Etrolizumab as induction and maintenance therapy in patients with moderately to severely active Crohn's disease (BERGAMOT): a randomised, placebo-controlled, double-blind, phase 3 trial

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Summary

Background Etrolizumab is a gut-targeted anti-β7 monoclonal antibody targeting α4β7 and αEβ7 integrins. We aimed to compare the safety and efficacy of two doses of etrolizumab with placebo in patients with Crohn's disease.

Methods BERGAMOT was a randomised, placebo-controlled, double-blind, phase 3 study done at 326 treatment centres worldwide. We included patients aged 18–80 years with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220–480, and a mean daily stool frequency score of ≥6 or a mean daily stool frequency score of >3, and a mean daily abdominal pain score of >1, as well as the presence of active inflammation on screening ileocolonoscopy) who had intolerance, inadequate response, or no response to one or more of corticosteroids, immunosuppressants, or anti-TNF therapy within the past 5 years. BERGAMOT consisted of three induction cohorts (a placebo-controlled, double-blind exploratory cohort [cohort 1]; an active treatment cohort not containing a placebo control [cohort 2]; and a placebo-controlled, double-blind pivotal cohort [cohort 3]) and one maintenance cohort. In induction cohort 3, during the 14-week induction, patients were randomly assigned (2:3:3) to receive matched placebo, 105 mg etrolizumab subcutaneously every 4 weeks (at weeks 0, 4, 8, and 12) or 210 mg etrolizumab subcutaneously (at weeks 0, 2, 4, 8, and 12), stratified by concomitant treatment with oral corticosteroids, concomitant treatment with immunosuppressants, baseline disease activity, and previous exposure to anti-TNF therapy. To preserve masking, all patients received two injections at weeks 0, 4, 8, and 12 and one injection at week 2. Week 14 etrolizumab responders from all cohorts were re-randomly assigned (1:1) to receive 105 mg etrolizumab (etrolizumab maintenance group) or placebo (placebo maintenance group) every 4 weeks for 52 weeks; patients in the induction placebo group underwent a sham re-randomisation to preserve masking. During maintenance, randomisation was stratified by CDAI remission status, concomitant treatment with oral corticosteroids, induction dose regimen, and previous exposure to anti-TNF therapy. All participants and study site personnel were masked to treatment assignment for both induction and maintenance. Co-primary induction endpoints at week 14 (placebo *vs* 210 mg etrolizumab) were clinical remission (mean stool frequency ≤3 and mean abdominal pain ≤1, with no worsening) and endoscopic improvement (≥50% reduction in Simple Endoscopic Score for Crohn's Disease [SES-CD]). Co-primary maintenance endpoints at week 66 (placebo *vs* etrolizumab) were clinical remission and endoscopic improvement. Efficacy was analysed using a modified intention-to-treat (mITT) population, defined as all randomised patients who received at least one dose of study drug (induction) and as all patients re-randomised into maintenance who received at least one dose of study drug in the maintenance phase (maintenance). Safety analyses included all patients who received at least one dose of study drug. Maintenance safety analyses include all adverse events occurring in both induction and maintenance. This trial is registered with ClinicalTrials.gov, NCT02394028, and is closed to recruitment.

Findings Between March 20, 2015, and Sept 7, 2021, 385 patients (209 [54%] male and 326 [85%] white) were randomly assigned in induction cohort 3 to receive placebo (n=97), 105 mg etrolizumab (n=143), or 210 mg etrolizumab (n=145). 487 patients had a CDAI-70 response in any of the induction cohorts and were enrolled into the maintenance cohort, of whom 434 had a response to etrolizumab and were randomly assigned to placebo (n=217) or 105 mg etrolizumab (n=217). At week 14, 48 (33%) of 145 patients in the 210 mg induction etrolizumab group versus 28 (29%) of 96 patients in the placebo induction group were in clinical remission (adjusted treatment difference 3·8% [95% CI −8·3 to 15·3]; p=0·52), and 40 (27%) versus 21 (22%) showed endoscopic improvement (5·8% [−5·4 to 17·1]; p=0·32). At week 66, a significantly higher proportion of patients receiving etrolizumab than those receiving placebo had clinical remission (76 [35%] of 217 *vs* 52 [24%] of 217; adjusted treatment difference 11·3% [95% CI 2·7–19·7]; p=0·0088) and endoscopic improvement (51 [24%] *vs* 26 [12%]; 11·5% [4·1–18·8]; p=0·0026). Similar proportions of patients reported one or more adverse events during induction (95 [66%] of 143 in the 105 mg etrolizumab group, 85 [59%] of 145 in the 210 mg etrolizumab group, and 51 [53%] of 96 in the placebo group) and maintenance (189 [87%] of 217 in the etrolizumab group and 190 [88%] of 217 in the placebo group). During induction, the most common treatment-related adverse

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See Online for appendix

events were injection site erythema (six [4%] of 143 in the 105 mg etrolizumab group, four [3%] of 145 in the 210 mg etrolizumab group, and none of 96 in the placebo group), and arthralgia (two [1%], one [1%], and four [4%]). In the maintenance cohort, the most common treatment-related adverse events were injection site erythema (six [3%] of 217 in the etrolizumab group *vs* 14 [6%] of 217 in the placebo: group), arthralgia (five [2%] *vs* eight [4%]), and headache (five [2%] *vs* seven [3%]). The most common serious adverse event was exacerbation of Crohn's disease (14 [6%] of 217 patients taking placebo and four [2%] of 217 patients taking 105 mg etrolizumab in the maintenance cohort).

Interpretation **A significantly higher proportion of patients with moderately to severely active Crohn's disease achieved clinical remission and endoscopic improvement with etrolizumab than placebo during maintenance, but not during induction.**

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Introduction

Crohn's disease is a chronic, relapsing-remitting, progressive gastrointestinal inflammatory disease that substantially affects patient quality of life.[1] About two-thirds of patients with Crohn's disease go on to develop stricturing, penetrating disease, or both, eventually requiring surgical intervention.[1–3] Treatment options for moderately to severely active Crohn's disease include corticosteroids and immunosuppressants, as well as biological therapies, such as TNF inhibitors, anti-integrin therapies (including vedolizumab and natalizumab), and the IL-12 and IL-23 antagonist ustekinumab.[4–7] Despite widespread use of these biological therapies, the disease does not go into long-term remission for many patients, and rates of surgical intervention have decreased only slightly in the

Research in context

Evidence before this study

We searched PubMed for clinical trials published in English between April 1, 2017, and March 31, 2022, using the search terms "Crohn's disease treatment" and "moderate to severe". The search was limited to positive phase 1–3 clinical trials of existing and emerging biological therapies in adults with moderately to severely active Crohn's disease, and trials were included if they were of therapies, not procedures, protocols, or diets. Our search revealed that etrolizumab was one of 11 therapies (others were adalimumab, brazikumab, mirikizumab, ozanimod, PF-04236921, risankizumab, tofacitinib, upadacitinib, ustekinumab, and vedolizumab) that have entered or completed phase 2 and phase 3 clinical trials for the treatment of Crohn's disease. A second PubMed search on July 11, 2022, of clinical trials published in English using the term "etrolizumab" revealed 11 results, including one manuscript reporting results from a phase 2 study (EUCALYPTUS) and five phase 3 studies of etrolizumab in patients with moderate-to-severe ulcerative colitis (HIBISCUS I and II, LAUREL, GARDENIA, and HICKORY), as well as additional pharmacology and tolerability studies in various participant groups. Etrolizumab is a humanised monoclonal antibody that binds to the β7 subunit of heterodimeric integrins α4β7 and αEβ7, thereby blocking the α4β7–MAdCAM-1 and αEβ7–E-cadherin interactions, and is hypothesised to restrict both ingress and retention of immune cells within the gut. Previous phase 3 studies of etrolizumab in patients with moderately to severely active ulcerative colitis showed mixed results, with 105 mg etrolizumab demonstrating significant improvements over placebo in two induction studies but not in maintenance studies.

Added value of this study

In this randomised, blinded, placebo-controlled induction and maintenance study of etrolizumab in patients with moderately to severely active Crohn's disease, we present results achieved with two induction regimens—105 mg etrolizumab, previously studied in phase 3 trials of patients with ulcerative colitis, and 210 mg etrolizumab, a higher dose than has been previously reported—followed by a maintenance regimen of 105 mg etrolizumab every 4 weeks. Results from this study validate rates of clinical remission and endoscopic response previously observed with etrolizumab; however, this study demonstrated unexpectedly high placebo rates in both co-primary endpoints, and no significant differences were observed between placebo and etrolizumab for either co-primary induction endpoint. A significantly higher proportion of patients receiving etrolizumab than placebo achieved both co-primary maintenance endpoints.

Implications of all the available evidence

Despite promising results from phase 2 studies, etrolizumab did not show significant improvement over placebo for induction outcomes in this study—a result driven largely by unexpectedly high placebo rates. Notably, higher than expected placebo rates were observed in endoscopic measures in addition to clinical measures despite the use of a central reading paradigm for endoscopy. These results, in combination with results of other Crohn's disease induction studies, underscore the ongoing need to minimise placebo rates in clinical studies of patients with Crohn's disease.

past decades,[3] highlighting the need for additional treatment options with durable efficacy and safety.

Etrolizumab is the first biologic, dual integrin-receptor inhibitor to target amelioration of inflammation in the gut. In contrast to approved anti-integrin therapies, etrolizumab selectively targets the β7 integrin, controlling trafficking of immune cells into the gut and their inflammatory effects on the intestinal lining via the α4β7 and αEβ7 integrins.[5,8,9] This dual mechanism is proposed to control intestinal inflammation via two complementary actions: blocking the interaction between MAdCAM1 and α4β7, thus reducing the trafficking of lymphocytes into the gut, and by blocking the interaction between E-cadherin and αEβ7, limiting the retention of lymphocytes in the intraepithelial compartment. In a phase 2 study, induction with etrolizumab was well tolerated and yielded significantly higher rates of clinical remission versus placebo in patients with moderately to severely active ulcerative colitis.[10]

The phase 3 etrolizumab study programme consisted of six pivotal studies: five in patients with moderately to severely active ulcerative colitis (HIBISCUS I, HIBISCUS II, GARDENIA, HICKORY, and LAUREL),[11–14] and one in patients with moderately to severely active Crohn's disease (BERGAMOT).[15] In the ulcerative colitis studies, etrolizumab showed mixed results, achieving primary induction endpoints in two studies,[11,13] while missing primary maintenance endpoints in the three studies investigating maintenance therapy.[11,12,14]

Here, we present results of the BERGAMOT study, in which we compared the safety and efficacy of two doses (105 mg and 210 mg) of etrolizumab with placebo in patients with moderately to severely active Crohn's disease refractory to corticosteroids, immunosuppressants, or anti-TNF therapy.

Methods

Study design

BERGAMOT was a randomised, placebo-controlled, double-blind, phase 3 study done at 326 treatment centres worldwide. The trial comprised a 35-day screening phase, 14-week induction phase, 52-week maintenance phase, and 12-week safety follow-up phase.

BERGAMOT consisted of three induction cohorts and one maintenance cohort (appendix p 1). Induction cohort 1 (a placebo-controlled, double-blind exploratory cohort) served as a proof-of-concept study for developing the primary endpoints and establishing clinical assumptions for the pivotal induction cohort; top-line results for induction cohort 1 have been previously reported.[16] Induction cohort 2 was an active treatment cohort not containing a placebo control, and induction cohort 3 was a placebo-controlled, double-blind pivotal cohort. Patients in all three induction cohorts who had a decrease of at least 70 points on the Crohn's Disease Activity Index (CDAI; ie, a CDAI-70 response) were eligible to enter the pivotal maintenance cohort. This manuscript refers to results from exploratory induction cohort 1 and details results from pivotal induction cohort 3 and the maintenance cohort.

This trial was conducted in accordance with 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 the University of California, San Diego, Institutional Review Board (La Jolla, CA, USA) and the institutional review boards and ethics committees at each investigational site. Written informed consent was obtained from all participants before study inclusion.

Participants

Patients were aged 18–80 years with moderately to severely active Crohn's disease, defined as a CDAI score of 220–480, and a mean daily stool frequency score of at least 6 or a mean daily stool frequency score of more than 3, and a mean daily abdominal pain score of more than 1, as well as the presence of active inflammation on screening ileocolonoscopy (Simple Endoscopic Score for Crohn's Disease [SES-CD] of ≥7 [or ≥4 in cases of isolated ileitis]), as confirmed by central review.[16] Patients had established diagnoses of Crohn's disease for 3 months or longer at screening corroborated by clinical, endoscopic, and histopathological evidence, with involvement of the ileum, colon, or both and with at least four colonic segments traversable by a paediatric endoscope or at least three traversable segments for patients who had undergone bowel resections for Crohn's disease. Patients must have had intolerance, inadequate response, or no response to one or more of corticosteroids, immunosuppressants, or anti-TNF therapy within 5 years of screening. Patients receiving stable doses of oral corticosteroids (≤20 mg per day prednisone or equivalent or ≤6 mg per day budesonide) for at least 2 weeks before screening or immunosuppressants (eg, azathioprine, 6-mercaptopurine, and methotrexate) for at least 8 weeks before screening were included.

Patients with short-bowel syndrome, ileostomies, or diagnoses of ulcerative colitis or indeterminate colitis were excluded, as were patients who had undergone total colectomy or subtotal colectomy with ileorectal anastomosis. Patients with previous exposure to antiadhesion molecule therapy were not allowed. Patients were excluded if they had taken one or more of adalimumab, certolizumab pegol, or infliximab within 8 weeks before randomisation or had taken ustekinumab within 14 weeks before randomisation. Additional exclusion criteria were suspicion of ischaemic colitis, radiation colitis, or microscopic colitis; evidence of abdominal or perianal abscess; history of adenomatous colonic polyps that had not been removed; and patients expecting to require surgery for Crohn's disease-related complications. Patients were also excluded if they had the following laboratory values: serum creatinine of more than twice the upper limit of normal (ULN), serum

aminotransferases more than three times the ULN, alkaline phosphatase more than three times the ULN, total bilirubin 2·5 times the ULN, platelet count of less than 100 000 per µL, haemoglobin concentration of less than 8 g/dL, absolute neutrophil count of less than 1500 cells per µL, and absolute lymphocyte count of less than 500 cells per µL.

Randomisation and masking

An independent, interactive voice web-based response system provided by Parexel (Newton, MA) was used to generate the randomisation list and randomly assign patients to a treatment group. A permuted stratified block (dynamic) randomisation method was used, with block sizes of eight (induction cohort 3) and four (maintenance cohort), and blinded kit identification numbers were used to dispense study treatment. For induction, randomisation was stratified by concomitant treatment with oral corticosteroids (yes *vs* no), concomitant treatment with immunosuppressants (yes *vs* no), baseline CDAI of 330 or lower (yes *vs* no), and previous exposure to anti-TNF therapy (yes *vs* no). During maintenance, randomisation among CDAI-70 responders was stratified by CDAI remission status at weeks 10 and 14 (yes *vs* no), concomitant treatment with oral corticosteroids (yes *vs* no), induction dose regimen (105 mg etrolizumab *vs* 210 mg etrolizumab), and previous exposure to anti-TNF therapy (yes *vs* no). A stratified permuted block randomisation method ensured an approximately 2:3:3 ratio in induction cohort 3 among the placebo, 105 mg etrolizumab, and 210 mg etrolizumab treatment group, and an approximately 1:1 ratio between the placebo maintenance and 105 mg etrolizumab maintenance groups. All patients, study site personnel, and the sponsor and its agents were masked to treatment assignment throughout the 14-week induction and 52-week maintenance treatment periods. In addition, a double-dummy design was used to ensure masking between patients receiving treatment with etrolizumab and those receiving placebo.

Procedures

During the 14-week induction phase, patients received either subcutaneous 105 mg etrolizumab every 4 weeks; subcutaneous 210 mg etrolizumab at weeks 0, 2, 4, 8, and 12; or matched placebo (if in cohorts 1 and 3; appendix p 1). Eligibility for entry into the maintenance phase was determined at week 14. Patients with a CDAI-70 response in the 105 mg and 205 mg etrolizumab groups in the induction phase were randomly assigned again in the maintenance phase to receive subcutaneous 105 mg etrolizumab (etrolizumab maintenance group) or placebo (placebo maintenance group) every 4 weeks for 52 weeks. Patients randomly assigned to placebo during induction who achieved CDAI-70 responses received blinded placebo during the maintenance phase after sham re-randomisation; these patients were not included in maintenance efficacy results. Etrolizumab dose escalation or reduction was not allowed during the study.

During induction, oral corticosteroids were kept stable at 20 mg or less per day prednisone equivalent or 6 mg or less per day budesonide. Patients entering maintenance at week 14 underwent mandatory corticosteroid tapers. Patients receiving 20 mg or less per day oral prednisone or equivalent reduced the dose by 2·5 mg per week until discontinuation; patients receiving 6 mg or less per day oral budesonide reduced the dose by 3 mg every 2 weeks until discontinuation. Patients who could not tolerate the corticosteroid taper could increase their corticosteroid dose up to the baseline dose but had to reinitiate the taper within 2 weeks following dose increase. Baseline doses of immunosuppressant therapy were kept stable throughout the study.

Efficacy assessments were performed at baseline, at weeks 10, 14, and 66, and at early withdrawal (as needed). Ileocolonoscopies were performed on all patients at screening and at weeks 14 and 66. Endoscopies were centrally read by an independent gastroenterologist who was masked to timepoint, clinical activity, and treatment allocation.[16]

Safety was assessed via the monitoring and recording of adverse events, including serious adverse events and adverse events of special interest, laboratory parameters, and vital signs. Severity of adverse events was graded using the US National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Investigators or patients could discontinue from the study at any time for any reason, including (but not limited to) withdrawal of consent, any medical condition that might jeopardise patient safety, patient non-compliance, or if the investigator determines that it is in the best interest of the patient.

Outcomes

Separate co-primary endpoints were defined for induction and maintenance. Co-primary induction endpoints at week 14 were clinical remission and endoscopic improvement for the 210 mg etrolizumab versus placebo groups. Co-primary maintenance endpoints at week 66 were clinical remission and endoscopic improvement among patients with CDAI-70 responses at week 14 for the etrolizumab maintenance group versus the placebo maintenance groups. Clinical remission was defined as a stool frequency mean daily score of 3 or less and an abdominal pain mean daily score of 1 or less, with no worsening in either subscore compared with baseline and averaged over the previous 7 days. Endoscopic improvement was defined as a 50% or more reduction in baseline SES-CD score.

Key secondary induction endpoints for both induction doses were clinical remission at week 6, CDAI remission (CDAI score of <150) at week 14, endoscopic remission (SES-CD ≤4 [≤2 for patients with ileal Crohn's disease only] with no segment having a subcategory score of >1)

at week 14, and change from baseline to week 14 in Crohn's disease signs and symptoms, as assessed by the Crohn's Disease Patient-Reported Outcomes/Signs and Symptoms (CD-PRO/SS) measure.[17] Key secondary maintenance endpoints, assessed at week 66, were clinical remission in patients who showed clinical remission at week 14, CDAI remission, corticosteroid-free clinical remission (clinical remission with no corticosteroid use for 24 weeks before week 66 in patients receiving corticosteroids at baseline), endoscopic improvement of patients who showed endoscopic improvement at week 14, endoscopic remission, durable clinical remission (clinical remission at four or more of six assessment visits at weeks 24, 28, 32, 44, 56, and 66, which must include the week 66 visit), and change from baseline in Crohn's disease signs and symptoms as assessed by CD-PRO/SS.[17] Changes in certain biomarkers, including C-reactive protein and faecal calprotectin, were evaluated as prespecified exploratory endpoints.

Safety endpoints included the incidences and severities of adverse events, serious adverse events, injection-site reactions, laboratory abnormalities, and hypersensitivity reactions. Additional endpoints are defined in the full protocol (appendix pp 31–215).

Statistical analysis

The planned sample size for induction cohort 3 was 496 patients (124 in the placebo group, 186 in the 105 mg etrolizumab group, and 186 in the 210 mg etrolizumab group). Using a two-sided χ^2 test at a significance level of 5%, this sample size was estimated to provide 85% power to detect a 15% absolute difference between the placebo and 210 mg etrolizumab groups for the co-primary induction endpoint of clinical remission, under the assumption of a week 14 clinical remission rate for placebo of 15%. Similarly, the same sample size was estimated to provide 80% power to detect a 10% absolute difference between the placebo and 210 mg etrolizumab groups for the co-primary induction endpoint of endoscopic improvement, under the assumption of a week 14 endoscopic improvement rate for placebo of 5%. The pivotal induction cohort was closed earlier than the planned sample size requirement because of several factors: the maintenance study was complete and available for analysis; clinically meaningful treatment differences were still preserved at the lower sample size; and difficulties with recruitment would probably delay study analysis. The final sample size for induction was 385, which provided statistical assurance by allowing minimum detectable differences of 10·5% for clinical remission and 8% for endoscopic improvement, assuming placebo rates of 15% and 5%, respectively.

The planned sample size for the maintenance cohort was 480 patients (210 in the placebo maintenance group, 210 in the etrolizumab maintenance group, and 60 patients on placebo in the induction phase and who had been sham randomised for maintenance). Using a two-sided χ^2 test at a significance level of 5%, this sample size was estimated to provide approximately 90% power to detect a 15% absolute difference between the etrolizumab maintenance and placebo maintenance groups for the co-primary maintenance endpoint of clinical remission, under the assumption of a week 66 clinical remission rate for the placebo maintenance group of 20%. Similarly, the same sample size was estimated to provide approximately 90% power to detect a 15% absolute difference between the etrolizumab maintenance and placebo maintenance groups for the co-primary maintenance endpoint of endoscopic improvement, under the assumption of a week 66 endoscopic improvement rate for the placebo maintenance group of 30%. As patients meeting maintenance inclusion criteria were re-randomised after week 14, the induction and maintenance phases were regarded as two independent studies and no adjustment to the α level was performed.

Statistical hypotheses for the co-primary and secondary endpoints were tested by means of a multistage gatekeeping procedure to ensure an overall type I error of 5% or less, with the co-primary endpoints tested first at a two-sided significance of a p values of less than 0·05. Formal testing of the secondary endpoints continued if both co-primary endpoints were met. Before unblinding, each secondary endpoint was assigned to one of several families based on clinical importance. Additional details are available in the appendix (pp 2–3) and in the statistical analysis plan (appendix pp 216–337).

Efficacy was analysed using a modified intention-to-treat (mITT) population. For induction, the mITT population was defined as all randomised patients who received at least one dose of study drug. For maintenance, the mITT population was defined as all patients re-randomised in the maintenance phase who received at least one dose of study drug in the maintenance phase and who were treated with etrolizumab as induction therapy. Safety analyses included all patients who received at least one dose of study drug. Maintenance safety analyses include all adverse events occurring in both induction and maintenance.

The co-primary endpoints were compared between the etrolizumab and placebo groups with a two-sided Cochran-Mantel-Haenszel test for both induction and maintenance, wherein the 210 mg etrolizumab dose was the primary treatment comparison for induction. The analysis was adjusted for three stratification factors used at randomisation, and the stratum-adjusted proportion differences were obtained, along with the 95% Newcombe CIs. The treatment group estimates are presented with 95% Wilson CIs. To ensure that all patients in the mITT population contributed to the Cochran-Mantel-Haenszel test, the fourth stratification factor was dropped from the analysis: immunosuppressant use at baseline was not included for the induction analysis, and CDAI remission

at weeks 10 and 14 was not included for maintenance analysis.

The statistical analysis plan incorporated an estimands framework, wherein treatment withdrawal, rescue therapy, and death were defined as intercurrent events for all endpoints. Within the framework, patients were treated as non-responders for binary endpoints under the composite strategy. For site-based endpoints involving endoscopy and CDAI, COVID-19 was specified as an additional intercurrent event and was handled by way of a hypothetical strategy wherein multiple imputation was used for endoscopic outcomes and the site's last available assessment for affected subscores of CDAI. Further estimand attributes are detailed in the statistical analysis plan. For missing data, endoscopic endpoints were handled via multiple imputation. Non-integer patient counts obtained via multiple imputation were rounded to the nearest whole number for presentation. A wider, 10-day window was used for the eDiary components of clinical remission and CDAI endpoints (otherwise set to non-responder); and missing site-based CDAI subscores were imputed using the last available score to enable a total CDAI score to be calculated. SAS (version 9.4) was used for all statistical analyses.

This study is registered at ClinicalTrials.gov, NCT02394028, and with the EU Clinical Trials Register, 2014-003824-36.

Role of the funding source

The funder had roles in the study design, provision of study drugs, protocol development, regulatory and ethics approvals, safety monitoring, data collection, data analysis, data interpretation, the writing of the report in collaboration with the study authors, and in the decision to submit the article for publication.

Results

Between March 20, 2015, and Sept 7, 2021, in the induction phase, 300 patients were enrolled into cohort 1 and randomly assigned to receive placebo (n=59), 105 mg etrolizumab (n=120), or 210 mg etrolizumab (n=121; figure 1). During the same period, induction cohort 3, the pivotal induction cohort, enrolled 385 patients, who were randomly assigned to receive placebo (n=97), 105 mg etrolizumab (n=143), or 210 mg etrolizumab (n=145). 875 (85%) of 1035 patients in all cohorts completed induction. The maintenance phase consisted of 487 patients: 434 patients had a CDAI-70 response at week 14 with etrolizumab induction and were randomly assigned to receive 105 mg etrolizumab (n=217) or placebo (n=217); 53 patients had CDAI-70 responses on placebo and underwent sham re-randomisation to receive placebo during maintenance. Patients from all three induction cohorts were included in the maintenance population (figure 1). 259 (53%) of 487 patients completed maintenance. In both induction and maintenance, the most common reason for treatment discontinuation was lack of efficacy (33 [9%] of 385 in induction cohort 3 and 174 [36%] of 487 in the maintenance cohort).

Baseline characteristics were generally balanced across groups for both the induction and maintenance populations, although acceptable (within about 10%) distributional differences were noted for sex, region, disease location, and baseline faecal calprotectin concentrations in induction cohort 3 (table 1). In induction cohort 3, the median duration of disease for all patients was 6·9 years (IQR 2·7–13·0), and the mean CDAI at baseline was 327·7 (SD 61·4). In the maintenance phase, the median duration of disease for all patients was 7·2 years (IQR 2·8–13·0), and the mean CDAI at baseline was 325·0 (SD 62·2). In induction cohort 3, at baseline, 144 (37%) of 385 patients were taking corticosteroids, 99 (26%) were taking immunosuppressants, and 206 (54%) had previously received at least one anti-TNF therapy; similar proportions were observed in the maintenance population. Patient baseline characteristics for induction cohort 1 are provided in the appendix (p 8).

In the induction cohort 3 mITT population, 48 (33%) of 145 patients in the 210 mg etrolizumab group and 28 (29%) of 96 in the placebo group were in clinical remission at week 14 (adjusted treatment difference 3·8% [95% CI –8·3 to 15·3]; p=0·52), and 40 (27%) of 145 patients in the 210 mg etrolizumab group and 21 (22%) of 96 in the placebo group showed endoscopic improvement at week 14 (adjusted treatment difference 5·8% [–5·4 to 17·1]; p=0·32; figure 2A). Subgroup analyses for induction cohort 3 are presented in the appendix (pp 4–5).

In the maintenance mITT population, 76 (35%) of 217 patients in the etrolizumab maintenance group and 52 (24%) in the placebo maintenance group were in clinical remission at week 66 (adjusted treatment difference 11·3% [95% CI 2·7–19·7]; p=0·0088), and 51 (24%) patients in the etrolizumab maintenance group and 26 (12%) in the placebo maintenance group showed endoscopic improvement at week 66 (adjusted treatment difference 11·5% [4·1–18·8]; p=0·0026; figure 2B). Subgroup analyses for the maintenance population are presented in the appendix (pp 6–7).

In induction, because neither co-primary induction endpoint was met, secondary induction endpoints were considered statistically non-significant and were not formally compared in accordance with the conditions of prespecified hierarchical testing. Nominal p values shown in the figures should be considered exploratory. At week 14, similar proportions of patients receiving 210 mg etrolizumab and patients receiving placebo showed CDAI remission (56 [39%] of 145 *vs* 35 [37%] of 96; adjusted treatment difference 2·3%) and endoscopic remission (22 [15%] *vs* eight [9%]; adjusted treatment difference 6·5%; figure 3A). No significant differences were observed between 105 mg etrolizumab and placebo for the secondary endpoints of clinical remission (43 [30%] of 143 *vs* 28 [29%] of 96; adjusted treatment

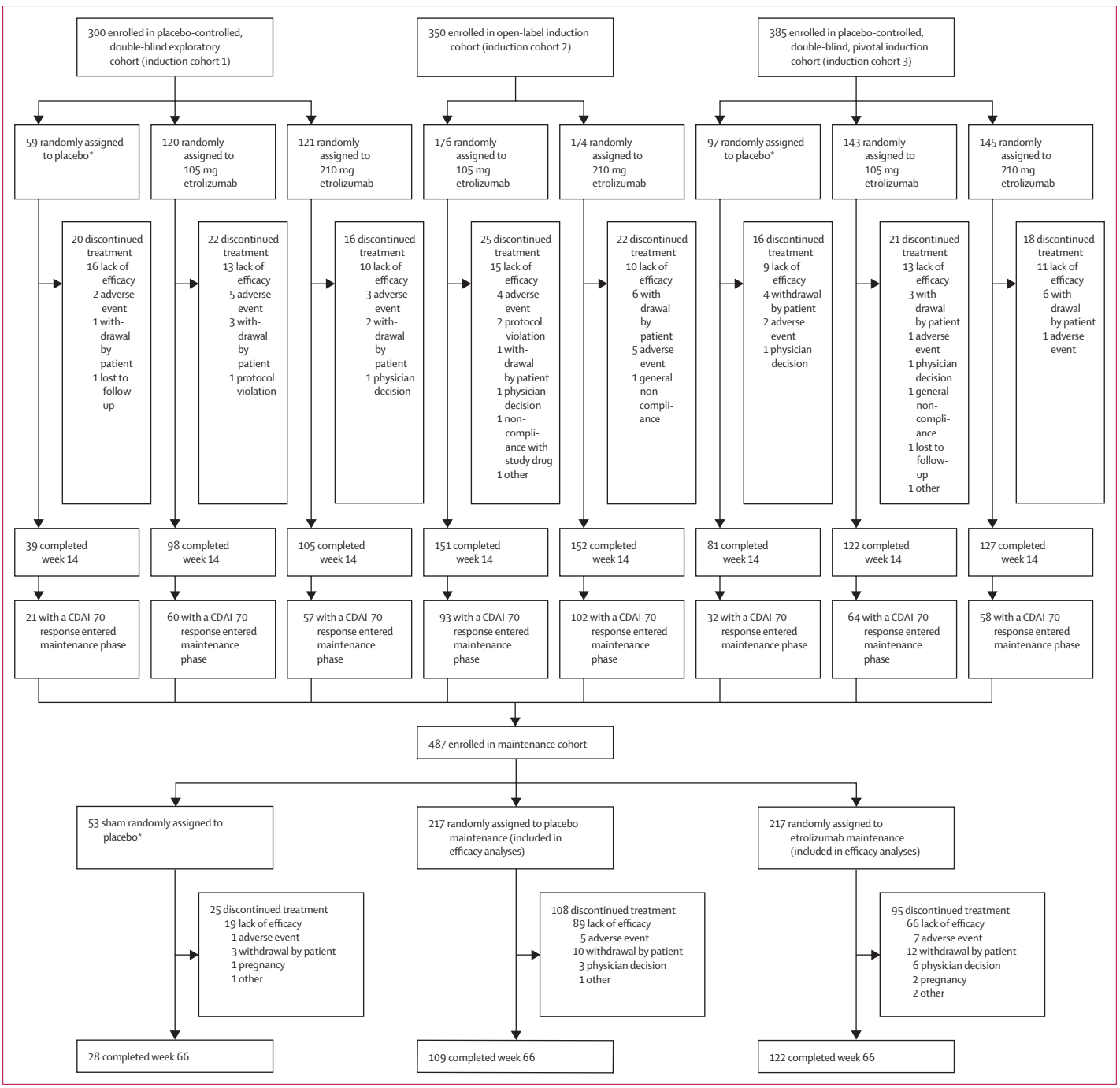

Figure 1: **Trial profile**
Patients were considered as completing induction if they completed the scheduled week 14 visit. Patients were considered as completing maintenance if they completed the scheduled week 66 visit. The CDAI-70 response is defined as a decrease of at least 70 points on the CDAI. CDAI=Crohn's Disease Activity Index. *Patients in the placebo groups in cohorts 1 and 3 were sham re-randomised to placebo and were not used as comparators according to the protocol. †One patient withdrew before first dose and was excluded from all efficacy and safety analyses. ‡Reasons for withdrawal of patient who completed the week 14 visit and did not enter maintenance are not included.

difference 1·1%), endoscopic improvement (37 [26%] *vs* 21 [22%]; adjusted treatment difference 4·9%), CDAI remission (49 [34%] *vs* 35 [37%]; adjusted treatment difference –1·7%), or endoscopic remission (15 [10%] *vs* eight [9%]; adjusted treatment difference 1·6%) at week 14 (figure 3B). No significant difference was observed between 210 mg etrolizumab and placebo (34 [23%] of 145 *vs* 20 [21%] of 96; adjusted treatment difference 2·3%) or between 105 mg etrolizumab and placebo (34 [24%] of 143 *vs* 20 [21%] of 96; adjusted treatment difference 3·1%) for

	Induction cohort 3			Maintenance cohort*	
	Placebo group (n=97)	105 mg etrolizumab group (n=143)	210 mg etrolizumab group (n=145)	Placebo maintenance group (n=217)	Etrolizumab maintenance group (n=217)
Age, years	37·4 (13·7)	38·3 (13·4)	36·5 (13·1)	37·9 (12·6)	38·8 (12·9)
Sex					
Male	59 (61%)	74 (52%)	76 (52%)	99 (46%)	119 (55%)
Female	38 (39%)	69 (48%)	69 (48%)	118 (54%)	98 (45%)
Race					
White	81 (84%)	117 (82%)	128 (88%)	193 (89%)	182 (84%)
Other	16 (16%)	26 (18%)	17 (12%)	24 (11%)	35 (16%)
BMI, kg/m²	24·4 (5·5)	26·0 (6·3)	24·9 (5·6)	24·9 (6·1)	25·7 (6·2)
Region					
Eastern or central Europe	31 (32%)	53 (37%)	65 (45%)	83 (38%)	87 (40%)
Western or northern Europe, Canada, Australia, New Zealand	34 (35%)	40 (28%)	34 (23%)	80 (37%)	54 (25%)
USA	12 (12%)	34 (24%)	33 (23%)	37 (17%)	54 (25%)
Asia	0	2 (1%)	0	6 (3%)	8 (4%)
Latin America	15 (15%)	8 (6%)	5 (3%)	7 (3%)	11 (5%)
Other	5 (5%)	6 (4%)	8 (5·5%)	4 (2%)	3 (1%)
Baseline use of oral corticosteroids	37 (38%)	54 (38%)	53 (37%)	92 (42%)	91 (42%)
Baseline use of immunosuppressants	24 (25%)	39 (27%)	36 (25%)	71 (33%)	67 (31%)
Previous use of anti-TNF therapy					
Anti-TNF therapy naive	40 (41%)	67 (47%)	72 (50%)	88 (41%)	92 (42%)
Refractory or loss of response	45 (46%)	70 (49%)	61 (42%)	115 (53%)	112 (52%)
Intolerant	9 (9%)	5 (3%)	10 (7%)	14 (6%)	9 (4%)
Unknown	3 (3%)	1 (1%)	2 (1%)	0	4 (2%)
Number of previous anti-TNF agents received					
0	40 (41%)	67 (47%)	72 (50%)	88 (41%)	92 (42%)
1	34 (35%)	34 (24%)	35 (24%)	71 (33%)	62 (29%)
2	21 (22%)	39 (27%)	34 (23%)	55 (25%)	55 (25%)
≥3	2 (2%)	3 (2%)	4 (3%)	3 (1%)	8 (4%)
Disease duration, years	7·9 (3·7–14·3)	6·1 (2·0–11·7)	6·9 (3·0–14·4)	7·8 (2·7–13·5)	6·6 (2·9–12·1)
Disease location					
Ileum only	23 (24%)	24 (17%)	25 (17%)	43 (20%)	35 (16%)
Colon only	17 (18%)	28 (20%)	37 (26%)	48 (22%)	41 (19%)
Ileum and colon	57 (59%)	91 (64%)	83 (57%)	126 (58%)	141 (65%)
CDAI	329·4 (64·0)	326·3 (60·4)	328·0 (61·0)	327·3 (65·2)	322·3 (58·4)
Abdominal pain score	2·03 (0·56)	1·98 (0·59)	1·97 (0·56)	1·93 (0·54)	1·97 (0·53)
Stool frequency score	6·40 (2·30)	6·59 (2·43)	6·76 (2·75)	6·55 (2·87)	6·38 (2·94)
SES-CD	13·32 (7·51)	14·36 (7·21)	13·12 (7·66)	13·02 (7·03)	13·63 (6·87)
Faecal calprotectin, µg/g					
<250	27 (28%)	24 (17%)	35 (25%)	46 (21·5%)	40 (19%)
250–500	15 (16%)	21 (15%)	18 (13%)	35 (16%)	32 (15%)
≥500	53 (56%)	95 (68%)	89 (63%)	133 (62%)	137 (66%)
C-reactive protein, mg/L					
≤2·87	30 (31%)	32 (22%)	42 (29%)	56 (26%)	61 (28%)
2·87–10	24 (25%)	44 (31%)	45 (31%)	70 (32%)	65 (30%)
>10	42 (44%)	67 (47%)	58 (40%)	91 (42%)	91 (42%)

Data are mean (SD), n (%), or median (IQR). CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease. *Baseline for the maintenance population refers to week 0 (ie, the timepoint of randomisation to induction).

Table 1: **Patient demographics and baseline characteristics**

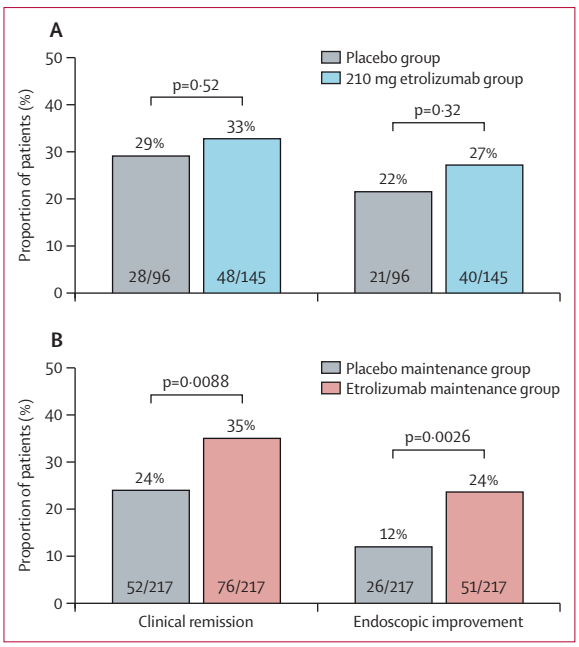

Figure 2: **Patients with moderately to severely active Crohn's disease with clinical remission and endoscopic improvement at week 14 (A) and at week 66 among patients with clinical responses after induction (B)**
Clinical remission was defined as stool frequency mean daily score of 3 or less and mean daily abdominal pain score of 1 or less with no worsening in either subscore compared with baseline and averaged over the 7 days before visit. Endoscopic improvement was defined as 50% or more reduction from baseline SES-CD. Difference between proportions were compared using a Cochran-Mantel-Haenszel test stratified for baseline oral corticosteroid use, previous anti-TNF therapy exposure, baseline CDAI score of 330 or less (induction only), and induction dose regimen (105 mg *vs* 210 mg; maintenance only). The adjusted treatment difference is presented. CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease.

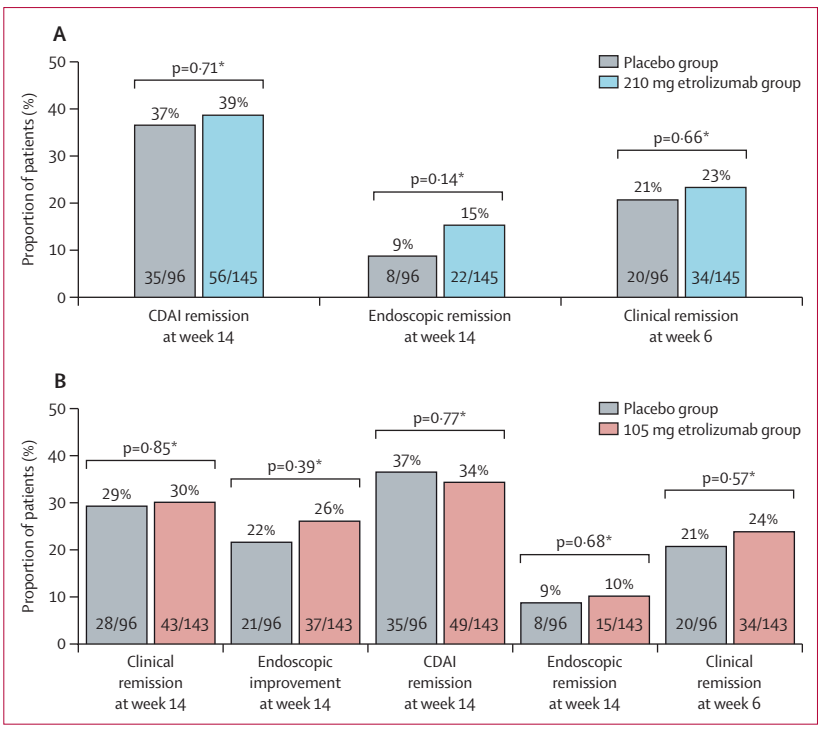

Figure 3: **Secondary induction endpoints with 210 mg etrolizumab (A) and 105 mg etrolizumab (B) in patients with moderately to severely active Crohn's disease**
CDAI remission was defined as a CDAI score of 150 or less. Endoscopic remission was defined as SES-CD of 4 or less (≤2 for ileal patients), with no segment having a subcategory score of more than 1. Secondary endpoints were not formally tested because of failure of the co-primary endpoints. CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease. *Nominal p value, not adjusted for multiplicity—exploratory only. Differences between proportions were compared using a Cochran-Mantel-Haenszel test stratified for baseline oral corticosteroid use, previous anti-TNF therapy, and baseline CDAI score of 330 or less. The adjusted treatment difference is presented.

clinical remission at week 6 (figure 3); no changes from baseline in CD-PRO/SS were seen for any group (appendix p 9). Induction endpoint data for cohort 1 are shown in the appendix (p 10).

In the maintenance cohort, patients in the etrolizumab maintenance group showed significant improvements over placebo for the secondary endpoints of endoscopic remission (26 [12%] of 217 *vs* 13 [6%] of 217; adjusted p=0·048; figure 4) and corticosteroid-free clinical remission in patients using corticosteroids at baseline (27 [29%] of 93 *vs* ten [11%] of 93; adjusted p=0·048) at week 66. Nominally significant differences in clinical remission among week 14 clinical remitters and durable clinical remission were also shown between the etrolizumab maintenance and placebo maintenance groups at week 66 (figure 4). Among patients with endoscopic improvement at week 14, 15 (25%) of 58 patients receiving placebo and 27 (38%) of 72 patients receiving etrolizumab also exhibited endoscopic improvement at week 66 (nominal p=0·1210). No significant changes from baseline in CD-PRO/SS were observed for any group (appendix p 9). Changes from baseline in faecal calprotectin and C-reactive protein were exploratory endpoints for induction and maintenance populations and are shown in the appendix (pp 11–12); similar results were observed across treatment groups.

Similar incidences of adverse events were reported between the 210 mg etrolizumab, 105 mg etrolizumab, and placebo groups, with most of the adverse events considered mild to moderate in severity across both study phases (table 2). During induction, 85 (59%) of 145 patients in the 210 mg etrolizumab group, 95 (66%) of 143 patients in the 105 mg etrolizumab group, and 51 (53%) of 96 patients in the placebo group had at least one adverse event. In the maintenance population, 189 (87%) of 217 patients in the etrolizumab maintenance group and 190 (88%) of 217 in the placebo maintenance group had at least one adverse event. During induction, the most common treatment-related adverse events were injection site erythema (six [4%] of 143 in the 105 mg etrolizumab group, four [3%] of 145 in the 210 mg etrolizumab group, and none of 96 in the placebo group), and arthralgia (two [1%], one [1%], and four [4%]). In the maintenance cohort, the most common treatment-related adverse events were injection site erythema

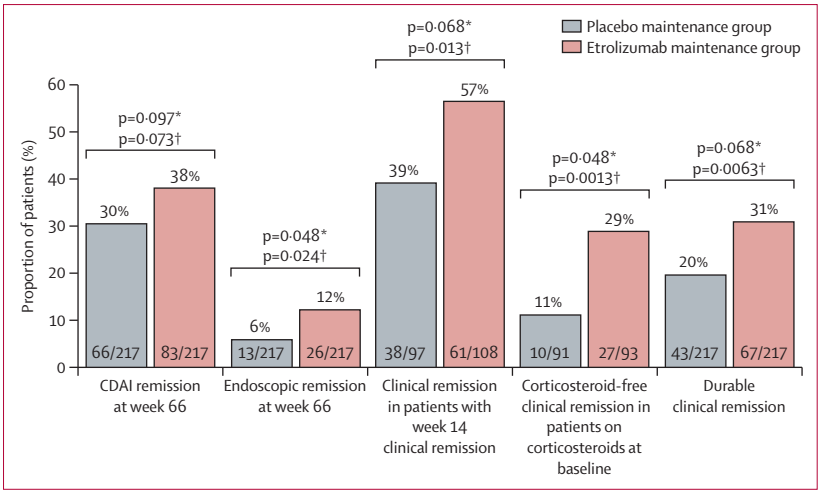

Figure 4: **Patients with moderately to severely active Crohn's disease achieving secondary maintenance endpoints at week 66**

CDAI remission was defined as a CDAI score of 150 or less. Endoscopic remission was defined as SES-CD of 4 or less (≤2 for ileal patients), with no segment having a subcategory score of more than 1. Corticosteroid-free clinical remission was defined as clinical remission without the use of corticosteroids for 24 weeks or more before the week 66 visit. Durable clinical remission was defined as clinical remission at four or more of the six assessment visits at weeks 24, 28, 32, 44, 56, and 66, which must include the week 66 visit. Difference between proportions were compared using a Cochran-Mantel-Haenszel test stratified for baseline oral corticosteroid use, previous anti-TNF therapy, baseline CDAI score of 330 or less, and etrolizumab induction dose (105 mg *vs* 210 mg). The adjusted treatment difference is presented. CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease. *p value adjusted for multiplicity. †Nominal p value.

	Induction cohort 3			Maintenance cohort	
	Placebo group (n=96)	105 mg etrolizumab group (n=143)	210 mg etrolizumab group (n=145)	Placebo maintenance group (n=217)	Etrolizumab maintenance group (n=217)
Patients with at least one adverse event	51 (53%)	95 (66%)	85 (59%)	190 (88%)	189 (87%)
Patients with at least one serious adverse event	8 (8%)	12 (8%)	8 (6%)	33 (15%)	30 (14%)
Patients with at least one adverse event leading to treatment discontinuation	3 (3%)	4 (3%)	5 (3%)	9 (4%)	9 (4%)
Infections	16 (17%)	40 (28%)	42 (29%)	121 (56%)	106 (49%)
Serious infections	1 (1%)	2 (1%)	2 (1%)	13 (6%)	12 (6%)
Gastrointestinal infections	1 (1%)	6 (4%)	8 (6%)	28 (13%)	27 (12%)
Deaths	0	0	0	0	1 (<1%)*
Progressive multifocal leukoencephalopathy	0	0	0	0	0
Serious adverse events occurring in more than 1% of patients in any etrolizumab group					
Gastrointestinal disorders	5 (5%)	7 (5%)	7 (5%)	19 (9%)	14 (6%)
Crohn's disease	3 (3%)	7 (5%)	5 (3%)	14 (6%)	4 (2%)
Abdominal pain	1 (1%)	0	2 (1%)	2 (1%)	0
Anal fistula	0	0	0	0	3 (1%)
Infections and infestations	1 (1%)	2 (1%)	2 (1%)	13 (6%)	12 (6%)
Anal abscess	0	1 (1%)	0	1 (<1%)	3 (1%)
Blood and lymphatic disorders	0	3 (2%)	0	0	2 (1%)
Anaemia	0	2 (1%)	0	0	2 (1%)

Data are n (%). Safety analyses included all patients who received at least one dose of study drug. Maintenance safety analyses include all adverse events occurring in both induction and maintenance. *One patient died of a cerebral gas embolism, which was deemed unrelated to study treatment.

Table 2: **Adverse events in the safety population**

(six [3%] of 217 in the etrolizumab group *vs* 14 [6%] of 217 in the placebo group), arthralgia (five [2%] *vs* eight [4%]), and headache (five [2%] *vs* seven [3%]). The most common serious adverse event was exacerbation of Crohn's disease (14 [6%] of 217 patients taking placebo and four [2%] of 217 patients taking 105 mg etrolizumab in the maintenance cohort). Crohn's disease flare was the most common adverse event leading to treatment discontinuation in all groups.

During induction, slightly more patients treated with etrolizumab than with placebo reported infection adverse events; the difference was driven primarily by non-serious gastrointestinal infections such as gastroenteritis and viral gastroenteritis (table 2). During induction and maintenance, roughly similar proportions of etrolizumab-treated and placebo-treated patients had serious infection adverse events. Fistulas and abscesses were generally balanced between the etrolizumab maintenance and placebo maintenance groups in the maintenance phase. One death (a white man aged 61 years) occurred during the maintenance phase in the etrolizumab maintenance group. The listed cause of death was cerebral gas embolism—occurring in combination with pneumonia after hemicolectomy and abscess evacuation—and was not considered related to study treatment. No progressive multifocal leuko-encephalopathy was reported.

Discussion

For patients with moderately to severe actively Crohn's disease, we found that 210 mg etrolizumab did not meet either co-primary induction endpoint of clinical remission or endoscopic improvement at week 14. However, 105 mg etrolizumab met both co-primary maintenance endpoints of clinical remission and endoscopic improvement at week 66 in patients responding at week 14. Significant improvements with 105 mg etrolizumab were also observed at week 66 for the secondary endpoints of endoscopic remission and corticosteroid-free clinical remission among patients taking corticosteroids at baseline. It is of note that the two doses of etrolizumab tested during induction did not appear to differentiate from each other in this study. In patients with moderately to severely active Crohn's disease, treatment with etrolizumab was generally well tolerated for 66 weeks. No new or unexpected safety signals occurred, and most adverse events were mild or moderate in severity.

For both co-primary induction endpoints, rates of placebo responders were markedly higher than anticipated (clinical remission: assumed 15%, observed 29%; endoscopic improvement: assumed 5%, observed 22%). Although the reasons for this are unclear, several factors might have contributed to these results either individually or in combination. Approximately 37–39% of patients in all groups were taking corticosteroids at baseline, and 25–27% of patients were

taking immunosuppressants at baseline. The presence of these medications during the study might have contributed to the observed improvement in patients receiving placebo. Although some distributional differences were noted for several baseline characteristics (eg, sex, region, disease location, and baseline faecal calprotectin concentration), these are unlikely to have been the main contributor of the study results. It is notable that the BERGAMOT study had an unusually long recruitment period of approximately 6 years. Although preliminary post-hoc analyses (unpublished data) do not suggest an effect of time on placebo rates within the cohort 3 recruitment period of 2018–22, it is possible that placebo rates evolved during the time between the recruitments of cohorts 1 and 3. No evidence suggests that our results were affected by the COVID-19 pandemic, and we believe the overall effect of COVID-19 on our study to be low (data not shown).

Intriguingly, the high placebo rates observed in cohort 3 were not within the bounds estimated by cohort 1. Placebo rates of endoscopic improvement at week 14 were 3·4% (90% CI 0–8·5) for cohort 1 versus 21·6% for cohort 3, and rates of clinical remission at week 14 were 11·9% (6·6–20·5) for cohort 1 versus 29·2% for cohort 3. The difference might be, at least in part, because of differences in baseline characteristics between the cohorts, wherein the patients receiving placebo appeared to have worse baseline characteristics in cohort 1 versus cohort 3. Furthermore, the high randomisation weighting to active treatment might have affected the patient-reported endpoint of clinical remission, but that does not explain the high placebo response on the objective endpoint of endoscopy. The lower-than-planned sample size did not contribute to the failure of induction. These study results raise important concerns and challenges with regard to the designing of future clinical trials, and they support the argument that better endpoints might be required.[18]

It has become apparent in the past several years that objective measures of intestinal inflammation (eg, endoscopy) should be included in inflammatory bowel disease clinical trials in combination with clinical assessment. However, even objective measures can be influenced by reader bias and interobserver variability, especially in patients with milder disease,[16,19] although the use of a central reading paradigm has shown notable reductions in placebo rates for studies in patients with ulcerative colitis.[10] In BERGAMOT, higher-than-expected placebo rates were observed in objective endoscopic endpoints despite the use of a central reading model. In this study, both local and central readers reported higher-than-expected placebo rates for endoscopic endpoints, suggesting that they were not corrected by central reading in this study.

Even though co-primary induction endpoints were not met in this study, 105 mg etrolizumab did achieve significant improvements over placebo for both of the co-primary maintenance endpoints. Although this result is potentially puzzling, it does appear to align with previous studies of anti-integrin therapies in this patient population. In ENACT-1, similar proportions of patients treated with 300 mg natalizumab and placebo achieved the primary induction endpoint of CDAI-70 response at week 10.[20] Despite this induction result, patients remaining on natalizumab in ENACT-2—a double-blind, placebo-controlled maintenance study—had significantly higher rates of sustained response and remission up to week 60 than did those switching to placebo. Similar results were seen in GEMINI-2 with 300 mg vedolizumab in patients with moderately to severely active Crohn's disease. In that study, the co-primary induction endpoint of clinical remission at week 6 (defined as CDAI ≤150) was achieved, and the co-primary induction endpoint of CDAI-100 response at week 6 was not achieved. The primary maintenance endpoint of clinical remission at week 52 was met in GEMINI-2.[21] Results from those studies highlight the difficulty of achieving induction of remission with anti-integrin therapy in patients with Crohn's disease.

One potential limitation of this study is the use of mITT analysis sets for efficacy endpoints. Although the use of mITT analysis sets can lead to selection bias in certain settings, only one patient in our study was excluded from the mITT population (induction cohort 3), and other potential confounders such as treatment non-compliance (outside those defined and handled as an intercurrent event) were very low (<2%). Additional limitations, discussed in the previous paragraphs, include underestimation of placebo response (possibly due to corticosteroid use) and the unusually long (about 6 years) study duration. Finally, the early closing of induction cohort 3 might have reduced the power and precision of treatment estimates; however, we do not believe this to substantially affect study conclusions.

In conclusion, etrolizumab did not achieve co-primary induction endpoints at week 14 but did achieve co-primary maintenance endpoints at week 66. Unexpectedly high placebo rates were observed during the induction phase, although the reasons are not fully known. Etrolizumab treatment was well tolerated for 66 weeks, with mostly mild or moderate adverse events reported. Further analyses of these data and an ongoing open-label extension programme (JUNIPER) might reveal additional insights regarding placebo rates in Crohn's disease studies and may highlight distinct patient subpopulations that could be more or less amenable to anti-integrin therapy.

Contributions

WJS, JP, and SV contributed to conceptualisation, data curation, formal analysis, investigation, methodology, supervision, and writing (original draft), and writing (review and editing). SD was involved in study design, data collection, data analysis, data interpretation, writing (review and editing). ZS was involved in conceptualisation, data curation, formal analysis, methodology, project administration, supervision, and writing (original draft). AH contributed to conceptualisation, data curation, formal

analysis, funding acquisition, methodology, supervision, validation, and visualisation. RJ-M was involved in study design, statistical methodology, data analysis, data interpretation, and supervision. CE contributed to data interpretation. MD was involved in data collection, analysis, and interpretation. JFV contributed to data collection and interpretation. DL was involved in data collection, data analysis, data interpretation, and manuscript approval. CB, GR, and HR collected data. RA and RP contributed to data analysis and data interpretation. AH, ZS, and RJ-M verified the underlying data. All authors contributed to review and editing of the manuscript and had access to the data in the study and had responsibility for the decision to submit for publication.

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Declaration of interests

WJS has received grants from Alimentiv, Arena, Boehringer Ingelheim, Celgene, Gilead, GSK, Janssen, Lilly, Pfizer, Prometheus, Roche/Genentech, Series Therapeutics, Shire, Takeda, and Theravance; personal fees from Alfasigma, Alimentiv, Alivio, Allakos, Amgen, Applied Molecular Transport, Arena, AstraZeneca, Atlantic Pharmaceuticals, Bausch Health, BeiGene, Bellatrix, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Celgene, Celltrion, Celularity, ClostraBio, Codexis, Cosmo Pharmaceuticals, Equillium, Escalier Biosciences, Forbion, Galapagos, Gilead, Glenmark, Gossamer Bio, GSK, Immunic, InDex Pharmaceuticals, Inotrem, Intact Therapeutics, iota Biosciences, Janssen, Kiniksa, Kyverna, Landos Biopharma, Lilly, Morphic Therapeutics, Novartis, Ono, Oppilan Pharma, Otsuka, Pandion Therapeutics, Pfizer, Pharm-Olam, Progenity, Prometheus, Protagonist Therapeutics, Provention Bio, PTM Therapeutics, Quell Therapeutics, Reistone Biopharma, Roche/Genentech, Series Therapeutics Shanghai Pharma Biotherapeutics, Shire, Shoreline Biosciences, Sterna Biologicals, Sublimity, Surrozen, Takeda, Theravance, Thetis, Tillotts Pharma, UCB, Vedanta Biosciences, Ventyx Biosciences, Vivelix, Vividion, Vivreon Gastrosciences, Xencor, and Zealand Pharma; and stock or stock options from Allakos, BeiGene, Gossamer Bio, Oppilan Pharma, Progenity, Prometheus, Protagonist Therapeutics, Shoreline Biosciences, Ventyx Biosciences, Vimalan Biosciences, and Vivreon Gastrosciences. JP has received grants from MSD; consulting fees from AbbVie, Arena, Boehringer Ingelheim, Celgene, GSK, Janssen, MSD, Nestlé, Oppilan Pharma, Pfizer, Progenity, Roche/Genentech, Takeda, Theravance, and TiGenix; and other fees and support from AbbVie and Takeda. SD has received consulting fees from AbbVie, Alimentiv, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Dr Falk Pharma, Enthera, Ferring, Gilead, Hospira, Inotrem, Janssen, Johnson & Johnson, Lilly, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, TiGenix, UCB, and Vifor. ZS, AH, RJ-M, and CE are employees of Roche/Genentech and receive salary and stock options. MD has received speaker fees from AbbVie, Janssen, Pfizer, Roche, and Takeda; consulting fees from Bioclinica; and other fees and support from AbbVie, Chiesi, Ferring, Janssen, Roche, SOFAR, and Takeda. JFV has received grants from AbbVie, Applied Molecular Transport, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, and Takeda. DL has received grants from AbbVie, Amgen, Fresenius Kabi, and Takeda; speaker fees from AbbVie, Ferring, Fresenius Kabi, Galapagos, Janssen, Pfizer, Takeda, and Tillotts Pharma; consulting fees from AbbVie, Bristol Myers Squibb, Fresenius Kabi, Galapagos, Janssen, MSD, Pfizer, Roche, Takeda, and Tillotts Pharma; and other fees and support from AbbVie, Janssen, Pfizer, and Sandoz. CB has received grants from Roche; speaker fees from AbbVie and Janssen; and other fees and support from AbbVie, Janssen, and Takeda. RA has received grants from AbbVie, Biogen, InDex Pharmaceuticals, Takeda, and Tillotts Pharma; speaker fees from AbbVie, Amgen, Arena, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion Healthcare, Dr Falk Pharma, Ferring, Fresenius Kabi, Galapagos, InDex Pharmaceuticals, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Pfizer, Roche, Samsung Bioepis, Takeda, and Tillotts Pharma; consulting fees from AbbVie, Arena, Biogen, Boehringer Ingelheim, Galapagos, InDex Pharmaceuticals, Janssen-Cilag, Kliniksa Pharmaceuticals, Lilly, Samsung Bioepis, Stelic Institute, and Takeda; and other fees and support from AbbVie, Biogen, Dr Falk Pharma, and Janssen-Cilag. RP has received speaker fees and consulting fees from Roche/Genentech. SV has received grants from AbbVie, Galapagos, Janssen, Pfizer, and Takeda; speaker fees from AbbVie, Galapagos, Janssen, Pfizer, Roche/Genentech, and Takeda; and consulting fees from AbbVie, AbolerIS Pharma, AgomAb, Alimentiv, Arena, AstraZeneca, Avaxia, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, CVasThera, Dr Falk Pharma, Ferring, Galapagos, Gilead, GSK, Hospira, IMIDomics, Janssen, Johnson & Johnson, Lilly, Materia Prima, MiroBio, Morphic, MRM Health, MSD, Mundipharma, Pfizer, ProDigest, Progenity, Prometheus, Robarts Clinical Trials, Roche/Genentech, Second Genome, Shire, Surrozen, Takeda, Theravance, Tillotts Pharma, and Zealand Pharma. All other authors declare no competing interests.

Data sharing

For eligible studies, qualified researchers can request access to individual patient-level clinical data through a data request platform. At the time of writing this request platform is Vivli. Up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents are available online. Anonymised records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

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References

1 Kumar A, Cole A, Segal J, Smith P, Limdi JK. A review of the therapeutic management of Crohn's disease. *Therap Adv Gastroenterol* 2022; **15:** 17562848221078456.

2 Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002; **8:** 244–50.

3 Golovics PA, Mandel MD, Lovasz BD, Lakatos PL. Inflammatory bowel disease course in Crohn's disease: is the natural history changing? *World J Gastroenterol* 2014; **20:** 3198–207.

4 Grossberg LB, Papamichael K, Cheifetz AS. Review article: emerging drug therapies in inflammatory bowel disease. *Aliment Pharmacol Ther* 2022; **55:** 789–804.

5 Dotan I, Allez M, Danese S, Keir M, Tole S, McBride J. The role of integrins in the pathogenesis of inflammatory bowel disease: approved and investigational anti-integrin therapies. *Med Res Rev* 2020; **40:** 245–62.

6 Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohn's Colitis* 2020; **14:** 4–22.

7 Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol* 2018; **113:** 481–517.

8 Stefanich EG, Danilenko DM, Wang H, et al. A humanized monoclonal antibody targeting the β7 integrin selectively blocks intestinal homing of T lymphocytes. *Br J Pharmacol* 2011; **162:** 1855–70.

9 Tang MT, Keir ME, Erickson R, et al. Review article: nonclinical and clinical pharmacology, pharmacokinetics and pharmacodynamics of etrolizumab, an anti-β7 integrin therapy for inflammatory bowel disease. *Aliment Pharmacol Ther* 2018; **47:** 1440–52.

10 Vermeire S, O'Byrne S, Keir M, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet* 2014; **384:** 309–18.

11 Peyrin-Biroulet L, Hart A, Bossuyt P, et al. Etrolizumab as induction and maintenance therapy for ulcerative colitis in patients previously treated with tumour necrosis factor inhibitors (HICKORY): a phase 3, randomised, controlled trial. *Lancet Gastroenterol Hepatol* 2022; **7:** 128–40.

12 Danese S, Colombel JF, Lukas M, et al. Etrolizumab versus infliximab for the treatment of moderately to severely active ulcerative colitis (GARDENIA): a randomised, double-blind, double-dummy, phase 3 study. *Lancet Gastroenterol Hepatol* 2022; **7:** 118–27.

13 Rubin DT, Dotan I, DuVall A, et al. Etrolizumab versus adalimumab or placebo as induction therapy for moderately to severely active ulcerative colitis (HIBISCUS): two phase 3 randomised, controlled trials. *Lancet Gastroenterol Hepatol* 2022; **7:** 17–27.

14 Vermeire S, Lakatos PL, Ritter T, et al. Etrolizumab for maintenance therapy in patients with moderately to severely active ulcerative colitis (LAUREL): a randomised, placebo-controlled, double-blind, phase 3 study. *Lancet Gastroenterol Hepatol* 2022; **7:** 28–37.

15 Sandborn WJ, Vermeire S, Tyrrell H, et al. Etrolizumab for the treatment of ulcerative colitis and Crohn's disease: an overview of the phase 3 clinical program. *Adv Ther* 2020; **37:** 3417–31.
16 Reinisch W, Mishkin DS, Oh YS, et al. Impact of various central endoscopy reading models on treatment outcome in Crohn's disease using data from the randomized, controlled, exploratory cohort arm of the BERGAMOT trial. *Gastrointest Endosc* 2021; **93:** 174–182.
17 Higgins PDR, Harding G, Leidy NK, et al. Development and validation of the Crohn's disease patient-reported outcomes signs and symptoms (CD-PRO/SS) diary. *J Patient Rep Outcomes* 2017; **2:** 24.
18 Bossuyt P, Louis E, Mary JY, Vermeire S, Bouhnik Y. Defining endoscopic remission in ileocolonic Crohn's disease: let's start from scratch. *J Crohn's Colitis* 2018; **12:** 1245–48.
19 Panés J, Feagan BG, Hussain F, Levesque BG, Travis SP. Central endoscopy reading in inflammatory bowel diseases. *J Crohn's Colitis* 2016; **10** (suppl 2)**:** S542–47.
20 Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2005; **353:** 1912–25.
21 Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; **369:** 711–21.