Journal	Lancet Gastroenterology & Hepatology
Article Type	Article
Editorial Considerations	Word count: Max 4500 Abstract word count: Max 300 References: Max 30 Tables/Figures: No limit given
Current Counts	Word count: 2878 Abstract word count: 252 References: 12 Tables/Figures: 2 tables/ 5 figures

LAUREL: Etrolizumab for maintenance therapy in patients with moderately to severely active ulcerative colitis

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for clinical trials of existing and emerging biological therapies for moderately to severely active ulcerative colitis (UC) using the search terms “ulcerative colitis treatment” and “moderate to severe” published between Jan 1, 2010, and December 14, 2020. The search was limited to positive, phase 1–3 clinical trials and trials were included if they were of therapies, not procedures, and included adult patients with moderately to severely active UC who were outpatients (studies that included patients with severe ulcerative colitis admitted to hospital were excluded). We found that etrolizumab was one of nineteen therapies (including infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, estrasimod, and tralokinumab) that have entered or completed phase 2 and phase 3 clinical trials for the treatment of UC.

Added value of this study

The etrolizumab phase 3 UC study program consisted of several randomised, controlled studies examining the safety and efficacy of etrolizumab, a humanized monoclonal antibody that selectively binds the b7 subunit of the heterodimeric integrins α4β7 and αEβ7, in patients with moderately to severely active UC. This study reports results from LAUREL, a randomized, placebo-controlled maintenance study of etrolizumab in patients naive to tumor necrosis factor inhibitors (anti-TNFs) with moderately to severely active UC. In these patients, no significant difference between etrolizumab and placebo was observed in the primary endpoint of remission at Week 62 among patients with a clinical response at Week 10; however, a numerical benefit over placebo was observed for the primary and several secondary endpoints. Etrolizumab was well tolerated and no new safety signals were identified.

Implications of all the available evidence

Gut-targeted therapies, such as etrolizumab, have the potential to effectively mitigate inflammatory bowel disease symptoms while avoiding the broad-spectrum immunosuppression observed with systemic therapies. By targeting the β7 integrin, etrolizumab has the potential to control both trafficking of immune cells into the gut and their inflammatory effects on the gut lining. Etrolizumab is currently being evaluated as an induction and maintenance treatment in patients with moderately to severely active Crohn's disease, with and without prior anti-TNF treatment, in a global phase 3 study (BERGAMOT; NCT02394028) and an open-label extension and safety monitoring study (JUNIPER; NCT02403323).

ABSTRACT

Background: In a previous phase 2 induction study, etrolizumab significantly improved clinical remission versus placebo in patients with moderately to severely active ulcerative colitis (UC).

Methods: LAUREL (NCT02165215) was a multicenter, phase 3, placebo-controlled study evaluating etrolizumab for maintenance of remission in patients with moderately to severely active UC who were naive to tumor necrosis factor inhibitors. During the open-label induction phase, all patients received etrolizumab 105 mg every 4 weeks. Patients achieving clinical response (≥3-point decrease and ≥30% reduction in MCS plus ≥1 point decrease in RB subscore or absolute RB subscore of 0 or 1) at Week 10 were randomized into the double-blind maintenance phase to receive etrolizumab 105 mg every 4 weeks or matched placebo through Week 62. The primary endpoint was remission (Mayo Clinic total score [MCS] ≤2 with individual subscores ≤1 and a rectal bleeding [RB] subscore of 0) at Week 62 among patients with a clinical response at Week 10.

Findings: At Week 62, 32/108 [29·6%] patients in the etrolizumab group and 21/106 [20·6%] patients in the placebo group achieved the primary endpoint(p=0·19). Nominally significant improvements were reported for histologic remission (etrolizumab: 42·4%, placebo 21·8%; p=0·02), endoscopic remission (etrolizumab: 30·6%, placebo: 16·7%; p=0·03), and endoscopic improvement at Week 62 (etrolizumab: 38·0%, placebo: 22·5%; p=0·01). No new or unexpected safety signals occurred, and most adverse events were low grade.

Interpretation: No significant differences were observed between etrolizumab and placebo in the primary endpoint of remission at Week 62 among patients with a clinical response at Week 10. Etrolizumab was well tolerated in this patient population.

Funding: F. Hoffmann–La Roche Ltd.

Trial Registry: ClinicalTrials.gov, NCT02165215

Keywords: anti-TNF, etrolizumab, inflammatory bowel disease, laurel, ulcerative colitis

INTRODUCTION

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease (IBD), characterized by chronic or recurrent mucosal inflammation of the rectum and colon, that severely limits patient quality of life.[1-4] Current treatments for moderately to severely active UC include corticosteroids, immunomodulators, and tumor necrosis factor inhibitors (anti-TNFs). Despite these treatment options, a large proportion of patients do not maintain a durable response to therapy.[5] Targeted therapy with the ability to achieve and maintain sustained remission and prevent long-term complications may provide a valuable therapeutic option for these patients.

Etrolizumab is a next-generation, gut-targeted anti-integrin biologic therapeutic. Etrolizumab is a dual-action, anti-β7 monoclonal antibody that selectively targets α4β7 and αEβ7 integrins to control both trafficking of immune cells into the gut and their inflammatory effects on the gut lining.[6,7] In a Phase 2 study, the etrolizumab induction regimen was well tolerated and provided significantly higher rates of clinical remission compared with placebo in patients with moderately to severely active UC.[8]

The Etrolizumab phase 3 UC study program consists of five studies, including two head-to-head studies, assessing the safety and efficacy of etrolizumab in patients with moderately to severely active UC. This program comprises the largest phase 3 IBD clinical trial program to date. Here, we describe results from LAUREL, a phase 3 study which evaluated the efficacy and safety of etrolizumab for maintenance of remission in patients with moderately to severely active UC naive to anti-TNF therapy.

METHODS

Study Design

LAUREL consisted of a 10-week open-label induction phase, a double-blind 52-week maintenance phase, and a 12-week safety follow-up phase. An extended safety monitoring period is ongoing in COTTONWOOD, an open-label extension and safety monitoring study of patients with moderately to severely active disease previously enrolled in etrolizumab phase 2/3 studies.

This trial was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The trial protocols, informed consent forms, and other relevant information were approved by (add IRB name) and the institutional review boards at each investigational site.

Participants

Eligible patients were adults between 18 to 80 years of age with a diagnosis of moderately to severely active UC, defined as a Mayo Clinic total score (MCS) of 6–12 with an endoscopic score ≥2, a rectal bleeding (RB) subscore ≥1, and a stool frequency (SF) subscore ≥1. All patients had an established diagnosis of UC ≥3 months, corroborated by both clinical and endoscopic evidence. Included patients were naive to treatment with anti-TNFs and had an inadequate response, loss of response, or intolerance to prior immunosuppressant and/or corticosteroid treatment. Patients taking stable doses of oral 5-aminosalicylates, oral corticosteroids (prednisone ≤ 30 mg/day), azathioprine (AZA), 6-mercaptopurine (6-MP), and methotrexate (MTX) were allowed. Written informed consent was obtained from all participants.

Patients with prior exposure to anti-integrin therapy (including vedolizumab and natalizumab) or anti-adhesion molecule therapy were excluded. Patients with prior extensive colonic resection, subtotal or total colectomy, colostomy or ileostomy or planned surgery for UC were excluded.

Randomisation and masking

Patients who achieved clinical response at Week 10 with open-label etrolizumab were randomized into the maintenance phase using a centralized voice/Web-based response system into parallel treatment groups. A permuted blocked randomisation method ensured a 1:1 ratio between groups. Randomisation was stratified by Week 10 remission status, concomitant treatment with corticosteroids (yes vs no) at baseline, concomitant treatment with immunosuppressants (yes vs no), and baseline disease activity (MCS ≤9 vs MCS ≥10). All patients, study site personnel, and the sponsor and its agents were blinded to treatment assignment throughout the 52-week maintenance period.

Procedures

During the open-label induction phase, all patients received subcutaneous (SC) etrolizumab 105 mg every 4 weeks for 10 weeks. Between Weeks 10 and 12, eligibility for entry into the blinded maintenance phase was determined based on clinical response. Patients who achieved clinical response at Week 10 were randomised 1:1 to receive etrolizumab SC 105 mg or matching placebo every 4 weeks during the maintenance phase.

During the induction phase, patients were required to maintain stable doses of their concomitant medications (oral 5-ASA, corticosteroids, immunosuppressants). During the maintenance phase, patients who received corticosteroids underwent mandatory tapering from Week 10. Patients at the US sites discontinued immunosuppressants (i.e., azathioprine, mercaptopurine, methotrexate) at entry to the maintenance phase; all other patients maintained their stable baseline doses, unless reduction or discontinuation was required due to toxicity.

Patients who did not achieve a clinical response by Week 10, who had clinical relapse during the maintenance phase, or who completed the maintenance phase in full (up to Week 62) were

eligible to enroll in the open-label extension (OLE) study. Patients who did not enroll in the OLE entered a 12-week safety follow-up period and were requested to enroll in the safety monitoring study for 92 weeks of extended monitoring for progressive multifocal leukoencephalopathy (PML).

The serum concentrations of etrolizumab were measured at Weeks 12, 24, 44, and 62 (two weeks after etrolizumab administration). Serum concentrations were also measured at pre-etrolizumab administration time (trough) at Weeks 24 and 44. The validated pharmacokinetic (PK) assay used for measuring etrolizumab concentration was based on the Gyrolab Immunoassay platform, which provides a higher level of matrix tolerance. This immunoassay has a minimum quantifiable concentration of 80 ng/mL etrolizumab. The anti-drug antibody (ADA) assay strategy used a tiered approach in a bridging assay format. Samples were screened and confirmed for ADA presence and then titered.

Outcomes

The primary efficacy endpoint was remission (defined as MCS ≤2 with individual subscores ≤1 and RB subscore of 0) at Week 62 among randomized patients with a clinical response (defined as decrease in MCS of ≥ 3 points and 30% reduction from baseline and ≥ 1 point decrease in RB subscore or absolute RB subscore of 0 or 1) at Week 10. Secondary efficacy endpoints evaluated at Week 62 included: clinical remission (defined as MCS ≤ 2 with individual subscores ≤ 1), endoscopic improvement (Mayo endoscopic subscore ≤ 1), endoscopic remission (Mayo endoscopic subscore = 0), histologic remission (Nancy histological index [NHI] ≤ 1), and corticosteroid-free remission in patients receiving corticosteroids at baseline (defined as remission with no corticosteroid use for 24 weeks prior to Week 62). Safety endpoints included the incidence and severity of adverse events (AEs), serious adverse events (SAEs), laboratory

abnormalities, and hypersensitivity reactions. Additional endpoints are defined in the full protocol available online (add link).

Statistical analyses

Approximately 350 patients were to be enrolled in the induction phase, under the assumption that 60% of patients would be clinical responders at Week 10 (n = 210). It was estimated that a sample size of 105 patients per treatment group was required in the maintenance phase to provide >90% power to detect a 25% absolute difference in remission rates between the etrolizumab and placebo treatment groups using a Chi-squared test at <0·05, under the assumption of a placebo true remission rate of 30 to 45%.

All statistical hypotheses for the primary and key secondary endpoints were tested with a multistage gatekeeping procedure to ensure an overall type I error of no greater than 5%, with the primary endpoint tested first at a two-sided significance of $p < 0·05$. Additional details are available in **Supplementary Figure 1** and in the Statistical Analysis Plan available online (add link).

Efficacy for the maintenance phase was analyzed using a modified intent-to-treat population, (mITT) defined as all randomized patients who received at least one dose of study drug. Patients with missing data, who were non-evaluable for efficacy at a particular timepoint, who began concomitant medications not permitted with etrolizumab, or who received increased doses of or initiated permitted concomitant medications relative to baseline were considered non-responders. The histology evaluable population included all patients in the mITT population for whom a baseline histology sample was available and showed baseline neutrophilic inflammation (NHI ≥ 1). The safety analysis population for the maintenance phase included all

patients who received study drug in the maintenance phase. This study is registered at www.ClinicalTrials.gov, number NCT02165215.

Role of the funding source

This study was funded by Hoffmann-La Roche (South San Francisco, CA). Hoffmann-La Roche participated in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

RESULTS

LAUREL was conducted from August 12, 2014 to June 4, 2020 at 111 sites worldwide. A total of 359 patients were enrolled in the trial, and 347 (96·7%) completed the induction phase to Week 10. Of those who completed the induction phase, 214 (59·6%) were clinical responders and were randomly assigned to receive either placebo (n=106) or etrolizumab (n=108) in the maintenance phase (**Figure 1**). Eighty (74·1%) etrolizumab patients and 42 (39·6%) placebo patients completed Week 62. In both treatment groups, the most common reason for discontinuation of study treatment was lack of efficacy (placebo, 43·4%; etrolizumab, 16·7%). Median treatment duration was 64·4 and 42·1 weeks and the median number of doses was 16·0 and 10·5 in the etrolizumab and placebo groups, respectively. Characteristics (efficacy measures, albumin, and weight) of patients who withdrew vs completed the study were matched for both treatment groups (ie, patients receiving placebo did not withdraw for reasons other than loss of efficacy).

Baseline characteristics were generally balanced across treatment groups (**Table 1**). For the etrolizumab and placebo groups, respectively, the median (range) duration of disease was 5·41 (0·6-44·0) and 5·85 (0·3-40·4) years and the median (range) MCS at baseline was 8·0 (5·0-11·0) and 9·0 (6·0-12·0). In both treatment groups, approximately 34% of patients were not

receiving either corticosteroids or immunosuppressants at baseline. Characteristics of patients randomised to receive maintenance therapy were balanced between treatment groups with regard to end of induction characteristics (eg, efficacy measures, albumin, histology).

In the mITT population, 32 (29·6%) patients in the etrolizumab and 21 (20·6%) patients in the placebo group achieved the primary endpoint of remission at Week 62 among responders at Week 10 (treatment difference 9·0%; p=0·19; **Figure 2**). As this difference was not statistically significant, the study did not meet its primary endpoint. Because the primary endpoint was not met, p-values of the secondary endpoints are reported as nominal per prespecified hierarchical testing.

Etrolizumab treatment was associated with nominally significant improvements in the proportion of patients with histologic remission (etrolizumab, 42·4%; placebo, 21·8%; p=0·02), endoscopic remission (etrolizumab, 30·6%; placebo, 16·7%; p=0·03), and endoscopic improvement at Week 62 (etrolizumab, 38·0%; placebo, 22·5%; p=0·01) **(Figure 3)**. No significant differences were observed in the endpoints of remission at Week 62 among Week 10 remitters (etrolizumab, 40·0%; placebo, 26·8%; p=0·31) or corticosteroid-free remission at Week 62 (etrolizumab, 18·2%; placebo, 8·0%; p=0·14) **(Figure 3)**.

In patients receiving maintenance therapy with etrolizumab, serum etrolizumab concentrations gradually increased from Week 4 to Week 64 (**Figure 4**). The mean etrolizumab concentration at Week 62 (15·4 µg/mL) was >11-fold higher than the target exposure associated with 90% β7 receptor occupancy (EC90 of 1·3 µg/mL).[9] The mean trough serum concentrations of etrolizumab at Week 24 and Week 44 were 10·0 ug/mL, >7-fold higher than the target exposure.

The incidence of ADA in the maintenance phase was 32·4% (33/102) in the etrolizumab/placebo group and 32.4% (35/108) in the etrolizumab/etrolizumab group. There was no impact of ADA on pharmacokinetic outcomes. The median concentrations of etrolizumab in ADA-positive patients in the etrolizumab/etrolizumab group were similar to those in ADA-negative patients at Weeks 4, 12, 24, 44, and 62 (**Figure 5**).

Etrolizumab was generally well tolerated and the majority of adverse events were Grade 1 or 2 and considered non-serious by the investigators (**Table 2**). Higher rates of adverse events were reported in the placebo group (etrolizumab: 64·8%, placebo 80·4%): most notably UC (etrolizumab: 14·8%, placebo 36·3%), abdominal pain (etrolizumab: 5·6%, placebo 8·8%), diarrhea (etrolizumab: 3·7%, placebo 8·8%), and pyrexia (etrolizumab: 1·9%, placebo 6·9%). Nasopharyngitis occurred more frequently with etrolizumab (etrolizumab: 10·2%, placebo 6·9%).

Three adverse events of special interest occurred in the maintenance population – all in the placebo group. One suspected case of PML that was deemed unrelated to the study drug, 1 case of anaphylaxis in a patient that had general body itching, seasonal and drug allergies, and 1 case of elevated cryptogenic hepatitis considered unrelated to the study drug. The rates and nature of serious adverse events were otherwise comparable (**Table 2**). No deaths were reported in either treatment group.

DISCUSSION

Moderately to severely active UC remains an area of high unmet need. Targeted therapy with an improved safety profile and the ability to achieve remission and prevent long-term complications would provide a valuable therapeutic option for UC patients and was the rationale for the development of anti-integrin treatments.[4] Etrolizumab can be distinguished from anti-TNF

biologics and integrin receptor antagonists such as natalizumab and vedolizumab by virtue of selectively targeting β7 integrin. It not only targets the gut-specific α4β7:MAdCAM-1 interaction that plays a pivotal role in migration of lymphocytes into the gut, but also the αEβ7:E-cadherin interaction which mediates the retention of pro-inflammatory lymphocytes within the gut mucosa.[10]

The etrolizumab phase 3 UC study program was highly ambitious, enrolled over 2,000 patients worldwide, and included two head-to-head studies. In the current study, the efficacy of etrolizumab as maintenance therapy was investigated in patients with moderately to severely active UC who were naïve to anti-TNFs. Although LAUREL did not meet its primary endpoint, a numerically higher proportion of etrolizumab recipients achieved remission on etrolizumab compared with placebo (29·6% vs 20·6%). In addition, while the pre-specified hierarchal study design precluded any formal statistical testing of secondary endpoints, nominally significant benefits were achieved across several key secondary endpoints including endoscopic improvement, endoscopic remission, and histologic remission. Of particular note, among patients on corticosteroids at baseline, a two-fold increase in corticosteroid-free remission was observed following treatment with etrolizumab. Maintenance therapy with etrolizumab over a period of 62 weeks was well tolerated in this population, and the rates of serious adverse events and infections were similar between the two treatment groups. No new or unexpected safety signals occurred and most adverse events were low grade.

Several factors may have influenced the results of this study. First, the sample size of 105 patients per treatment group was designed to provide >90% power to detect a 25% absolute difference in remission rates at Week 62 between treatment groups at the 5% significance level. The observed difference in remission rates (9%) was much lower than expected, although

numerically in favor of etrolizumab. It is possible that larger sample sizes may have revealed a statistically significant benefit of etrolizumab in this population.

Secondly, the 105 mg dose of etrolizumab was chosen for this study based on results from the phase 2 study EUCALYPTUS.[8] In that study, etrolizumab 105 mg once every 4 weeks was sufficient to maintain β7 receptor occupancy in both blood and colonic tissue during the entire dosing interval. Further, no apparent difference in exposure-response relationship was observed between the 105 mg and 300 mg doses.[8] Although further analysis is needed, initial examination of the exposure-response relationship in the phase 3 etrolizumab studies suggests that higher etrolizumab exposure in the early treatment phase is likely associated with improved clinical outcomes. Although full β7 receptor occupancy was achieved for most patients, the findings of this and other studies suggest that increasing the dose beyond full receptor occupancy in the peripheral circulation may provide additional benefit in this class of therapies.[11]

Thirdly, the ADA incidence rate observed in this study (32·4% for both treatment groups) is unexpectedly higher than observed during phase 1 and phase 2 studies of etrolizumab (≈5%).[8,12] This may be attributed to a number of factors, including the shorter duration of previous studies of up to 10 weeks and the fact that many patients were treated with higher etrolizumab exposure levels in early stage trials compared to the dose in the current study. Nevertheless, a robust evaluation of the potential impact of ADA response on etrolizumab exposure levels showed minimal impact both by between-patient and within-patient assessment (data not shown).

Of note, 8 patients in the etrolizumab group were missing data for primary endpoint analysis; however, it is unlikely that this is responsible for the failure of etrolizumab to meet the primary

endpoint. In addition, as most patients in both groups were off corticosteroids at Week 62, it is unlikely that an imbalance in corticosteroid use explains this result.

While the LAUREL study did not reach its primary endpoint, further analyses of these data are expected to provide deeper insights into the characteristics of patients most likely to benefit from this class of biologics and also on the correlation of clinical, endoscopic and patient-reported outcomes. The data from the etrolizumab global clinical trial program in UC (~2,000 patients overall) and ongoing open label extension program (COTTONWOOD) will serve to further elucidate some of the key questions on patient selection and the correlation between early and longer-term outcomes in this challenging-to-treat patient population. Etrolizumab is currently being evaluated as an induction and maintenance treatment in patients with moderately to severely active Crohn's disease with and without prior anti-TNF treatment in a global phase 3 study (BERGAMOT; NCT02394028) and open-label extension and safety monitoring study (JUNIPER; NCT02403323).

Author Contributions

TBD

Ethics Committee Approval Statement

TBD

Declaration of Interests

SV reports having received grants from AbbVie, J&J, Pfizer, and Takeda; and has received consulting and/or speaking fees from AbbVie, Arena Pharmaceuticals, Avaxia, Boehringer Ingelheim, Celgene, Dr Falk Pharma, Ferring, Galapagos, Genentech-Roche, Gilead, Hospira, Janssen, Mundipharma, MSD, Pfizer, Prodigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Takeda, Theravance, and Tillots Pharma AG

371 TBA. **PLL** reports personal fees from AbbVie, Arena, Genetech, Janssen, Merck, Pfizer, and
372 Takeda, during the conduct of the study. **TR** reports personal fees from AbbVie, Arena,
373 Boehringer-Ingelheim, Ferring, Rebiotix, Gilead, Intercept, Janssen, Lilly, Pfizer, Prometheus
374 and Takeda, outside the submitted work; and personal fees and other fees from
375 Roche/Genetech, during the conduct of the study. **SH** is a consultant for AbbVie, Allergan,
376 Amgen, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Genentech,
377 Gilead, GSK, Janssen, Lilly, Merck, Nestle, Novartis, Pfizer, Progenity, Prometheus, Receptos,
378 Salix, Samsung Bioepis, Seres Therapeutics, Takeda, Tigenex, UCB Pharma, and VHsquared;
379 performs clinical research for AbbVie, Allergan, Amgen, Celgene, Genentech, GSK, Janssen,
380 Lilly, Novartis, Pfizer, Prometheus, Receptos, Takeda, and UCB Pharma; and serves as a
381 speaker for AbbVie, Janssen, Pfizer, and Takeda. **BB** reports TBA. **RK** reports TBA. **KI** reports
382 TBA**. SS** reports TBA**. CE, YSO, ST, AC** and **WZ** are employees of Genentech, Inc., and
383 receive salary and stock options. **HT** and **JP** are employees of Roche Pharma AG and receive
384 salary and stock options. **BF** reports TBA.
385
386 **Acknowledgments**
387 We thank the patients and study staff who participated in this study. This study was funded by
388 Hoffmann-La Roche (South San Francisco, CA). Hoffmann-La Roche participated in the study
389 design; in the collection, analysis and interpretation of data; in the writing of the report; and in
390 the decision to submit the article for publication. Third-party medical writing assistance was
391 provided by ApotheCom; San Francisco, CA, and was funded by F. Hoffmann-La Roche Ltd. All
392 authors have contributed significantly to the work and have reviewed and approved the final
393 version of the manuscript. These findings were presented in part at United European
394 Gastroenterology Week 2020; the annual meeting of the American College of Gastroenterology,
395 2020; and the Congress of the European Crohn's and Colitis Organization, 2021.
396

DATA SHARING STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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FIGURES

Figure 1. Patient disposition. Patients who completed treatment are those who received all doses of study treatment specified by the protocol. Patients who completed the study are all patients who either rolled into the open-label extension or completed 12 weeks of safety follow-up, following treatment completion or treatment discontinuation.

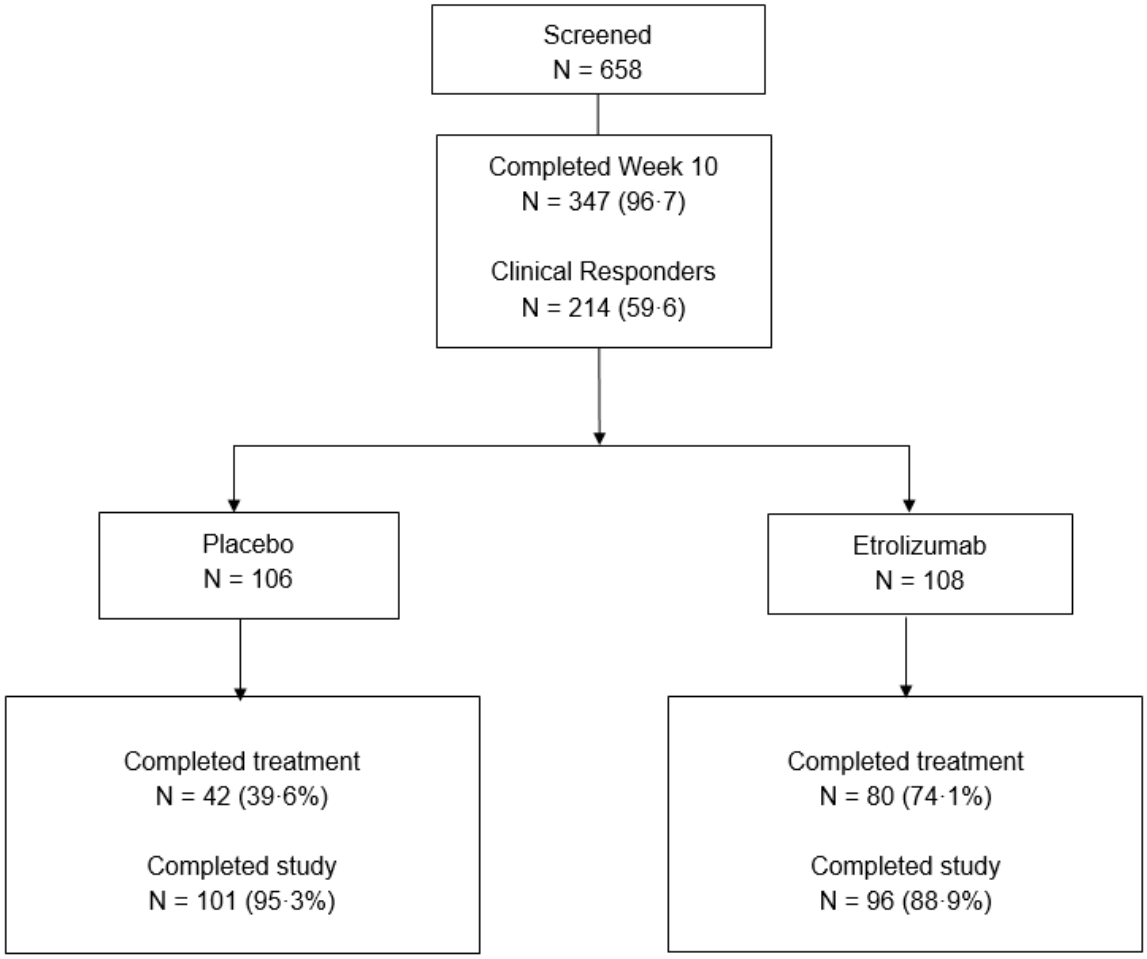


Figure 2. Patients achieving remission at Week 62 among clinical responders at Week 10. 95% CIs were constructed using the Wilson method. *p-value constructed using the Cochran-Mantel-Haenszel method adjusting for stratification factors. Remission: MCS ≤2, with individual subscores ≤1 and RB subscore of 0. Clinical response: MCS with ≥3-point decrease and 30% reduction from baseline as well as ≥1-point decrease in RB subscore or an absolute RB score of 0 or 1. MCS, Mayo Clinic total score; RB, rectal bleeding.

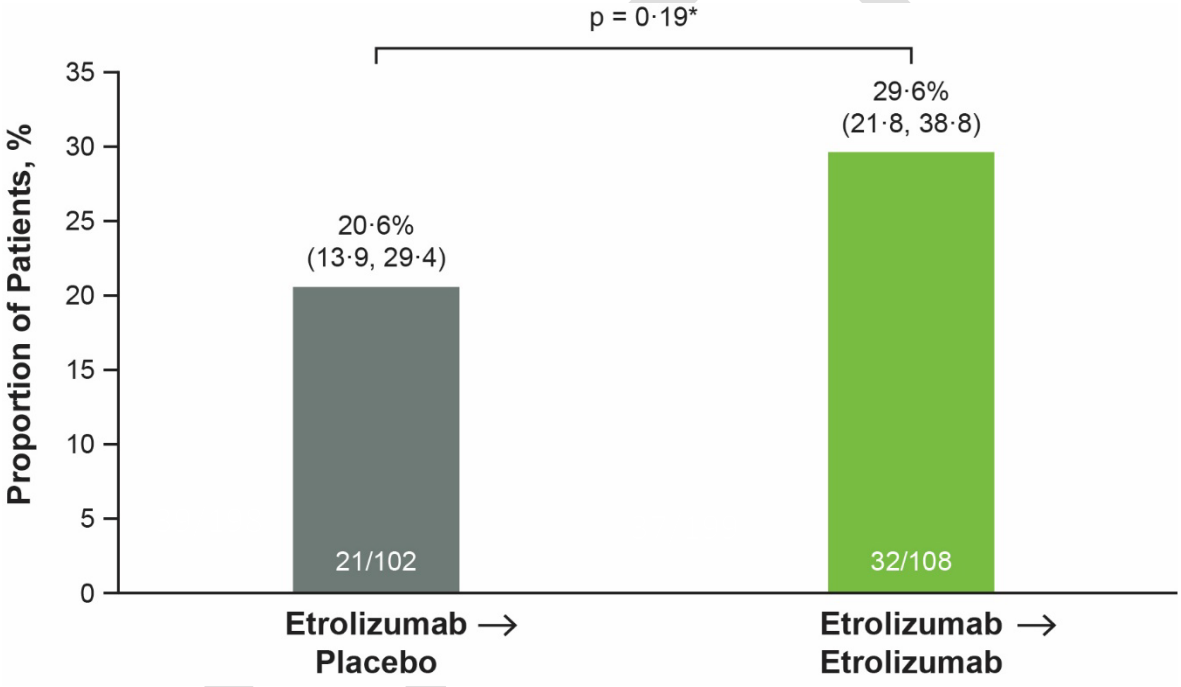


Figure 3. Patients achieving secondary endpoints at Week 62. 95% CIs were constructed using the Wilson method. *Nominal p-values are based on analysis adjusting for stratification factors. †In patients receiving baseline CS, remission with no CS use for 24 weeks before Week 62. Histologic remission: NHI ≤ 1. Endoscopic remission: Mayo endoscopic subscore = 0. Endoscopic improvement: Mayo endoscopic subscore ≤ 1; Remission: MCS ≤ 2, with individual subscores ≤1 and RB subscore of 0. NHI ≤1. CS, corticosteroids; NHI, Nancy Histologic Index; MCS, Mayo Clinic total score; RB, rectal bleeding.

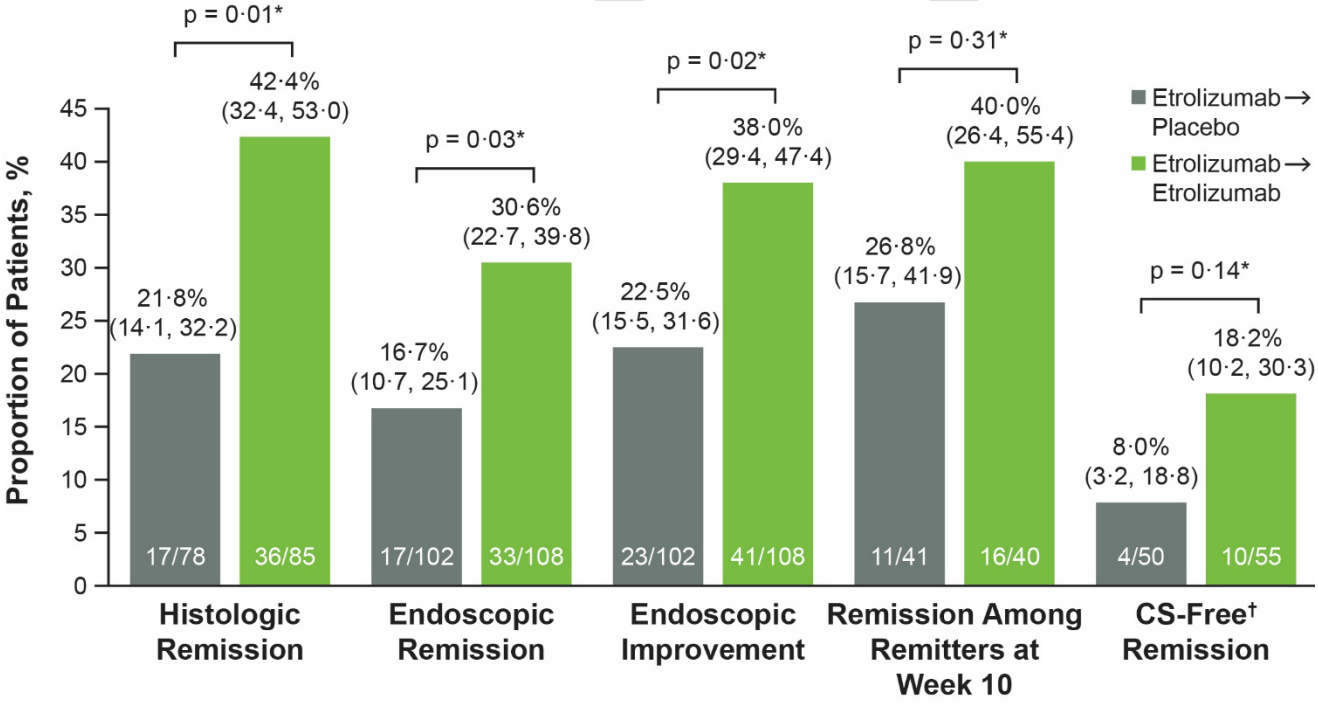


Figure 4. Group mean serum etrolizumab concentrations over time. Data shown are mean and standard deviation (error bar) from data of available patients at each timepoint. Horizontal dashed line indicates EC90 concentrations associated with 90% of β7 receptor occupancy. Arrows indicate times of etrolizumab administration.

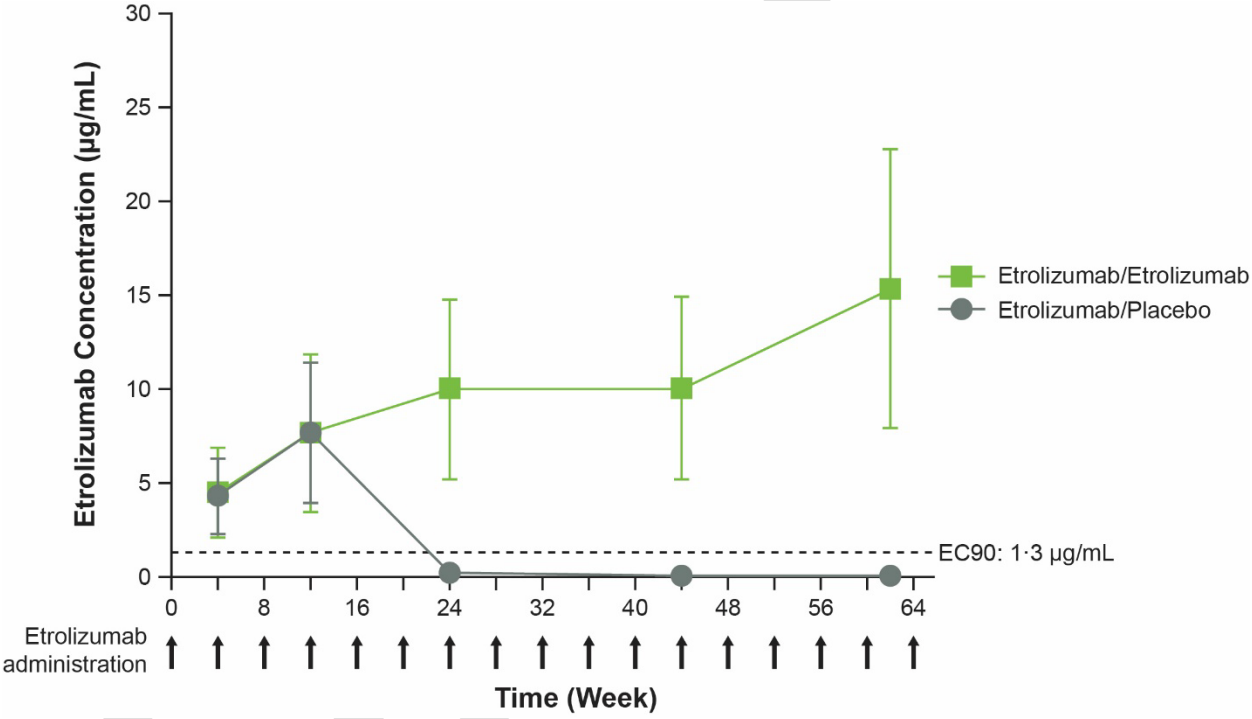
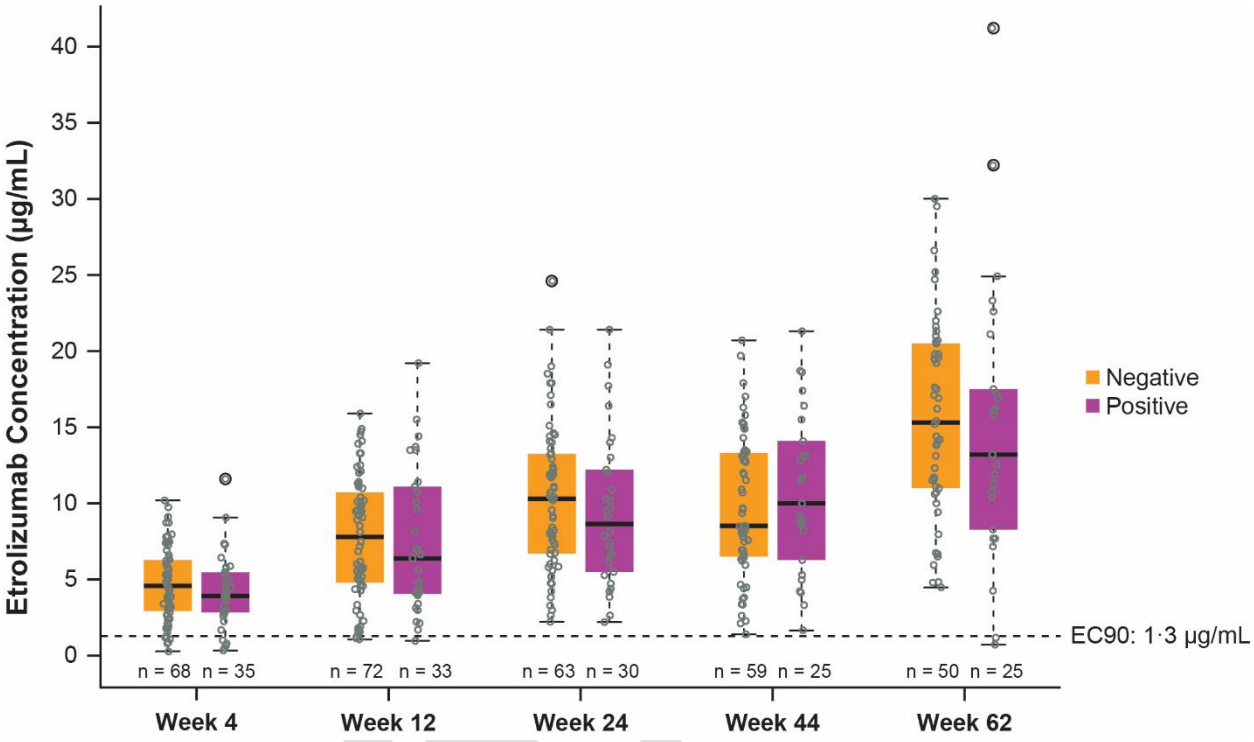


Figure 5. Etrolizumab concentration by ADA response (positive vs negative) over time. Horizontal dashed line indicates EC90 concentration associated with 90% of β7 receptor occupancy. ADA, anti-drug antibody.



TABLES

Table 1. Patient demographics and baseline characteristics

	Etrolizumab 105 mg/ Placebo (N=106)	**Etrolizumab 105 mg/ Etrolizumab 105 mg (N=108)**
Age, median (range), years	37·5 (18–69)	36·0 (18–77)
Male, n (%)	52 (49·1%)	60 (55·6%)
BMI, median (range), kg/m^2	24·9 (15–46)	23·8 (13–80)
Duration of disease, median (range), years	5·85 (0·3–40·4)	5·41 (0·6–44·0)
Mayo Clinic total score, median (range)	9·00 (6·0–12·0)	8·00 (5·0–11·0)
Nancy Histological Index, median (range)	3·00 (0·0–4·0)	3·00 (0·0–4·0)
Fecal calprotectin, median (Q1-Q3), µg/g	1517 (552–2865)	814 (347–1553)
C-reactive protein, median (Q1-Q3), mg/L	3·92 (1·39–9·34)	2·57 (0·95–8·17)
Disease location, n (%)		
Left-Sided Colitis	65 (61·3)	62 (57·4)
Extensive Colitis	12 (11·3)	14 (13·0)
Pancolitis	29 (27·4)	32 (29·6)
Baseline treatment, n (%)		
5-ASA use	80 (75·5)	89 (82·4)
No CS or IS	37 (34·9)	37 (34·3)
CS alone	40 (37·7)	44 (40·7)
IS alone	16 (15·1)	16 (14·8)
CS and IS	13 (12·3)	11 (10·2)

5-ASA, 5-aminosalicylate; BMI, body mass index; CS, corticosteroids; IS, immunosuppressants; Q1, quarter 1; Q3, quarter 3.

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499 **Table 2.** Adverse events (safety population)

AE, n (%)*	Etrolizumab/Placebo N=102	Etrolizumab/Etrolizumab N=108
Any AE	82 (80·4)	70 (64·8)
Any SAE	8 (7·8)	10 (9·3)
≥1 AE leading to treatment discontinuation	9 (8·8)	5 (4·6)
Infections	34 (33·3)	37 (34·3)
Serious infections	2 (2·0)	2 (1·9)
Deaths	0	0
PML	0	0
AEs occurring in ≥ 5% of any treatment group		
Ulcerative colitis	37 (36·3)	16 (14·8)
Arthralgia	12 (11·8)	10 (9·3)
Abdominal pain	9 (8·8)	6 (5·6)
Diarrhea	9 (8·8)	4 (3·7)
Upper respiratory tract infection	8 (7·8)	3 (2·8)
Nasopharyngitis	7 (6·9)	11 (10·2)
Pyrexia	7 (6·9)	2 (1·9)
Headache	5 (4·9)	7 (6·5)
Fatigue	4 (3·9)	6 (5·6)
SAEs occurring in ≥ 1% of any treatment group		
Ulcerative colitis	2 (2·0)	2 (1·9)
Hepatitis	2 (2·0)	0

Rectal abscess	1 (1·0)	1 (0·9)
Anal fistula	1 (1·0)	0
Diarrhoea haemorrhagic	1 (1·0)	0
Upper respiratory tract infection	1 (1.0)	0
Systemic inflammatory response syndrome	1 (1·0)	0
Pulmonary embolism	1 (1·0)	0
Deep vein thrombosis	1 (1·0)	0

**n* represents individual patients, not individual events.

AE, adverse event; SAE, serious adverse event; PML, progressive multifocal leukoencephalopathy; URTI, upper respiratory tract infection.

505 **Supplementary Figure 1.** Multiple testing procedure for endpoints. Multiplicity control via
506 multistage gatekeeping. Ordering of endpoints within a family were based on the p value results
507 from the hypotheses tests of the endpoints listed here. *Off corticosteroids for ≥ 24 weeks prior
508 to Week 62. UC-PRO/SS, Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms.
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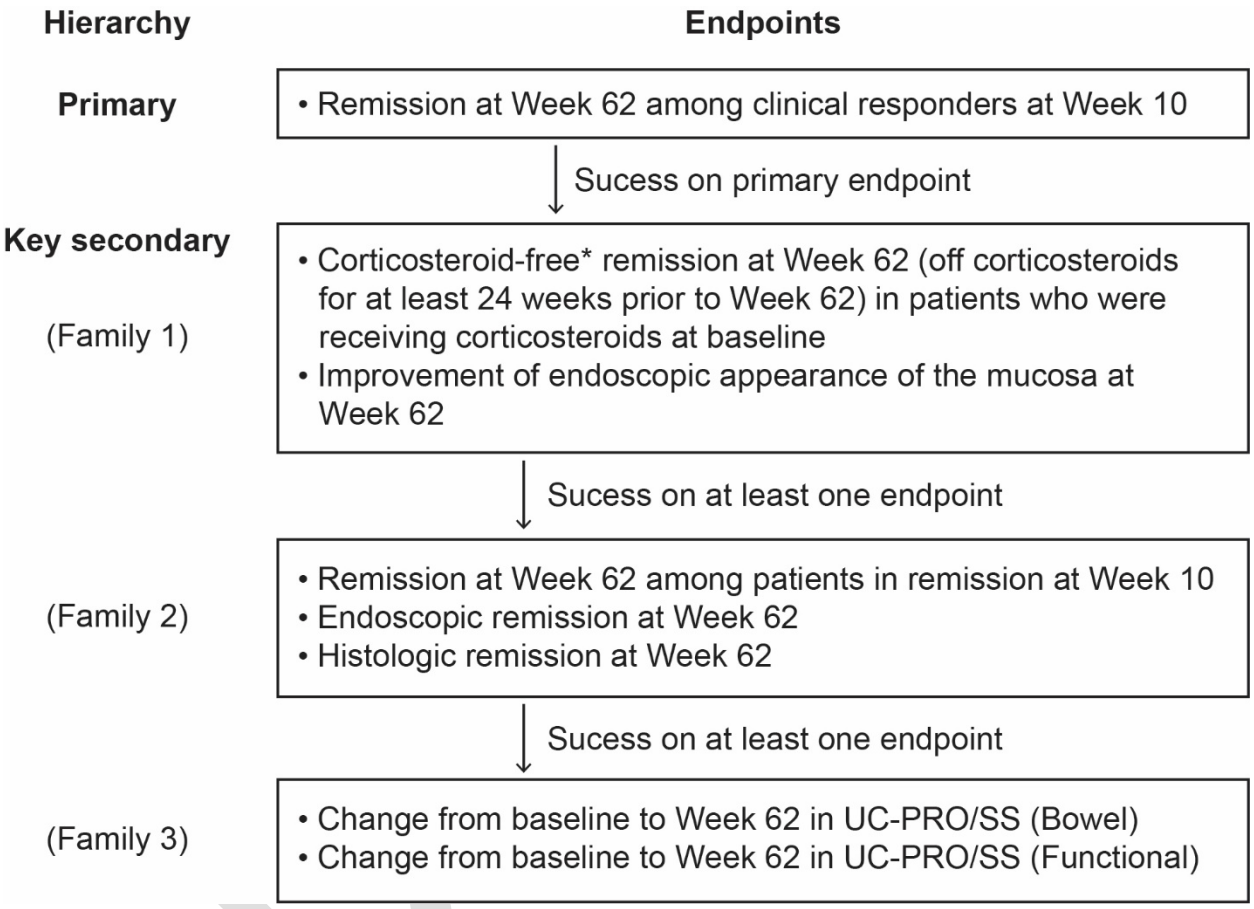

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