mucosal inflammation, variability in the histopathologic severity within the colonic mucosa may occur.^{10, 15} One study showed microscopic heterogeneity in biopsy samples of patients with UC.³² Sampling errors could be reduced by taking multiple samples with visible endoscopic inflammation for histologic assessment.^{9, 10, 16} However, endoscopists were mandated to select the most severely affected area. Future studies may benefit from sampling multiple areas. The Geboes and RHI thresholds used to define the histologic outcomes, in particular for minimal disease activity, should not be viewed as directly comparable without

providing additional context around the presence or absence of neutrophils in the lamina propria or epithelium due to differences in the way the final RHI score can be reached (see supplemental Tables 1 and 2). Third, the study protocol did not specify a schedule for corticosteroid tapering, which can vary between clinicians. Fourth, dose escalation was not possible in either treatment arm to maintain treatment group blinding. Finally, no long-term follow-up was conducted among these patients, which could have been useful to determine changes in histologic outcomes along the natural course of disease. The duration of disease and treatment could have affected the biopsy results.^{9, 16} Large, prospective studies are also recommended to assess the impact of histologic outcomes on the natural disease course.

In conclusion, VARSITY demonstrated favorable histologic outcomes with vedolizumab compared with adalimumab, with vedolizumab showing consistent superiority across multiple therapeutic endpoints, including the key outcome of histologic remission. Associations between histologic outcomes and endoscopic improvement in this study were greater using the RHI scoring system. This is important given the recent position statement from the European Crohn's and Colitis Organisation (ECCO) supporting the need to consider mucosal healing based on endoscopy and histology.¹³

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FIGURE LEGENDS

Figure 1. Histologic Remission (Geboes Grade <2) at (A) Week 14 and (B) Week 52. Point estimates and 95% CIs were obtained using the Cochran-Mantel-Haenszel method with stratification by randomization stratification factor: concomitant use of oral corticosteroids (Yes/No) and prior use of anti-TNF (Yes/No); or by the Fisher's exact method if the numerator was ≤ 5 . Patients with missing endpoint data were considered treatment failures (ie, nonresponders). CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous; TNF, tumor necrosis factor. ^aNominal *P* value.

Figure 2. Minimal Histologic Disease Activity (Geboes Grade ≤ 3.1) at (A) Week 14 and (B) Week 52. Point estimates and 95% CIs were obtained using the Cochran-Mantel-Haenszel method with stratification by randomization stratification factor: concomitant use of oral corticosteroids (Yes/No) and prior use of anti-TNF (Yes/No); or by the Fisher's exact method if the numerator was ≤ 5 . Patients with missing endpoint data were considered treatment failures (ie, nonresponders). CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous; TNF, tumor necrosis factor. ^aNominal *P* value.

Figure 3. Histologic Remission (RHI Score ≤ 2) at (A) Week 14 and (B) Week 52. Point estimates and 95% CIs were obtained using the Cochran-Mantel-Haenszel method with stratification by randomization stratification factor: concomitant use of oral corticosteroids (Yes/No) and prior use of anti-TNF (Yes/No); or by the Fisher's exact method if the numerator was ≤ 5 . Patients with missing endpoint data were considered treatment failures (ie, nonresponders). CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; RHI, Robarts Histopathology Index; SC, subcutaneous; TNF, tumor necrosis factor.

^aNominal *P* value. From N Engl J Med, Sands BE, Peyrin-Biroulet L, Loftus EV, Jr, et al, Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. 381, 1215-1226..

Figure 4. Minimal Histologic Disease Activity (RHI Score ≤ 4) at (A) Week 14 and (B) Week 52. Point estimates and 95% CIs were obtained using the Cochran-Mantel-Haenszel method with stratification by randomization stratification factor: concomitant use of oral corticosteroids (Yes/No) and prior use of anti-TNF (Yes/No); or by the Fisher's exact method if the numerator was ≤ 5 . Patients with missing endpoint data were considered treatment failures (ie, nonresponders). CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; RHI, Roberts Histopathology Index; SC, subcutaneous; TNF, tumor necrosis factor.

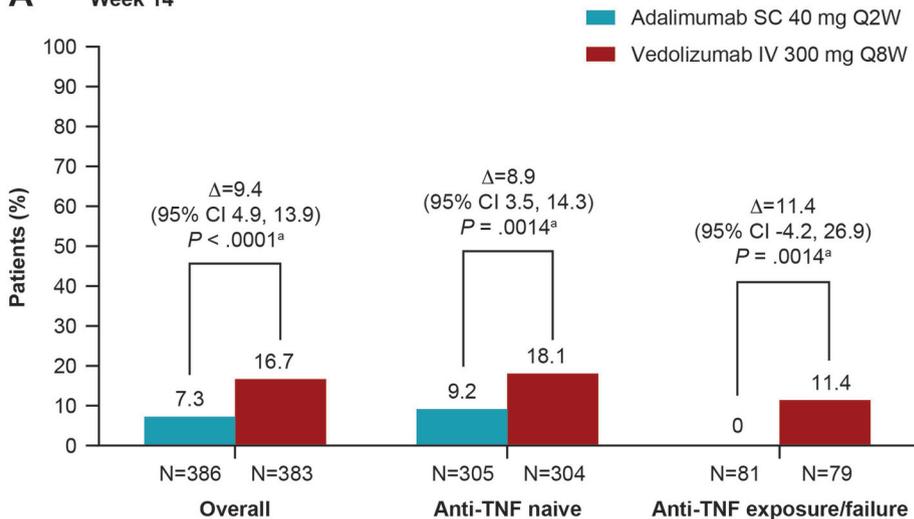
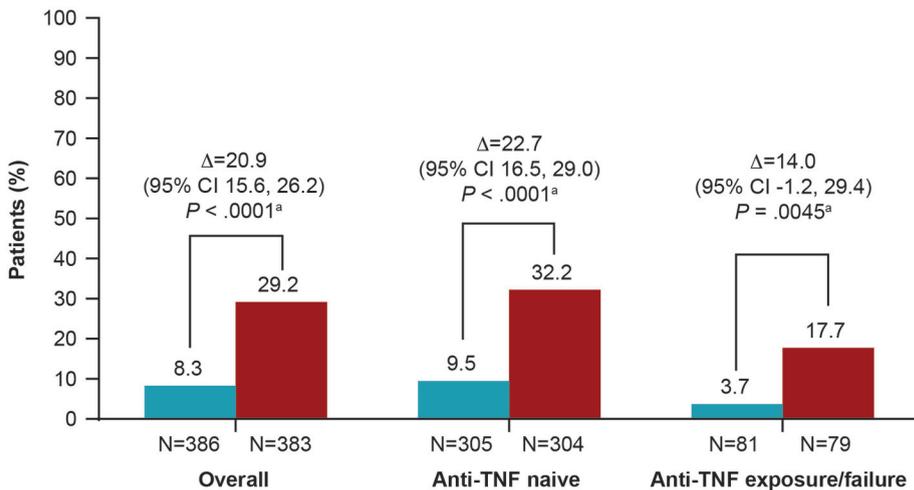
^aNominal *P* value. From N Engl J Med, Sands BE, Peyrin-Biroulet L, Loftus EV, Jr, et al, Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. 381, 1215-1226.

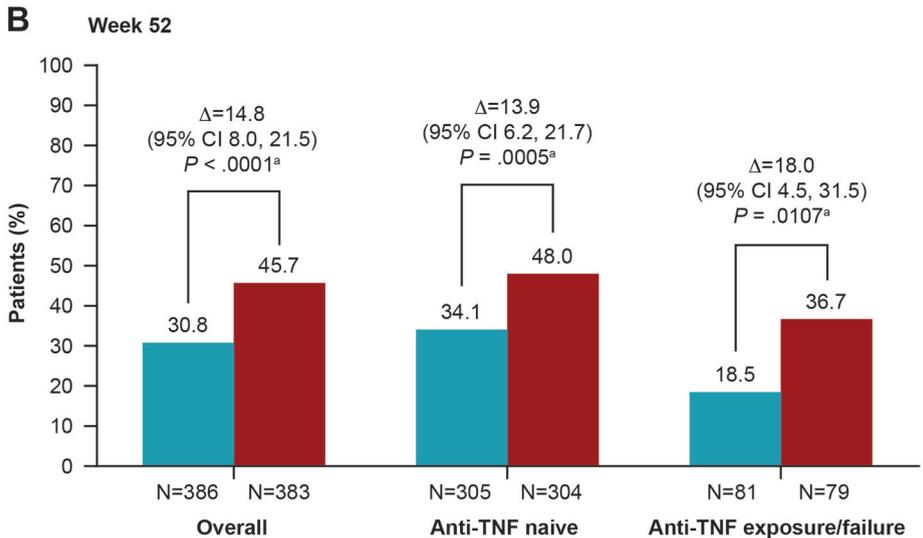
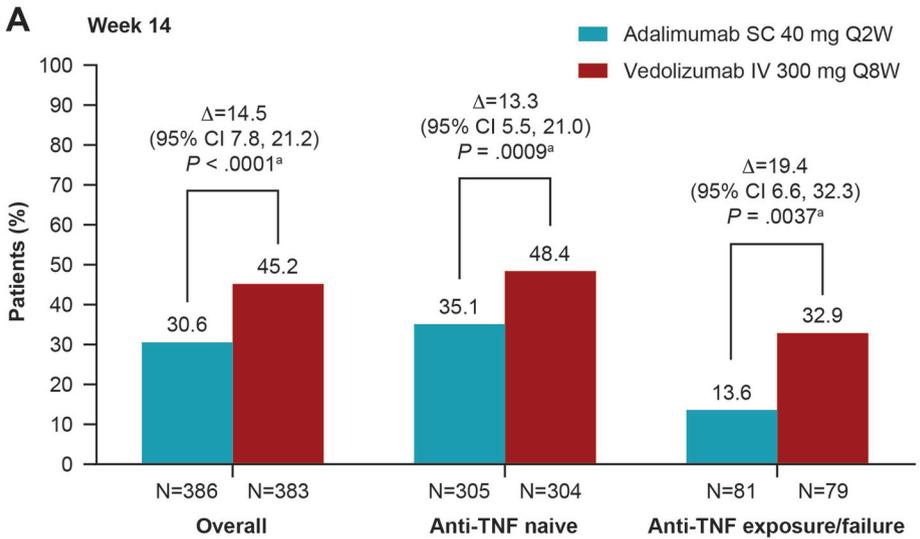
Figure 5. Histologic Remission ([A] Geboes Grade < 2 , [B] RHI Score ≤ 2) Plus Endoscopic Improvement (Mayo Endoscopic Subscore ≤ 1) at Week 52. Point estimates and 95% CIs were obtained using the Cochran-Mantel-Haenszel method with stratification by randomization stratification factor: concomitant use of oral corticosteroids (Yes/No) and prior use of anti-TNF (Yes/No); or by the Fisher's exact method if the numerator was ≤ 5 . Patients with missing endpoint data were considered treatment failures (ie, nonresponders). CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; RHI, Roberts Histopathology Index; SC, subcutaneous; TNF, tumor necrosis factor. ^aNominal *P* value.

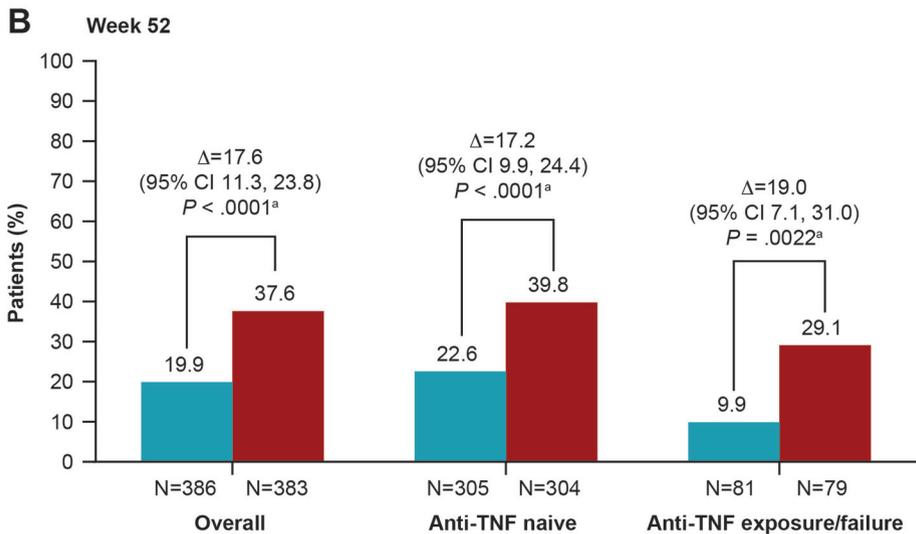
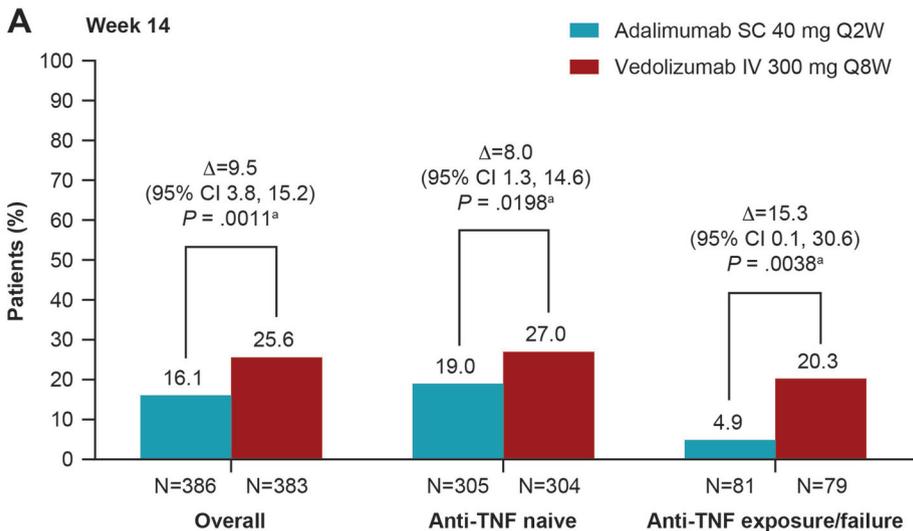
Figure 6. Minimal Histologic Disease Activity ([A] Geboes Grade ≤ 3.1 , [B] RHI Score ≤ 4) Plus Endoscopic Improvement (Mayo Endoscopic Subscore ≤ 1) at Week 52. Point

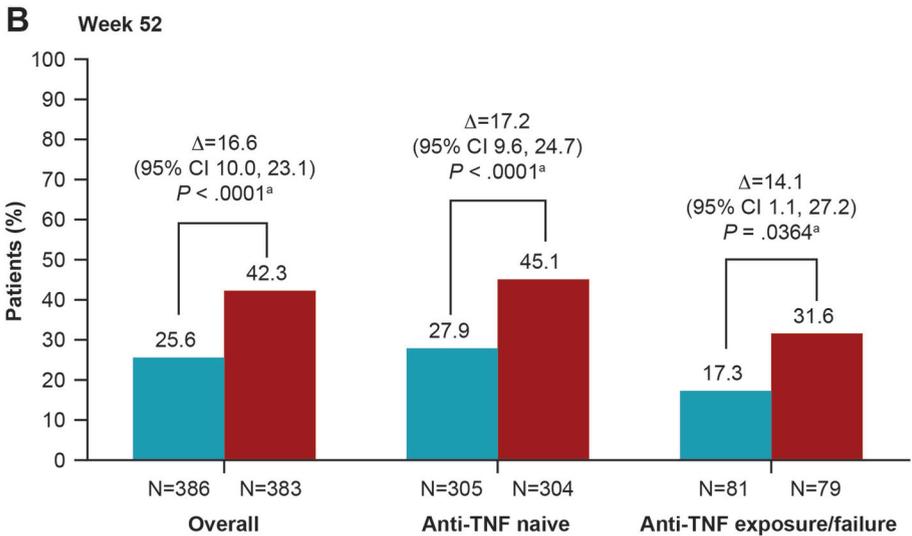
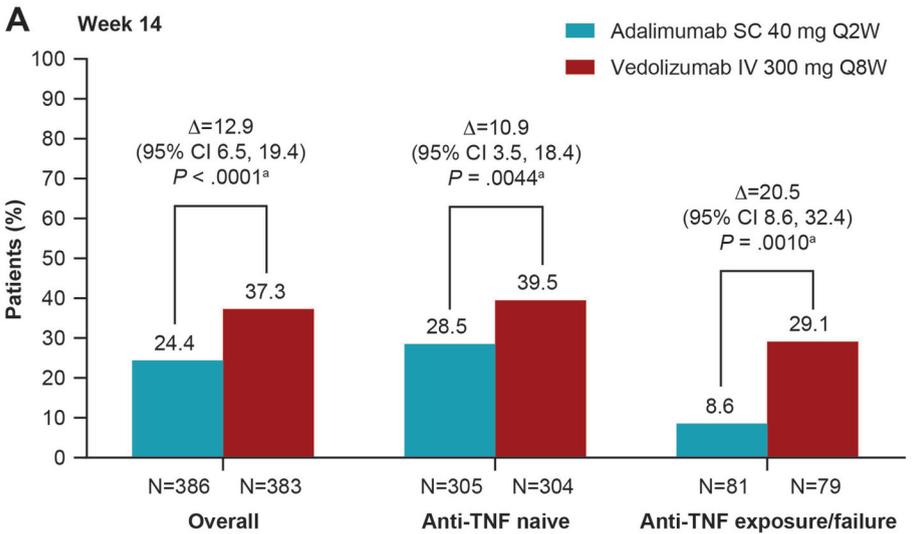
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^aNominal *P* value.

A**Week 14****B****Week 52**

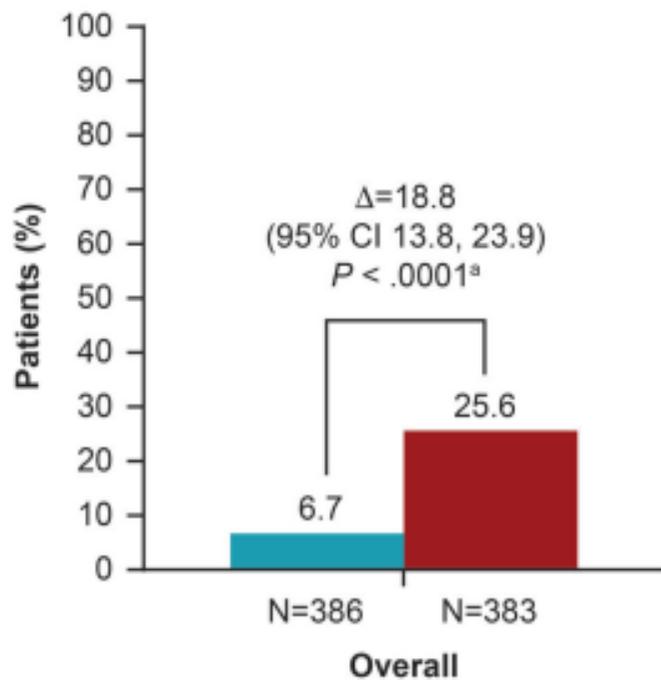
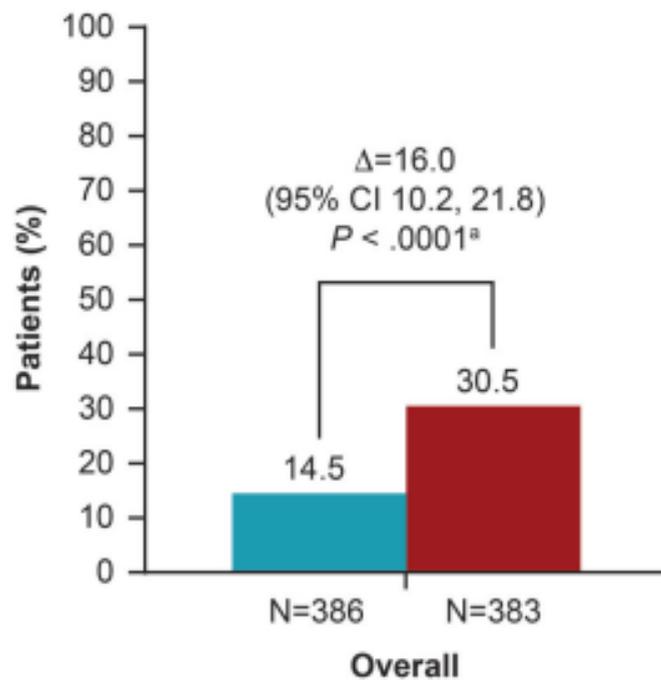






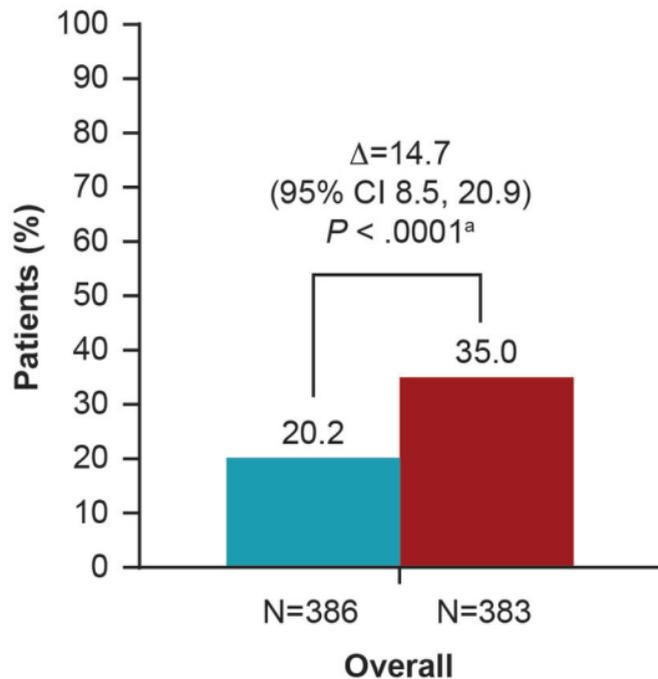
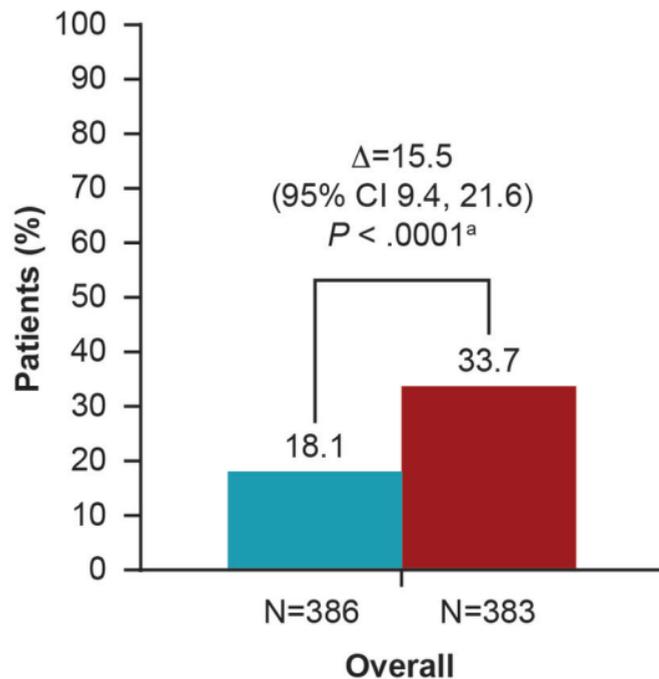
A

Geboes grade <2

**B**RHI score ≤ 2 

■ Adalimumab SC 40 mg Q2W

■ Vedolizumab IV 300 mg Q8W

A**Geboes grade ≤ 3.1** **B****RHI score ≤ 4** 

■ Adalimumab SC 40 mg Q2W

■ Vedolizumab IV 300 mg Q8W

TABLES

Table 1. Patient Demographics and Baseline Disease Characteristics

Age, years, mean (SD)	40.5 (13.4)	40.8 (13.7)
Sex, male, n (%)	216 (56.0)	234 (60.8)
Weight, kg at Week 0, mean (SD) [n]	73.4 (18.4) [386]	72.7 (17.0) [383] ^a
Duration of UC, years, mean (SD) [n]	6.4 (6.0) [385] ^b	7.3 (7.2) [383] ^a
Prior anti-TNF use, n (%) ^c	81 (21.0)	80 (20.8)
Concomitant steroids, n (%) ^c	140 (36.3)	139 (36.1)
Concomitant immunomodulators, n (%)	100 (25.9)	101 (26.2)
Baseline complete Mayo score, n (%)		
Mild (Mayo score <6)	5 (1.3)	9 (2.3)
Moderate (Mayo score = 6 to 8)	169 (43.8)	154 (40.0)
Severe (Mayo score = 9 to 12)	210 (54.4)	217 (56.4)
Fecal calprotectin, µg/g, mean (SD) [n]	2,770.8 (4,064.5) [332]	2,928.6 (5,920.4) [341]
Geboes score ^d , mean (SD) [n]	15.1 (5.0) [354]	15.0 (4.9) [365]
RHI score, mean (SD) [n]	19.6 (8.9) [356]	19.5 (8.7) [365]

IV, intravenous; RHI, Roberts Histopathology Index; SC, subcutaneous; SD, standard deviation; UC, ulcerative colitis; TNF, tumor necrosis factor.

^aDoes not include 2 patients randomized but not treated.

^bOne patient in the adalimumab group had an unknown duration of UC.

^cAs reported in the interactive web response system.

^dContinuous Geboes score (on a scale of 0 – 22).

Histologic Outcomes in Ulcerative Colitis from the VARSITY Study

Study Design

Study Duration 52 weeks

Randomized
N=769

Adalimumab SC
40 mg Q2W
n=386

Vedolizumab IV
300 mg Q8W
n=383

Baseline Histologic
Disease Activity

Robarts Histology Index

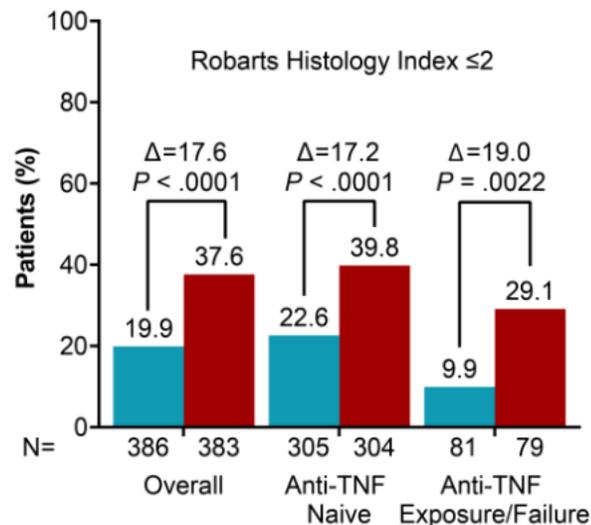
19.6

Adalimumab SC
40 mg Q2W

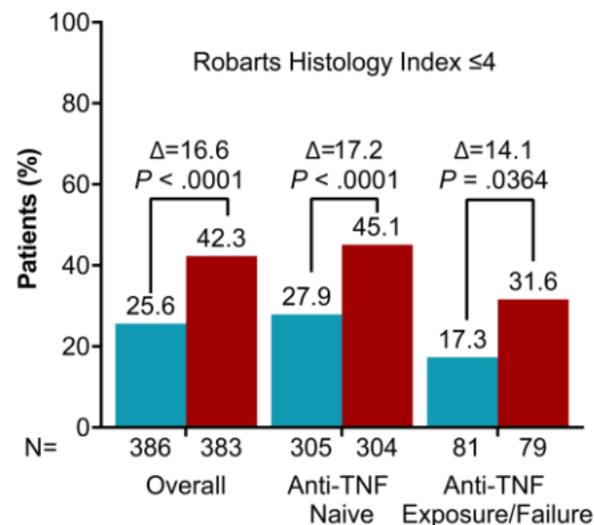
19.5

Vedolizumab IV
300 mg Q8W

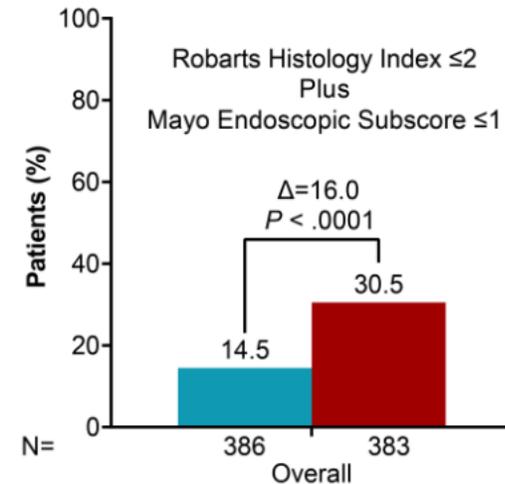
Vedolizumab-treated patients had higher rates of **histologic remission at Week 52**



Vedolizumab-treated patients had higher rates of **minimal histologic disease activity at Week 52**



Vedolizumab-treated patients had higher rates of **histologic remission plus endoscopic improvement at Week 52**



Gastroenterology