Agreement Between Rectosigmoidoscopy and Colonoscopy Analyses of Disease Activity and Healing in Patients With Ulcerative Colitis

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BACKGROUND & AIMS: Endoscopy limited to the rectosigmoid colon is the standard technique used to measure endoscopic healing in ulcerative colitis (UC) clinical trials. We evaluated whether rectosigmoidoscopy adequately measures UC activity in the more proximal colon.

METHODS: We analyzed data from a phase 2, placebo-controlled study that evaluated the efficacy and safety of etrolizumab in patients with moderate to severely active UC who had not responded to standard therapy. Central readers determined Mayo Clinic endoscopic subscores (MCSe) and ulcerative colitis endoscopic index of severity (UCEIS) scores from the rectosigmoid and proximal colon in videos of 331 examinations performed at baseline, week 6, and week 10.

Rates of endoscopic healing (MCSe ≤ 1, MCSe = 0) and scores from rectosigmoidoscopy and colonoscopy analyses were compared among 239 examinations with endoscopic assessment proximal to the rectosigmoid colon.

RESULTS: There was a high degree of correlation between findings from rectosigmoidoscopy vs colonoscopy in assessment of disease activity based on MCSe of 2 or higher (r = 0.84) or MCSe of 1 or higher (r = 0.96), or the UCEIS score (r = 0.92). In 230 of 239 videos, findings from rectosigmoidoscopy agreed with those from colonoscopy in the detection of active disease (MCSe ≥ 2; n = 205) or healing (MCSe ≤ 1; n = 25). In 9 videos (2 taken at baseline, 7 taken after treatment), colonoscopy found proximal disease activity not detected by rectosigmoidoscopy. Post-treatment discordance was more frequent in the placebo group, affecting assessment of efficacy at week 10. When endoscopic healing was defined as MCSe of 0, there were discordant findings from only 1 video.

CONCLUSIONS: There is a high degree of correlation in assessments of UC activity made by rectosigmoidoscopy vs colonoscopy. For detection of endoscopic healing (MCSe ≤ 1), colonoscopy found persistent proximal lesions in the placebo group, which affected efficacy analyses. When endoscopic healing was defined as MCSe of 0, the concordance between rectosigmoidoscopy and colonoscopy was nearly perfect.

Keywords: Anti-Integrin; EUCALYPTUS; Inflammatory Bowel Disease; IBD.

Ulcerative colitis (UC) is a chronic relapsing inflammatory bowel disease (IBD) characterized by superficial mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain. Until the late 1990s, the therapeutic goal for UC was clinical remission as defined by symptom management. However, a growing body of evidence indicates that healing of the mucosa is an important therapeutic endpoint in clinical trials and in clinical practice. This altered therapeutic paradigm has increased the role of endoscopy in UC further.

Colonoscopy with intubation of the terminal ileum is the standard of care for the diagnosis of patients with suspected UC.3–5 Once the diagnosis is established, and when UC patients are included in clinical trials, endoscopy limited to the rectum and sigmoid is the standard to assess disease activity and endoscopic healing because it is believed that the most severe activity of UC is located in the distal colon. However, little evidence supports this assertion, and some UC patients may harbor more severe endoscopic inflammation proximal to the sigmoid colon.

Etrolizumab is a humanized monoclonal anti-β7 antibody with a dual mechanism of action, inhibiting both α4β7:MadCAM-1-mediated lymphocyte trafficking to the gut mucosa and αEβ7: E-cadherin-mediated lymphocyte retention in the intraepithelial compartment.6–12 In a double-blind, placebo-controlled, randomized, phase 2 study, etrolizumab led to significantly greater rates of clinical remission at week 10 compared with placebo in patients with moderately to severely active UC.13 During this study, 72% of endoscopic examinations assessed disease activity beyond the rectosigmoid. This circumstance allowed us to evaluate whether endoscopic assessment limited to the rectosigmoid adequately represents endoscopic activity of the more proximal colon, and how potential discrepancies might affect assessment of efficacy in the context of a randomized controlled clinical trial.

Abbreviations used in this paper: EUCALYPTUS, IBD, inflammatory bowel disease; MC5, Mayo Clinic Score; MCSe, Mayo Clinic endoscopic subscore; PPV, positive predictive value; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.
Materials and Methods

Patient Cohort

The EUCALYPTUS trial evaluated the efficacy and safety of etrolizumab (Genentech, South San Francisco, CA) in patients with moderately to severely active UC, who had not responded to conventional therapy, including immunosuppressants and/or at least one anti-tumor necrosis factor agent. For this randomized, double-blind, placebo-controlled, multicenter, phase 2 study, patients were recruited from 40 centers in 11 countries. Of 124 patients, 41 patients were assigned to 100-mg etrolizumab administered subcutaneously at weeks 0, 4, and 8; 40 patients were assigned to 300-mg etrolizumab at weeks 2, 4, and 8, plus a 420-mg loading dose administered between weeks 0 and 2; and 43 patients were assigned to monthly subcutaneous injections of placebo for 3 months. Five patients were excluded from the modified intent-to-treat population because they had a centrally read screening endoscopic score of less than 2, leaving 41 analyzed from the placebo group, 39 from the 100-mg etrolizumab group, and 39 from the 300-mg etrolizumab plus loading dose group. Details of patient demographics, methods, and eligibility criteria have been described previously. Briefly, patients included were adults diagnosed with UC for a minimum of 12 weeks, who had a Mayo Clinic Score (MCS) of 5 or greater, with an MCS endoscopic subscore (MCSe) of 2 or greater, a rectal bleeding symptom score of 1 or greater, and disease extending 25 cm or more from the anal verge. The primary efficacy end point was clinical remission at week 10, defined as the proportion of patients with an MCS of 2 or less, with no individual subscore greater than 1. The post hoc analyses described here received institutional review board approval under the EUCALYPTUS protocol (ClinicalTrials.gov, NCT01336465).

Analysis of Endoscopic Examinations

The current study examined 331 videos of endoscopies captured during the EUCALYPTUS trial, after exclusion of videos without associated patient identification numbers and videos of patients excluded because of protocol violations (Supplementary Figures 1 and 2). Videos of patient endoscopies were recorded at the baseline screening visit (week 0), and after randomization at week 6 and week 10. Of the 331 videos, 239 (100 from baseline and 139 from weeks 6 and 10) included assessment of colonic segments proximal to the rectosigmoid region, and were analyzed for disease activity and endoscopic healing in this study (Supplementary Figure 2). Endoscopic severity was assessed using the MCSe and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). For the MCSe, active disease was defined as a score greater than 1, and endoscopic healing was defined as MCSe of 0 or less. We included analyses with endoscopic healing defined as MCSe of 0 because of emerging evidence that a score of 0 may be linked to different patient outcomes compared with a score of 1. Currently, the UCEIS does not specify a cut-off score to distinguish active disease from endoscopic healing and, therefore, was not used to calculate positive predictive values (PPV) and negative predictive values. Central readers performed a preliminary evaluation of videos to determine parameters for scoring the MCSe and the UCEIS. Of note, the location of segments explored was not annotated on the videos during recording and not all patients received full colonoscopies with examination of all 5 colonic segments (rectum, sigmoid, descending colon, transverse colon, and ascending colon). Four central readers (2 per video) from 2 sites estimated the number of colonic segments examined, guided by the length of the segments and identification of anatomic characteristics such as the hepatic, splenic, and rectosigmoid flexures. Readers also determined the extent of disease.

For determining endoscopic healing based on the MCSe, the worst score of the rectosigmoid alone was compared with the worst score of the whole colon (including the rectosigmoid). A separate, independent, central reader adjudicated the final score when discrepancies emerged between the 2 readers of the same video.

For the analysis of individual endoscopic severity scores (Figure 1), all 331 videos were scored with both the MCSe and the UCEIS, with 2 reads per video (1 from each reader, without adjudication; 662 reads). Reads with 2 or fewer segments were excluded (251), resulting in a total of 411 reads (Supplementary Figure 1). The rectosigmoid and the proximal colon (descending, transverse, and ascending colon) were scored separately, according to the worst-affected segment. Each component of the UCEIS (vacular pattern, bleeding, and erosions and ulcers) was scored separately. The total UCEIS scores were generated from each reader from the sum of their respective subscores.

Statistical Analysis

To determine the level of correlation between rectosigmoidoscopy and colonoscopy for detecting disease activity and endoscopic healing, contingency tables were generated that tabulated the number of adjudicated MCSe scores above and below the indicated MCSe cut-off values. The degree of inter-method agreement and correlation was determined by the calculation of the kappa coefficient (κ) and the Spearman correlation coefficient (r) for each contingency table, respectively. The interpretation of the κ and the correlation coefficients was based on the proposed cut-off values by Landis and Koch, who recommended the following standards for strength of agreement for the κ coefficient: 0, poor; 0.01–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1, nearly perfect. Negative predictive values and PPVs also were calculated. P values were based on the 2-sided Fisher exact test. Because this analysis was retrospective and not a prespecified goal of the EUCALYPTUS protocol, formal sample size calculations were not performed.

Results

Number of Bowel Segments Evaluated and Description of Disease Extent

Comparable numbers of videos were examined at each visit for each treatment group (Table 1). Across the 3 treatment groups, the average number of total segments examined was 3.2, and the number of segments examined across different visits (weeks 0, 6, and 10) and between treatment groups did not differ significantly.

Across all treatment groups, 25% of patients had UC limited to the rectosigmoid region and 75% of patients had...
disease in the proximal colon, defined as any region beyond the rectosigmoid (Table 2).

Overall Evaluation
Among all of the videos, regardless of the number of segments read, 67 videos (67 of 354; 19%) were sent for adjudication. Among videos with more than 2 segments, 55 videos (55 of 239; 23%) were sent for adjudication. The MCSe in videos in which only 2 segments or fewer were examined (mean ± SD, 2.66 ± 0.63) did not differ significantly from videos with more than 2 segments examined (mean ± SD, 2.54 ± 0.75) (Supplementary Table 1).

Across all visits and examinations, 239 videos examined colonic segments proximal to the rectosigmoid. For 230 videos, rectosigmoidoscopy and colonoscopy analyses agreed, determining that active disease (MCSe ≥ 2) was present in 205, but absent in 25 videos (Table 3, left). There was a strong correlation between the scores based on the 2 techniques (κ = 0.83; r = 0.84). However, for 9 of the 239 videos, the scores were discordant in assessing active disease, for example, rectosigmoidoscopy found evidence of endoscopic healing, but examination of the more proximal colon with colonoscopy found mucosal lesions (MCSe ≥ 2). These 9 videos came from 7 patients: 3 with left-sided colitis, 2 with pancolitis, 1 with disease previously limited to the rectosigmoid, and 1 in whom the previous extent of disease was not specified. If endoscopic healing was defined as MCSe of 0 and endoscopic activity was defined as MCSe of 1 or more, the concordance between rectosigmoidoscopy and colonoscopy increased (κ = 0.95; r = 0.96), because only 1 video showed endoscopic healing in the rectosigmoid whereas significant mucosal lesions were found in the proximal colon (Table 3, right).

We then analyzed whether the severity of disease differed in the proximal colon compared with the rectosigmoid, using both the MCSe and the UCEIS (Figure 1 and Supplementary Figure 3). For this analysis, each region was scored separately and there was no adjudication between readers; each score given by the readers was considered an individual piece of data. In general, we observed more severe disease in the rectum and sigmoid according to the MCSe, but 19 of the 411 (4.6%) individual reads with more than 2 segments showed greater disease severity in the proximal colon than in the rectosigmoid region (Figure 1A, gray cells). Of those 19 scores, 14 (rectosigmoid ≤ 1, proximal colon ≥ 2) affected the assessment of endoscopic healing in the colon. In addition, assessment of endoscopic disease using the UCEIS confirmed the presence of more severe disease in the rectosigmoid compared with the proximal colon (3.98 ± 1.82 vs 2.38 ± 1.98; P < .0001), but in a small proportion of the videos (31 of 411; 7.5%), more severe disease was found in the proximal colon. Scoring with the UCEIS, using both the total UCEIS and individual subscores, also showed a high correlation between rectosigmoidoscopy and colonoscopy (r = 0.92) (Figure 1B and Supplementary Figure 3).

Evaluation of Endoscopic Activity at Baseline
When we assessed endoscopic activity (MCSe ≥ 2) at baseline, we observed a moderate agreement/correlation (κ = 0.49, r = 0.57) between the scores based on rectosigmoidoscopy and colonoscopy (Table 4). This level of correlation was related to the highly skewed distribution of MCSe values toward scores of 2 and 3, given the study inclusion criteria. In 2 of 100 videos performed at baseline, rectosigmoidoscopy failed to find active disease whereas...
Evaluation of Endoscopic Healing

After treatment with etrolizumab, patients then were assessed for endoscopic healing (MCSe ≤ 1) at weeks 6 and 10 using a total of 139 available videos (Table 5, left). Although 31 videos showed endoscopic healing in the rectum and sigmoid colon, only 24 also had healing in the proximal colon, a difference of approximately 23% (PPV for endoscopic healing by rectosigmoidoscopy, 0.77). Colonoscopy and rectosigmoidoscopy showed a high correlation for the detection of endoscopic healing (k = 0.84; r = 0.85).

With endoscopic healing defined as MCSe of 0 at weeks 6 and 10 (Table 5, right), 12 videos showed healing in the rectum and sigmoid colon. Only 1 video did not show endoscopic healing in the proximal colon, a difference of approximately 9%. Therefore, when endoscopic healing was defined as an MCSe of 0, the correlation between the 2 techniques was very strong (k = 0.95; r = 0.85), and rectosigmoidoscopy was better able to predict endoscopic healing (PPV, 0.92) in the proximal colon.

When we investigated the efficacy of etrolizumab using rectosigmoidoscopy, we found that there was a trend toward higher rates of endoscopic healing, but there was no significant treatment effect for either dose group over placebo by weeks 6 and 10 (Figure 2A). Colonoscopy also showed no significant treatment effect at week 6 (Figure 2A). However, at week 10, colonoscopy determined that the proportion of patients with endoscopic healing in the placebo group was 8%, rather than 14%, the proportion measured by rectosigmoidoscopy (Figure 2B). Although this difference did not affect the efficacy assessment for the 300-mg dose group, this lower percentage of patients with healing increased the effect size to a significant level between the placebo and the 100-mg etrolizumab treatment groups (P = .035).

Discussion

In general, when we compared the ability of rectosigmoidoscopy with colonoscopy for determining either the presence of active disease or endoscopic healing in patients with moderately to severely active UC, we found strong correlations between the 2 examinations. Rectosigmoidoscopy was able to detect active disease reliably at the inclusion of patients in the study. We also found that the most severe disease was located more frequently in the rectosigmoid colon, a relevant finding for clinical practice because therapeutic decisions are based not only on the presence of active disease but also on severity.

The ability of rectosigmoidoscopy to detect disease activity compared with colonoscopy differed between baseline and post-treatment at week 6 and week 10. At baseline, rectosigmoidoscopy accurately reflected disease activity in the whole colon. In contrast, at weeks 6 and 10, when endoscopic healing was defined as MCSe of 1 or less, rectosigmoidoscopy indicated healing of the distal mucosa, although there was evidence of mucosal ulceration more proximally on colonoscopy. This resulted in a placebo remission rate that was almost 2-fold higher based on rectosigmoidoscopy compared with colonoscopy (14% vs 8%, respectively) (Figure 2B), and a decreased treatment effect size. However, when endoscopic healing was defined as MCSe of 0, concordance improved between rectosigmoidoscopy and colonoscopy, because only 1 of 11 videos had discordant scores between the 2 techniques (Table 5, right).

<table>
<thead>
<tr>
<th>Extent of disease, n (%)</th>
<th>Placebo (n = 41)</th>
<th>Etrolizumab 100 mg (n = 39)</th>
<th>Etrolizumab 300 mg (n = 39)</th>
<th>Total (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive/pancolitis</td>
<td>12 (29%)</td>
<td>14 (36%)</td>
<td>18 (46%)</td>
<td>44 (37%)</td>
</tr>
<tr>
<td>Left-sided colitis</td>
<td>17 (42%)</td>
<td>13 (33%)</td>
<td>13 (33%)</td>
<td>43 (36%)</td>
</tr>
<tr>
<td>Rectosigmoid</td>
<td>12 (29%)</td>
<td>10 (26%)</td>
<td>8 (21%)</td>
<td>30 (25%)</td>
</tr>
<tr>
<td>Nonspecified</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

n, number of patients.
According to guidelines and consensus panels, once the diagnosis is established, rectosigmoidoscopy alone is usually sufficient to assess endoscopic activity/severity in the management of UC.\(^3\) Few studies, however, and none in the context of a therapeutic trial, have formally compared endoscopic severity in the rectosigmoid vs the whole colon. In a retrospective analysis of medical charts and endoscopic images from 545 UC patients, Kato et al.\(^4\) determined the colonic locations of the maximum inflammatory activity. Although the majority of the patients analyzed (73%) had maximum inflammation in the rectum and sigmoid, 27% had maximum activity proximal to the sigmoid, in the descending colon, or in segments proximal to the splenic flexure. In addition, they found that 40% of patients had inflamed mucosa in the descending colon or in the more proximal portion of the colon, but showed no inflammation in the rectum and sigmoid. They concluded that total colonoscopy was warranted in patients who have a discrepancy between their symptoms and rectosigmoidoscopy results. A caveat of this study was that the use of rectal therapy with mesalazine or steroids was allowed. In the EUCALYPTUS trial, rectal therapy was withdrawn 2 weeks before endoscopy, and showed a very high correlation between rectosigmoidoscopy and colonoscopy.

One limitation of our study was that only 239 of 331 examinations progressed beyond the sigmoid colon. There may be some concern that the reasons for the unavailability of colonoscopy in those patients may have introduced bias into the study. Patients with severe disease above the sigmoid may have been underestimated because of concerns by the endoscopist in proceeding with the examination beyond the sigmoid colon. However, the number of segments analyzed between treatment groups was similar (Table 1) and disease severity (mean MCSe) also was similar between videos with fewer than 2 and those with more than 2 segments (Supplementary Table 1), which rules out a bias arising from performing rectosigmoidoscopy or colonoscopy based on the endoscopic severity of the disease. Another potential limitation was that because the explored segments were not annotated in the videos, the readers identified segments based on anatomic characteristics and the length of the segment; in particular, the boundary between the descending colon and the sigmoid could be difficult to distinguish, even for skilled endoscopists. However, it is unlikely that this would have affected the evaluation of the rectosigmoid significantly compared with the whole colon. We also acknowledge that, in this trial, the number of MCSe scores in which the proximal colon had more severe disease than the rectosigmoid (9 of 239) was low. However, the number of patients who typically achieve remission in induction studies is also low, which means that factors that influence placebo rates can have a direct effect on statistical significance and influence decisions about the further development of experimental therapies. Finally, because this

### Table 3. Identification of Endoscopically Active Disease as Assessed by Rectosigmoidoscopy vs Colonoscopy: All Visits

<table>
<thead>
<tr>
<th>MCSe ≥ 2 (n = 239)</th>
<th>Colonoscopy</th>
<th>MCSe ≥ 1 (n = 239)</th>
<th>Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>R/S Y 205</td>
<td>N 0</td>
<td>R/S Y 227</td>
<td>N 11</td>
</tr>
<tr>
<td>𝜂 = 0.83; 𝑟 = 0.84; P &lt; .0001; NPV, 0.74 (95% CI, 0.59–0.88)</td>
<td>𝜂 = 0.95; 𝑟 = 0.96; P &lt; .0001; NPV, 0.92 (95% CI, 0.76–1.07)</td>
<td></td>
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**NOTE.** This analysis only included assessments with more than 2 segments and all visits were pooled.

**Table 4. Identification of Endoscopically Active Disease (MCSe ≥ 2) as Assessed by Rectosigmoidoscopy vs Colonoscopy at Week 0/Baseline**

<table>
<thead>
<tr>
<th>MCSe ≥ 2 (n = 100)</th>
<th>Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>R/S Y 97</td>
<td>N 1</td>
</tr>
<tr>
<td>𝜂 = 0.49; 𝑟 = 0.57; P = .03; NPV = 0.33 (95% CI, -0.02 to 0.87)</td>
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**NOTE.** This analysis only included assessments with more than 2 segments.

**Cl, confidence interval; n, number of videos evaluated; N, no; NPV, negative predictive value; R/S, rectosigmoidoscopy; Y, yes.**

*Number of scores for endoscopic activity that were affected when the proximal colon was included in the evaluation. Presence of endoscopically active disease (MCSe ≥ 2).
was an induction study, we cannot extrapolate these findings to maintenance studies. Longer treatment duration with therapies that are effective may improve the concordance between rectosigmoidoscopy and colonoscopy, and consequently show that rectosigmoidoscopy is sufficient for measuring clinical effectiveness in maintenance trials.

Despite these limitations, this study has important implications for the use of rectosigmoidoscopy and/or colonoscopy in both clinical practice and during clinical trials. Because of its strong ability to detect active disease, rectosigmoidoscopy should be sufficient in clinical practice for evaluating previously diagnosed patients with new symptoms. Two notable exceptions may be pediatric patients and patients with primary sclerosing cholangitis in whom relative or complete rectal sparing has been observed.21,22 However, in cases in which rectosigmoidoscopy has detected endoscopic healing in response to induction therapy, but symptoms persist, performance of a more extensive examination with colonoscopy is justified.

In the clinical trial setting, this study suggests that if endoscopic healing is defined as an MCSe of 0, rectosigmoidoscopy is sufficient for efficacy analyses. However, if endoscopic healing is defined as an MCSe of 1 or less, these preliminary data suggest that colonoscopy is better than rectosigmoidoscopy for assessing the full extent of endoscopic healing for efficacy analyses of experimental therapies. Colonoscopy is more expensive than rectosigmoidoscopy because it frequently requires sedation and bowel preparation, which, in turn, may impose additional burdens on the patient, such as missing work and requiring a caregiver to transport the patient to and from the endoscopy suite. The balance between cost and performance is an important consideration and is most relevant in the development of experimental therapies. It may be preferable to use full colonoscopy in relatively small phase 2 induction studies. However, these results warrant further evaluation prospectively in a larger study before colonoscopy can be recommended for standard use in clinical trials.

### Table 5: Evaluation of Endoscopic Healing as Assessed by Rectosigmoidoscopy vs Colonoscopy at Weeks 6 and 10: Pooled

<table>
<thead>
<tr>
<th>MCSe ≤ 1 (n = 139)</th>
<th>Colonoscopy</th>
<th>R/S</th>
<th>N</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>108</td>
<td>0</td>
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<td></td>
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<td></td>
<td></td>
<td>Y</td>
</tr>
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<td></td>
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<td></td>
<td>7</td>
<td>24</td>
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<td></td>
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<td></td>
<td></td>
<td>Y</td>
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<table>
<thead>
<tr>
<th>MCSe = 0 (n = 139)</th>
<th>Colonoscopy</th>
<th>R/S</th>
<th>N</th>
<th>Y</th>
</tr>
</thead>
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<td>127</td>
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<td></td>
<td></td>
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<td>11</td>
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\( \kappa = 0.84; r = 0.85; P < .0001; \) PPV, 0.77 (95% CI, 0.63–0.92)

\( \kappa = 0.95; r = 0.95; P < .0001; \) PPV, 0.92 (95% CI, 0.76–1.07)

**NOTE.** This analysis only included assessments with more than 2 segments by visit (excluding the screening visit).

CI, confidence interval; n, number of videos evaluated; N, no; NPV, negative predictive value; R/S, rectosigmoidoscopy; Y, yes.

\( a \) Number of scores for endoscopic healing that were affected when the proximal colon was included in the evaluation.

**Figure 2.** Comparison of endoscopic healing using rectosigmoidoscopy and colonoscopy. The percentage of patients (modified intent-to-treat population) with endoscopic healing (MCSe ≤ 1) in the placebo and etrolizumab-treated groups was calculated at (A) week 6 and (B) week 10 from videos based on rectosigmoidoscopy only (white bars) and colonoscopy (black bars). *Scoring was based on adjudicated results. \( p < .05. \) Etro, etrolizumab; LD, loading dose; Pbo, placebo; R/S, rectosigmoidoscopy.
Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.10.016.

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Author names in bold designate shared co-first authorship.

Received June 26, 2015. Accepted October 19, 2015.

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Acknowledgments
Jean-Frédéric Colombel contributed to the concept and study design, interpretation of data, and drafting and critical revision of the manuscript; Ingrid Ordás contributed to the study design, interpretation of data, and drafting and revision of the manuscript; Timothy Lu contributed to the study design, interpretation of data, and the drafting and revision of the manuscript; and Julian Panés contributed to the study design, interpretation of data, and drafting and critical revision of the manuscript.

Conflicts of interest
Jean-Frédéric Colombel has served as a consultant or advisory board member for AbbVie, ABScience, Amgen, Bristol-Myers Squibb, Celtrion, Danone, Enterome, Ferring Pharmaceuticals, Genentech, Giuliani SPA, Given Imaging, Janssen, Immune Pharmaceuticals, MedImmune, Merck & Co, Millennium Pharmaceuticals, Inc, Neovacs, Nutrition Science Partners Ltd, Pfizer, Inc, Prometheus Laboratories, Protagonist Therapeutics, Receptos, Sanofi, Schering-Plough Corporation, Second Genome, Shire, Takeda, Teva Pharmaceuticals, Tigenix, UCB Pharma, Vertex, and Dr. August Wolff GmbH & Co, and has been a speaker for AbbVie, Ferring Pharmaceuticals, Janssen, Merck & Co, Nutrition Science Partners Ltd, and Takeda; Ingrid Ordás has been a speaker for AbbVie and MSD Pharmaceuticals; Thomas Ullman has served as a consultant to Takeda; Paul Rutgeerts has served as a consultant to Takeda; Jean-Frédéric Colombel has served as a consultant to Takeda; Timothy Lu has served as a consultant to AbbVie; Jean-Frédéric Colombel has served as a consultant to Takeda; and Ingrid Ordás has served as a consultant to AbbVie, Ferring Pharmaceuticals, Genentech, Genzyme, Janssen, Merck & Co, and Schering-Plough Corporation.
consultant, advisory board member, or speaker for AbbVie, Bristol-Myers Squibb, Genentech, Janssen, Merck & Co, Millennium Pharmaceuticals, Inc, Pfizer, Inc, Prometheus Laboratories, Takeda, UCB Pharma, Dr. Falk Pharma, and Robarts Research Institute; Akiko Chai, Sharon O’Byrne, and Timothy Lu are employees of Genentech, Inc; and Julián Panés has served as a consultant or advisory board member for AbbVie, Bristol-Myers Squibb, Celltrion, Genentech, Nutrition Science Partners Ltd, Pfizer, Inc, Merck Sharp and Dohme, Takeda, and Tigenix, and has been a speaker for AbbVie, Ferring Pharmaceuticals, Janssen, and Merck Sharp and Dohme.

**Funding**

Research support was provided by Genentech, Inc, and editing and writing support was provided by Deborah Solymar (Genentech, Inc, South San Francisco, CA), which was funded by Genentech, Inc.
Supplementary Figure 1. Flow diagram for the selection of endoscopy video reads used for the segment analyses (Table 1, Figure 1).

Supplementary Figure 2. Flow diagram for the selection of endoscopy videos analyzed from EUCALYPTUS.
Supplementary Figure 3. UCEIS subscores (unadjusted readings). Two readers assessed each video and scored the severity for each UCEIS subscore for the rectosigmoid colon and the proximal colon. Numbers in each cell represent the total number of scores of the individual site readers (2 scores per video) without adjudication (pooled across readers). Data was pooled across the sites. Any reading with ≤ 2 segments was not included (Supplementary Figure 1). Gray cells indicate where the proximal colon score was higher than the rectosigmoid colon score. \( \kappa \) and correlation coefficients are provided for the comparison of rectosigmoidoscopy and colonoscopy.
**Supplementary Table 1.** MCSe of Videos With 2 or Fewer and More Than 2 Segments

<table>
<thead>
<tr>
<th></th>
<th>Segments ≤ 2 (n = 92)</th>
<th>Segments &gt; 2 (n = 239)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MCSe (rectosigmoid)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.66 (0.63)</td>
<td>2.47 (0.80)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (1–3)</td>
<td>3 (0–3)</td>
</tr>
<tr>
<td><strong>MCSe (colon)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>N/A</td>
<td>2.54 (0.75)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>N/A</td>
<td>3 (0–3)</td>
</tr>
<tr>
<td><strong>Extent of disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive/pancolitis, n (%)</td>
<td>35 (38)</td>
<td>88 (37)</td>
</tr>
<tr>
<td>Left-sided colitis, n (%)</td>
<td>31 (34)</td>
<td>89 (37)</td>
</tr>
<tr>
<td>Rectosigmoid, n (%)</td>
<td>25 (27)</td>
<td>59 (25)</td>
</tr>
<tr>
<td>Nonspecified, n (%)</td>
<td>1 (1)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

n, number of videos evaluated; N/A, not applicable.