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

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Summary

Background Etrolizumab is a gut-targeted, anti-β7 integrin, monoclonal antibody. In an earlier phase 2 induction study, etrolizumab significantly improved clinical remission compared with placebo in patients with moderately to severely active ulcerative colitis. We aimed to evaluate the efficacy and safety of etrolizumab in patients with moderately to severely active ulcerative colitis who had been previously treated with anti-tumour necrosis factor (TNF) agents.

Methods HICKORY was a multicentre, phase 3, double-blind, placebo-controlled study in adult (18–80 years) patients with moderately to severely active ulcerative colitis (Mayo Clinic total score [MCS] of 6–12 with an endoscopic subscore of ≥2, a rectal bleeding subscore of ≥1, and a stool frequency subscore of ≥1) previously treated with TNF inhibitors. Patients were recruited from 184 treatment centres across 24 countries in North America, South America, Europe, Asia, Oceania, and the Middle East. Patients needed to have an established diagnosis of ulcerative colitis for at least 3 months, corroborated by both clinical and endoscopic evidence, and evidence of disease extending at least 20 cm from the anal verge. In cohort 1, patients received open-label etrolizumab 105 mg every 4 weeks for a 14-week induction period. In cohort 2, patients were randomly assigned (4:1) to receive subcutaneous etrolizumab 105 mg or placebo every 4 weeks for the 14-week induction phase. Patients in either cohort achieving clinical response to etrolizumab induction were eligible for the maintenance phase, in which they were randomly assigned (1:1) to receive subcutaneous etrolizumab 105 mg or placebo every 4 weeks through to week 66. Randomisation was stratified by baseline concomitant treatment with corticosteroids, concomitant treatment with immunosuppressants (induction randomisation only), baseline disease activity, week 14 MCS remission status (maintenance randomisation only), and induction cohort (maintenance randomisation only). All patients and study site personnel were masked to treatment assignment. Primary endpoints were remission (Mayo Clinic total score [MCS] ≤2, with individual subscores of ≤1 and a rectal bleeding subscore of 0) at week 14, and remission at week 66 among patients with a clinical response (MCS with ≥3-point decrease and ≥30% reduction from baseline, plus ≥1 point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1) at week 14. Efficacy was analysed using a modified intent-to-treat population. Safety analyses included all patients who received at least one dose of study drug during the induction phase. This study is registered at ClinicalTrials.gov, NCT02100696.

Findings HICKORY was conducted from May 21, 2014, to April 16, 2020, during which time 1081 patients were screened, and 609 deemed eligible for inclusion. 130 patients were included in cohort 1. In cohort 2,479 patients were randomly assigned to the induction phase (etrolizumab n=384, placebo n=95). 232 patients were randomly assigned to the maintenance phase (etrolizumab to etrolizumab n=117, etrolizumab to placebo n=115). At week 14, 71 (18·5%) of 384 patients in the etrolizumab group and six (6·3%) of 95 patients in the placebo group achieved the primary induction endpoint of remission (p=0·0033). No significant difference between etrolizumab and placebo was observed for the primary maintenance endpoint of remission at week 66 among patients with a clinical response at week 14 (27 [24·1%] of 112 *vs* 23 [20·2%] of 114; p=0·50). Four patients in the etrolizumab group reported treatment-related adverse events leading to treatment discontinuation. The proportion of patients reporting at least adverse event was similar between treatment groups for induction (etrolizumab 253 [66%] of 384; placebo 63 [66%] of 95) and maintenance (etrolizumab to etrolizumab 98 [88%] of 112; etrolizumab to placebo 97 [85%] of 114). The most common adverse event in both groups was ulcerative colitis flare. Most adverse events were mild or moderate. During induction, the most common serious adverse event was ulcerative colitis flare (etrolizumab ten [3%] of 384; placebo: two [2%] of 95). During maintenance, the most common serious adverse event in the etrolizumab to etrolizumab group was appendicitis (two [2%] of 112) and the most common serious adverse events in the etrolizumab to placebo group were ulcerative colitis flare (two [2%] of 114) and anaemia (two [2%] of 114).

Interpretation HICKORY demonstrated that a significantly higher proportion of patients with moderately to severely active ulcerative colitis who had been previously treated with anti-TNF agent were able to achieve remission at week 14 when treated with etrolizumab compared with placebo; however, there was no significant difference between groups in remission at week 66 among patients with a clinical response at week 14.

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See **Online** for appendix

Introduction

Ulcerative colitis is a chronic, relapsing and remitting gastrointestinal disease that has a long-term deleterious effect on quality of life.[1–4] Current treatments for moderately to severely active ulcerative colitis include corticosteroids, immunosuppressants, and targeted therapies, including tumour necrosis factor inhibitors (anti-TNFs), vedolizumab, ustekinumab, and tofacitinib. Despite these treatment options, a large proportion of patients do not maintain a durable response to therapy.[4–6] Thus, targeted therapy with a favourable safety profile and the ability to achieve remission and prevent long-term complications might provide a valuable therapeutic option for these patients.

Anti-integrin therapies were developed as therapeutic options for patients with ulcerative colitis due to their high selectivity and favourable safety profile. Etrolizumab is a gut-targeted, anti-integrin, biological therapeutic. In contrast to vedolizumab, which targets the α4β7 integrin, 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.[7–10] Etrolizumab is distinguished from other integrin receptor antagonists (natalizumab and vedolizumab) because it selectively targets β7 integrin. 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 ulcerative colitis.[11]

The etrolizumab ulcerative colitis study programme consisted of five studies, including three head-to-head studies, assessing the safety and efficacy of etrolizumab in patients with moderately to severely active ulcerative colitis. Results from the open-label induction phase of HICKORY have been previously reported.[12,13] Here we

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, using the search terms "ulcerative colitis treatment" and "moderate to severe", published in English between Jan 1, 2010, and Dec 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 adults with moderately to severely active ulcerative colitis who were outpatients (studies that included patients with severe ulcerative colitis admitted to hospital were excluded). We found that etrolizumab was one of 19 therapies that have entered or completed phase 2 and 3 clinical trials for the treatment of ulcerative colitis. The anti-integrin therapy vedolizumab is currently approved for the treatment of ulcerative colitis.

Added value of this study

The etrolizumab phase 3 ulcerative colitis study programme consisted of five randomised controlled studies examining the safety and efficacy of etrolizumab, a humanised monoclonal antibody that binds the β7 subunit of the heterodimeric integrins α4β7 and αEβ7, in patients with moderately to severely active ulcerative colitis. Herein results are reported from HICKORY, a placebo-controlled induction and maintenance study of patients with previous exposure to tumour necrosis factor inhibitors. In these patients, etrolizumab was significantly more effective than placebo for achieving induction of remission at week 14 (primary induction endpoint). No significant difference between etrolizumab and placebo was observed in the primary maintenance endpoint of remission at week 66 among patients with a clinical response at week 14; however, maintenance therapy with etrolizumab was well tolerated and had a beneficial effect (nominal statistical significance) on endoscopic improvement, endoscopic remission, and histological remission at week 66.

Implications of all the available evidence

Gut-targeted therapies, such as etrolizumab, have the potential to effectively mitigate inflammatory bowel disease activity while avoiding broad-spectrum immunosuppression. 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. Results from the etrolizumab phase 3 ulcerative colitis programme have been varied, with two of three induction studies and no maintenance studies meeting primary endpoints, despite positive results for several objective measures of disease activity. Etrolizumab is currently being evaluated as an induction and maintenance treatment in patients with moderately to severely active Crohn's disease, with and without previous treatment with tumour necrosis factor inhibitors, in a global phase 3 study (BERGAMOT; NCT02394028) and an open-label extension and safety monitoring study (JUNIPER; NCT02403323).

describe the primary results from HICKORY, a phase 3 induction and maintenance study comparing the safety and efficacy of etrolizumab with placebo in patients with moderately to severely active ulcerative colitis previously treated with anti-TNF therapy.

Methods

Study design

HICKORY was a phase 3, double-blind, placebo-controlled study consisting of a 14-week induction phase (cohort 1 open-label etrolizumab treatment; cohort 2 blinded, randomised to etrolizumab or placebo), a 52-week maintenance phase (blinded, re-randomised to etrolizumab or placebo), and a 12-week safety follow-up phase. Cohort 1, the open-label cohort, was included to ensure that sample size requirements for the maintenance phase were met while minimising unnecessary exposure to placebo. An extended safety monitoring period is ongoing in COTTONWOOD (NCT02118584), an open-label extension and safety monitoring study of patients with moderately to severely active disease previously enrolled in etrolizumab phase 2/3 studies. Patients were recruited from 184 treatment centres across 24 countries in North America, South America, Europe, Asia, Oceania, and the Middle East.

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 Agence Nationale de Sécurité du Médicament et des Produits de Santé (Saint Denis, France) and the institutional review board and ethics committee at each investigational site (appendix pp 17–21). Written informed consent was obtained from all participants.

Participants

Eligible patients were adults, aged 18–80 years, with moderately to severely active ulcerative colitis, defined as a Mayo Clinic total score (MCS) of 6–12 with a centrally read endoscopic subscore of 2 or more, a rectal bleeding subscore of 1 or more, and a stool frequency subscore of 1 or more. All patients had an established diagnosis of ulcerative colitis for 3 months or more, corroborated by both clinical and endoscopic evidence, and evidence of disease extending 20 cm or more from the anal verge. Patients must have had treatment with one or two induction regimens that contained anti-TNFs within the past 5 years (required washout of anti-TNF therapy for ≥8 weeks before day 1). Patients receiving stable doses of oral 5-aminosalicylates were eligible if the dose had been stable for 4 weeks or more before day 1. Oral corticosteroids (prednisone ≤30 mg/day) were allowed only if the corticosteroid dose was stable for 4 weeks or more before day 1 (≥2 weeks if corticosteroids were being tapered). Immunosuppressants such as azathioprine, 6-mercaptopurine, and methotrexate were allowed if patients received a stable dose for 8 weeks or more before day 1.

Patients who received treatment with corticosteroid enemas, suppositories, or topical (rectal) 5-aminosalicylate, or a combination of these preparations within 2 weeks of randomisation were not eligible. Patients with previous exposure to anti-integrin therapy (including vedolizumab and natalizumab) or anti-adhesion molecule therapy were excluded. Additional exclusion criteria included planned surgery for ulcerative colitis; history of extensive colonic resection, colectomy, ileostomy, or colostomy; past or present fistula or abdominal abscess; colonic mucosal dysplasia; colonic stricture; and an increased risk of infection (ie, congenital or acquired immune deficiency, HIV, hepatitis B and C virus, cytomegalovirus, tuberculosis, or history of other opportunistic infections or organ transplant). Eligibility criteria are described in full in the protocol (appendix pp 73–79).

Randomisation and masking

Patients were randomly assigned via an interactive voice or web-based response system (IxRS) provided by Paraxel International (Newton, MA, USA) into parallel treatment groups. In the induction phase, randomisation was stratified by baseline concomitant treatment with corticosteroids, including budesonide (yes *vs* no), concomitant treatment with immunosuppressants (yes *vs* no), and baseline disease activity (MCS ≤9 *vs* MCS ≥10). In the maintenance phase, randomisation among clinical responders was stratified by remission status at week 14 (yes *vs* no), baseline concomitant treatment with corticosteroids (yes *vs* no), baseline disease activity (MCS ≤9 *vs* MCS ≥10), and induction cohort. A permuted block randomisation method ensured an approximately 4:1 ratio (induction) and an approximately 1:1 ratio (maintenance) between treatment groups and within each stratum. All patients, study site personnel, and the funder and its agents were masked to treatment assignment throughout the 14-week induction (cohort 2) and 52-week maintenance treatment periods.

Procedures

The first 130 patients who enrolled during the screening phase (cohort 1) were treated with open-label subcutaneous etrolizumab 105 mg every 4 weeks through the 14-week induction period. Patients subsequently enrolled (cohort 2, double-blind cohort) were randomly assigned to receive subcutaneous etrolizumab 105 mg or saline placebo every 4 weeks through the induction period (appendix p 1). Eligibility for entry into the maintenance phase was determined between weeks 14 and 16. After the induction period, patients assigned to etrolizumab who achieved a clinical response at week 14 were randomly assigned into the maintenance phase to receive either subcutaneous etrolizumab 105 mg or placebo every 4 weeks for 52 weeks. Patients initially randomly assigned to placebo were assessed for clinical

response at week 14; those achieving clinical response continued to receive blinded placebo during the maintenance phase. Etrolizumab dose escalation or dose reduction was not allowed at any time during the study. Patients could enrol in the COTTONWOOD open-label extension study if they received permitted rescue treatment, did not achieve clinical response at week 14, completed 66 weeks of the study, or had a clinical relapse (defined as an increase in partial MCS of ≥3 *vs* week 14, an absolute partial MCS of ≥5, and an endoscopic subscore of ≥2) during the maintenance phase. All patients entering the study had colonic biopsies obtained during flexible sigmoidoscopy or full colonoscopy. Biopsy samples were taken from the most inflamed area of the colon within 20–40 cm from the anal verge. Stool samples for analysis of faecal calprotectin and other exploratory biomarkers were collected before bowel preparation at baseline, week 14, and week 66.

The dose of corticosteroids was kept stable during the induction phase. Patients entering the maintenance phase at week 14 underwent a mandatory corticosteroid tapering regimen (patients receiving >10 mg/day prednisone or equivalent reduced the dose by 5 mg/week until 10 mg/day was achieved; patients receiving ≤10 mg/day prednisone or equivalent reduced the dose by 2·5 mg/week until discontinuation). Patients who could not tolerate the corticosteroid taper could increase the corticosteroid dose up to the baseline dose but needed to re-initiate the taper after 2 weeks after this increase. Patients could continue in the study on a dose of no more than 10 mg/day prednisone or equivalent if required. Patients who were not receiving corticosteroids at baseline and patients who completed the corticosteroid taper, but subsequently required oral corticosteroids at a dose of more than 10 mg prednisone for 5 days or more could remain in the blinded study, or transfer to the open-label extension study. Baseline doses of immunosuppressant therapy were kept stable throughout the study.

Serum concentrations of etrolizumab were measured at weeks 14 and 66 (2 weeks after etrolizumab administration). Serum concentrations were also measured pre-etrolizumab administration (trough) at weeks 4, 24, and 44. The validated pharmacokinetic assay used for measuring etrolizumab concentration was based on the Gyrolab Immunoassay (Gyros Protein Technologies, Uppsala, Sweden) platform, which provides a high level of matrix tolerance. This immunoassay has a minimum quantifiable concentration of 80 ng/mL etrolizumab in sera from patients with ulcerative colitis and healthy volunteers.[14] Anti-drug antibodies in human serum were detected using a validated method based on a bridging ELISA format. The relative sensitivity of this assay was 15·7 ng/mL in serum of patients with ulcerative colitis, and drug tolerance of the assay was established using 28 ng/mL of positive control anti-drug antibodies, which could be detected in the presence of 50 µg/mL etrolizumab. Additional details of this assay are included in the appendix (p 9).

Safety was assessed via monitoring and recording adverse events, including serious adverse events and adverse events of special interest, laboratory parameters, and vital signs. Adverse events of special interest included potential drug-induced liver injury, systemic hypersensitivity, and neurological symptoms that might suggest progressive multifocal leukoencephalopathy. Severity of adverse events was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Outcomes

Separate primary endpoints were defined for the induction and maintenance phases. For the induction phase, the primary efficacy endpoint was induction of remission at week 14. For the maintenance phase, the primary efficacy endpoint was remission at week 66 among patients with a clinical response at week 14. Remission was defined as MCS of 2 or less, with individual subscores of 1 or less and a rectal bleeding subscore of 0. Clinical response was defined as MCS with at least a 3-point decrease and at least 30% reduction from baseline, plus a decrease of 1 point or more in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1. Key secondary induction endpoints, assessed at week 14, included clinical response, endoscopic improvement (defined as Mayo endoscopic subscore of ≤1), histological remission (defined as Nancy histological index [NHI] of 1 or less among patients with histological inflammation at baseline), and endoscopic remission (defined as Mayo endoscopic subscore of 0). Changes in rectal bleeding score and stool frequency score from baseline to week 6 were also assessed. Key secondary maintenance endpoints, assessed at week 66, included corticosteroid-free remission (defined as remission with no corticosteroid use for 24 weeks before week 66 among patients receiving corticosteroids at baseline), endoscopic improvement, sustained remission (defined as remission at week 66 among patients in remission at week 14), endoscopic remission, and histological remission. Additional secondary efficacy endpoints were clinical remission (defined as MCS ≤2 with individual subscores ≤1) at weeks 14 and 66, corticosteroid-free clinical remission at week 66, sustained clinical remission (defined as clinical remission at both weeks 14 and 66), change from baseline to weeks 14 and 66 in ulcerative colitis bowel movement signs and symptoms (as assessed by the Ulcerative Colitis Patient Reported Outcomes/Signs and Symptoms [UC-PRO/SS]),[15] change from baseline to weeks 14 and 66 in ulcerative colitis functional symptoms (as assessed by the UC-PRO/SS), and the change from baseline in patient-reported health-related quality of life at weeks 14 and 66 (assessed via the Inflammatory Bowel Disease Questionnaire). Change from baseline in faecal calprotectin level was also included as an exploratory endpoint. Safety endpoints included the incidence and severity of adverse events, serious adverse events, injection site reactions, laboratory abnormalities, and hypersensitivity reactions.

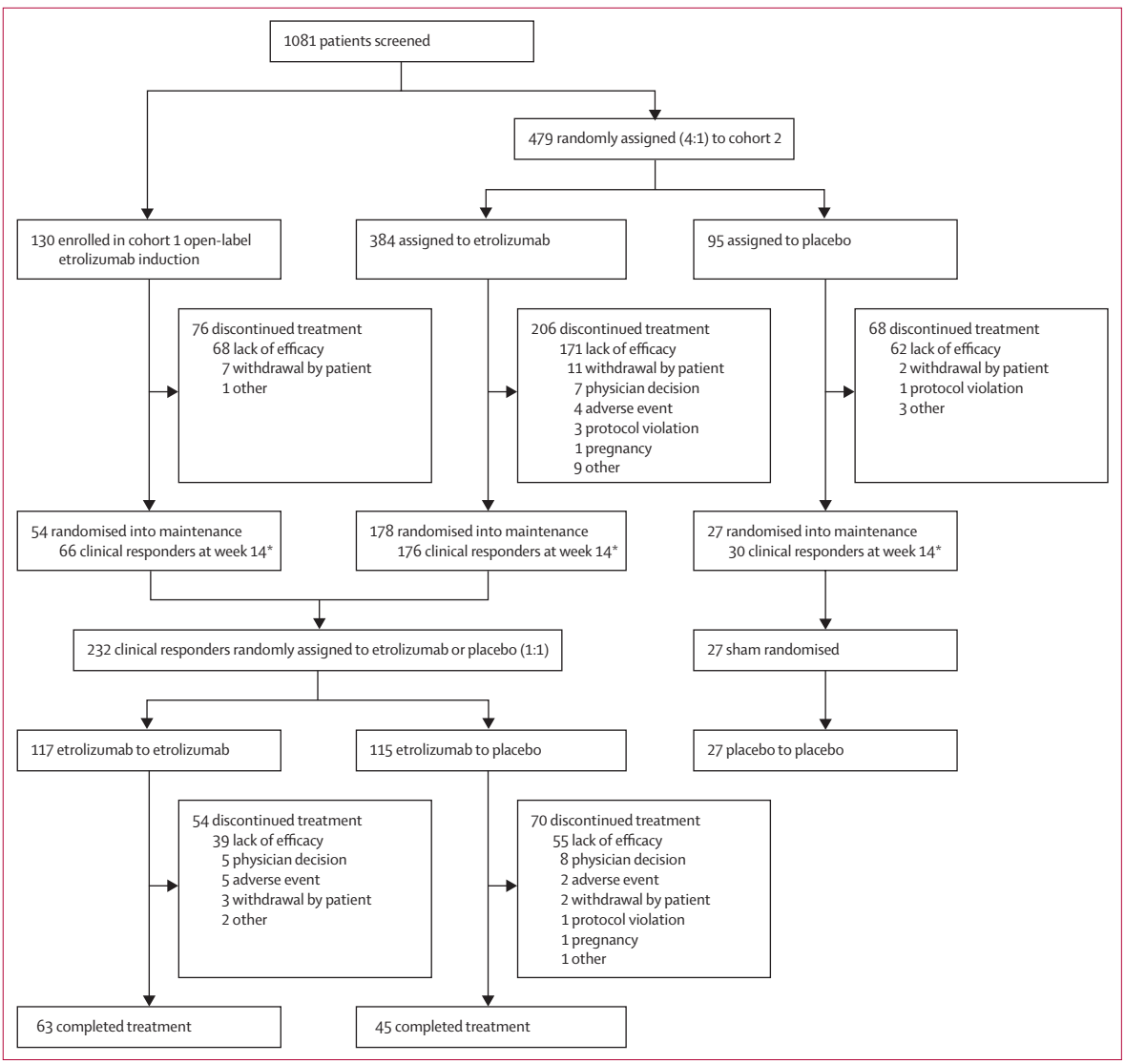

Figure 1: **Patient disposition**
Patients who completed the induction phase either entered maintenance or completed 12 weeks of safety follow-up or rolled into the open-label extension. Patients who completed treatment received all doses of study treatment specified by the protocol. *Not all patients who achieved clinical response during induction went on to enter maintenance due to differences in the assessment of clinical response during study conduct and final analysis.

Additional endpoints are defined in the full protocol available in the appendix (pp 71–73).

Statistical analysis

The planned sample size was 605 patients (open-label induction group, cohort 1, n=130; blinded induction cohort, cohort 2, n=475). Cohort 2 was estimated to provide approximately 80% power to detect a 10% absolute difference between treatment groups for the primary induction endpoint, under the assumption of a week 14 remission rate for placebo of 5% or less and a two-sided χ^2 at the 5% significance level. It was estimated that approximately 154 etrolizumab-treated patients would be randomly assigned in the maintenance phase based on a clinical response rate of 30% or more.[16] This sample size was estimated to provide more than 90% power to detect a 30% absolute difference in remission rates for the primary maintenance endpoint, under the assumption of a week 66 remission rate for placebo of 10% or less and a Fisher exact test at the 5% significance level. For the purpose of statistical analyses and sample size calculations, the induction and maintenance phases were treated as two independent studies; as such, no adjustment to α was required. Statistical hypotheses for the primary and key secondary endpoints were tested with a multistage gatekeeping procedure using truncated Holm[17] to ensure an overall type I error of 5% or less, with the primary endpoint

	Induction (cohort 2)		Maintenance	
	Placebo (n=95)	Etrolizumab (n=384)	Etrolizumab to placebo (n=115)	Etrolizumab to etrolizumab (n=117)
Age*, years	36·0 (18–76)	39·0 (18–76)	42·0 (18–74)	38·0 (18–75)
Sex				
Female	41 (43%)	160 (42%)	43 (37%)	57 (49%)
Male	54 (57%)	224 (58%)	72 (63%)	60 (51%)
Body-mass index*, kg/m²	24·4 (15·5–46·2)	24·3 (14·3–62·1)	24·6 (16·1–37·3)	25·1 (16·1–62·1)
Duration of disease*, years	7·36 (0·8–40·9)	7·10 (0·6–44·0)	7·85 (0·7–40·9)	7·19 (0·9–44·0)
Mayo Clinic total score category†				
MCS ≤9	54 (57%)	217 (57%)	68 (59%)	67 (57%)
MCS ≥10	41 (43%)	167 (44%)	47 (41%)	50 (43%)
Corticosteroid use at baseline†				
No	50 (53%)	202 (53%)	59 (51%)	62 (53%)
Yes	45 (47%)	182 (47%)	56 (49%)	55 (47%)
Immunosuppressant use at baseline†				
No	68 (72%)	272 (71%)	86 (75%)	83 (71%)
Yes	27 (28%)	112 (29%)	29 (25%)	34 (29%)
Mayo Clinic total score	9·02 (1·51)	8·95 (1·61)	8·90 (1·67)	8·75 (1·58)
Nancy histological index	2·82 (1·12)	2·75 (1·25)	2·73 (1·26)	2·70 (1·14)
Faecal calprotectin, µg/g	1634·0 (632·0–2984·0)	1675·5 (670·0–3881·5)	1597·0 (790·0–3439·0)	1431·0 (606·0–2825·0)
C-reactive protein, mg/L	6·40 (1·30–13·10)	4·93 (1·78–12·80)	4·38 (1·46–11·30)	3·9 (1·51–9·22)
Number of previous anti-TNFs received				
1	70 (74%)	229 (60%)	70 (61%)	73 (62%)
2	23 (24%)	136 (35%)	40 (35%)	40 (34%)
3	1 (1%)	11 (3%)	2 (2%)	2 (2%)
Unknown	1 (1%)	8 (2%)	3 (3%)	2 (2%)
Disease location, n (%)				
Left-sided colitis	47 (50%)	197/383 (51%)	56 (49%)	63/116 (54%)
Extensive colitis	13 (14%)	53/383 (14%)	15 (13%)	16/116 (14%)
Pancolitis	35 (37%)	133/383 (35%)	44 (38%)	37/116 (32%)
Baseline treatment				
5-aminosalicylate use	52 (55%)	232 (60%)	68 (59%)	69 (59%)
No corticosteroid or immunosuppressant	34 (36%)	134 (35%)	43 (37%)	42 (36%)
Corticosteroid, no immunosuppressant	35 (37%)	138 (36%)	43 (37%)	41 (35%)
Immunosuppressant, no corticosteroid	17 (18%)	68 (18%)	16 (14%)	20 (17%)
Corticosteroid and immunosuppressant	9 (10%)	44 (11%)	13 (11%)	14 (12%)

(Table 1 continues on next page)

tested first at a two-sided significance of a p value of less than 0·05. Formal testing of the key secondary endpoints continued if the primary endpoint was met. The key secondary endpoints were assigned into one of three families based on clinical importance, before unblinding. Hierarchal testing began with family 1, and at least one endpoint in each family must have been considered statistically significant after multiplicity adjustment to continue testing in subsequent families. Additional details are available in the appendix (pp 2, 219–224). The primary endpoint was compared between the etrolizumab and placebo groups using the Cochran-Mantel-Haenszel test statistic for both induction and maintenance endpoints. Each endpoint tested the null hypothesis that the proportion of patients achieving the primary endpoint was the same in each group and was adjusted for induction stratification factors (MCS [≤9 *vs* ≥10], corticosteroid use [yes *vs* no], and immunosuppressant use [yes *vs* no]) or maintenance stratification factors (MCS [≤9 *vs* ≥10], corticosteroid use [yes *vs* no], and cohort [cohort 1 *vs* cohort 2]). A strata-adjusted proportion difference was obtained by weighted average of stratum-specific proportion differences.[18]

Efficacy was analysed using a modified intent-to-treat (mITT) population, defined as all randomly assigned patients who received at least one dose of study drug.

	Induction (cohort 2)		Maintenance	
	Placebo (n=95)	Etrolizumab (n=384)	Etrolizumab to placebo (n=115)	Etrolizumab to etrolizumab (n=117)
(Continued from previous page)				
Previous failure on anti-TNF therapy				
No failures	0	2 (<1%)	1 (1%)	0
One failure	71 (75%)	233 (61%)	71 (62%)	77 (66%)
Two or more failures	23 (24%)	141 (37%)	40 (35%)	38 (32%)
Unknown	1 (1%)	8 (2%)	3 (3%)	2 (2%)
Refractory or intolerant to anti-TNF therapy‡				
Refractory or loss of response	90 (95%)	356 (93%)	104 (90%)	109 (93%)
Intolerant only	4 (4%)	18 (5%)	7 (6%)	6 (5%)
Response to anti-TNF therapy‡				
Loss of response	58 (61%)	264 (69%)	78 (68%)	79 (68%)
No loss of response§	36 (38%)	112 (29%)	34 (30%)	36 (31%)

Data are median (range), n (%), mean (SD), median (IQR), or n/N (%). For both the induction and maintenance populations, baseline is defined as the last available assessment before first treatment of study drug in the induction phase. MCS=Mayo Clinic total score. TNF=tumour necrosis factor. *Median (range). †Stratification factors at induction were MCS (≤9 *vs* ≥10), corticosteroid use (yes *vs* no), and immunosuppressant use (yes *vs* no). Stratification factors at maintenance were MCS (≤9 *vs* ≥10), corticosteroid use (yes *vs* no), and cohort (cohort 1 *vs* cohort 2). ‡Patients with no TNF failures or unknown failure status are not included. §Includes patients who responded and did not lose response, or never responded, to anti-TNFs.

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

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 (considered rescue therapy) were deemed non-responders. Safety analyses included all patients who received at least one dose of study drug. Histological outcomes were evaluated in all patients in the open-label and double-blind induction phases for whom a baseline histology sample was available and who showed neutrophilic inflammation (NHI >1) at baseline. This study is registered at ClinicalTrials.gov, NCT02100696.

Role of the funding source

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

Results

HICKORY was conducted from May 21, 2014, to April 16, 2020. 1081 patients were screened, with 609 deemed eligible for inclusion (figure 1). In the induction phase, 130 patients were enrolled into cohort 1 to receive etrolizumab at 105 mg, and 479 patients were enrolled in cohort 2 and randomly assigned to receive etrolizumab (n=384) or placebo (n=95). Most patients (563 [92%] of 609) completed the induction period (cohorts 1 and 2). The maintenance phase included 259 patients. 232 patients who achieved clinical response to etrolizumab induction were enrolled and randomly assigned to receive etrolizumab (n=117) or placebo (n=115), and 27 patients who received placebo during the induction phase and achieved a clinical response at week 14 continued to receive placebo. In both the induction and maintenance phases, the most common reason for treatment discontinuation was lack of efficacy (induction 301 [49%] of 609; maintenance 103 [40%] of 259). 112 patients in the etrolizumab group and 106 in the placebo group either rolled over into the open-label extension or completed 12 weeks of safety follow-up after treatment completion or treatment discontinuation.

Baseline characteristics were generally balanced across treatment groups in both the induction and maintenance phases (table 1). In the induction phase, the median duration of disease for all patients was 7·1 years (range 0·6–44·0), and the mean MCS at baseline was 9·03 (SD 1·54). In the maintenance phase, the median duration of disease for all patients was 7·7 years (range 0·7–44·0), and the mean MCS at baseline was 8·78 (SD 1·60). In the induction population at baseline, of 479 patients, 173 (36%) patients were receiving corticosteroids without immunosuppressants, 85 (18%) were receiving immunosuppressants without corticosteroids, and 53 (11%) were receiving both corticosteroids and immunosuppressants; similar proportions were observed in the maintenance population. On entering maintenance, approximately 45% of patients in each treatment group were on corticosteroids; however, this reduced over time. By week 28, less than 10% of patients in each treatment group were on corticosteroids, and the number of patients on corticosteroids remained less than 10% until the end of maintenance in both treatment groups.

Overall, two or more previous anti-TNF treatment failures were reported in 23 (24%) of 95 patients treated with placebo versus 141 (37%) of 384 patients treated with etrolizumab in the induction cohort 2. In the maintenance population, 40 (35%) of 115 patients who switched from etrolizumab to placebo and 38 (32%) of 117 patients who continued etrolizumab reported two or more previous anti-TNF treatment failures.

In the induction mITT population, 71 (18·5%) of 384 patients in the etrolizumab group and six (6·3%) of 95 in the placebo group achieved the primary induction endpoint of remission at week 14 (adjusted treatment difference 12·2%, 95% CI 4·0 to 17·7; p=0·0033; figure 2). In the maintenance mITT population, 27 (24·1%) of 112 patients in the etrolizumab group and 23 (20·2%) of 114 in the placebo group achieved the primary maintenance endpoint of remission at week 66 in patients with a response at week 14 (adjusted treatment difference 3·8%, 95% CI –7·1 to 14·6; p=0·50; figure 2). Subgroup analysis did not identify any one group of patients who appeared to perform better with regard to the primary endpoint; however, some subgroup analyses were limited by the sample size. Eight patients (three from the etrolizumab to placebo group and five from the etrolizumab to etrolizumab group) remained on corticosteroids at the end of the maintenance period and were included in the assessment of the primary endpoint. No relationship was observed between reaching the primary endpoint and corticosteroid use or corticosteroid dose. Additional subgroup analyses will be published at a later date.

At week 14, a significantly greater proportion of patients in the etrolizumab group had a clinical response, compared with the placebo group (176 [46%] of 384 *vs* 30 [32%] of 95; p=0·024; figure 3). No significant differences were observed between etrolizumab and placebo for endoscopic improvement (128 [33%] of 384 *vs* 24 [25%] of 95; p=0·16), endoscopic remission (66 [17%] of 384 *vs* nine [9%] of 95; p=0·39), or histological remission (92 [30%] of 310 *vs* 20 [25%] of 80; p=0·59) at week 14. The mean change from baseline to week 6 in rectal bleeding subscore was significantly greater with etrolizumab (–0·7) versus placebo (–0·4; p=0·035; appendix p 3). No significant difference was observed between etrolizumab and placebo for the mean change in stool frequency subscore from baseline (–0·6) to week 6 (–0·5; p=0·27).

Because the primary maintenance endpoint was not met, secondary maintenance endpoints were not formally compared as per the conditions of the prespecified hierarchical testing, and all nominal p values reported for these comparisons should be considered exploratory. A nominally statistically significantly greater proportion of patients treated with etrolizumab had endoscopic improvement at week 66 compared with those treated with placebo (40 [36%] of 112 *vs* 24 [21%] of 114; p=0·015; figure 4). Differences in histological remission were also nominally significantly greater in the etrolizumab group than in the placebo group (28 [31%] of 91 *vs* 13 [14%] of 92; p=0·0073) as were results for endoscopic remission (26 [23%] of 112 *vs* 13 [11%] of 114; p=0·017) at week 66. Among patients receiving corticosteroids at baseline, a higher proportion of

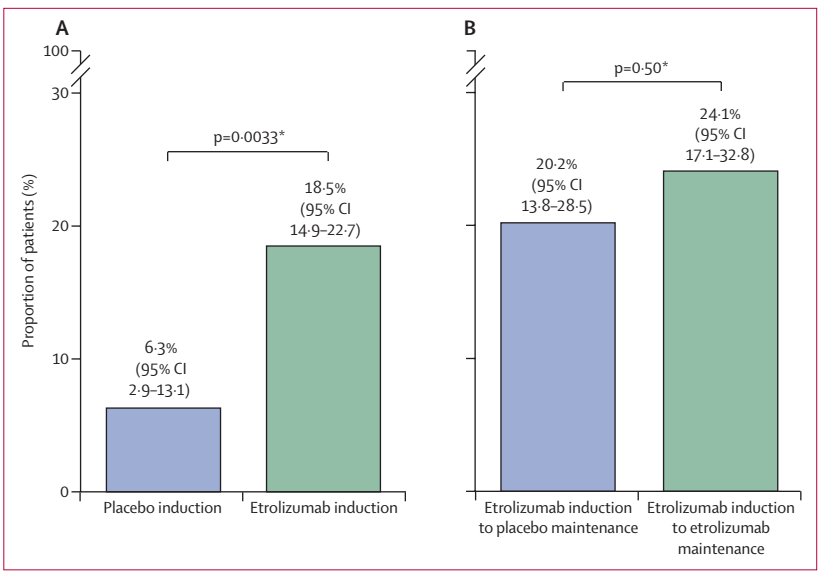

Figure 2: **Patients with moderately to severely active ulcerative colitis achieving remission at week 14 (A) and week 66 (B), among patients with a clinical response at week 14**
Remission was defined as an MCS of no more than 2, with individual subscores of no more than 1, and a rectal bleeding subscore of 0. Clinical response was defined as an MCS with a decrease of 3 points or more and a reduction of 30% or more, plus a decrease in rectal bleeding subscore of 1 or more or absolute rectal bleeding score of 0 or 1. 95% CIs were constructed using the Wilson method. MCS=Mayo Clinic total score. *p value was constructed using the Cochran-Mantel-Haenszel method adjusting for stratification factors.

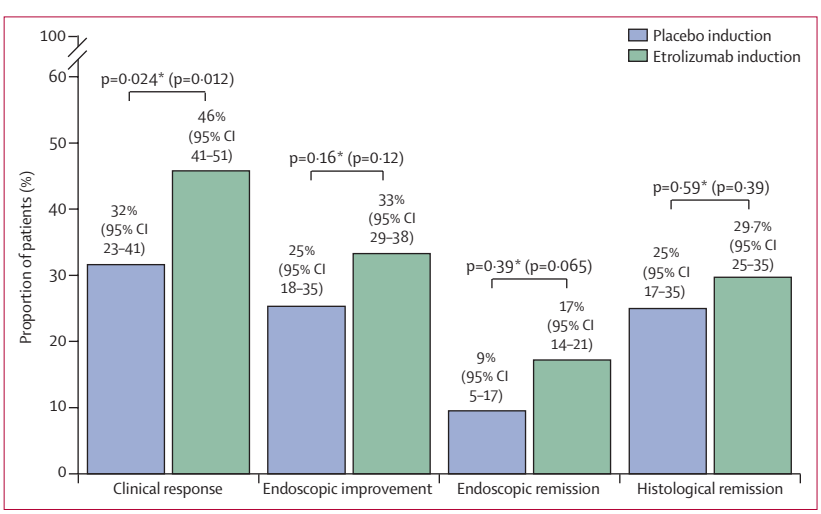

Figure 3: **Patients with moderately to severely active ulcerative colitis achieving secondary endpoints at week 14**
Clinical response was defined as an MCS with a decrease of 3 points or more and a reduction of 30% or more, plus a decrease in rectal bleeding subscore of 1 or more or absolute rectal bleeding score of 0 or 1. Endoscopic improvement was defined as a Mayo endoscopic subscore of no more than 1. Endoscopic remission was defined as a Mayo endoscopic subscore of 0. Histological remission was defined as an NHI of no more than 1 among patients with baseline histological inflammation. 95% CIs were constructed using the Wilson method. MCS=Mayo Clinic total score. NHI=Nancy histological index. *p values are based on analysis adjusting for stratification factors and control for type I error. Nominal p values not adjusted for type I error are included in brackets.

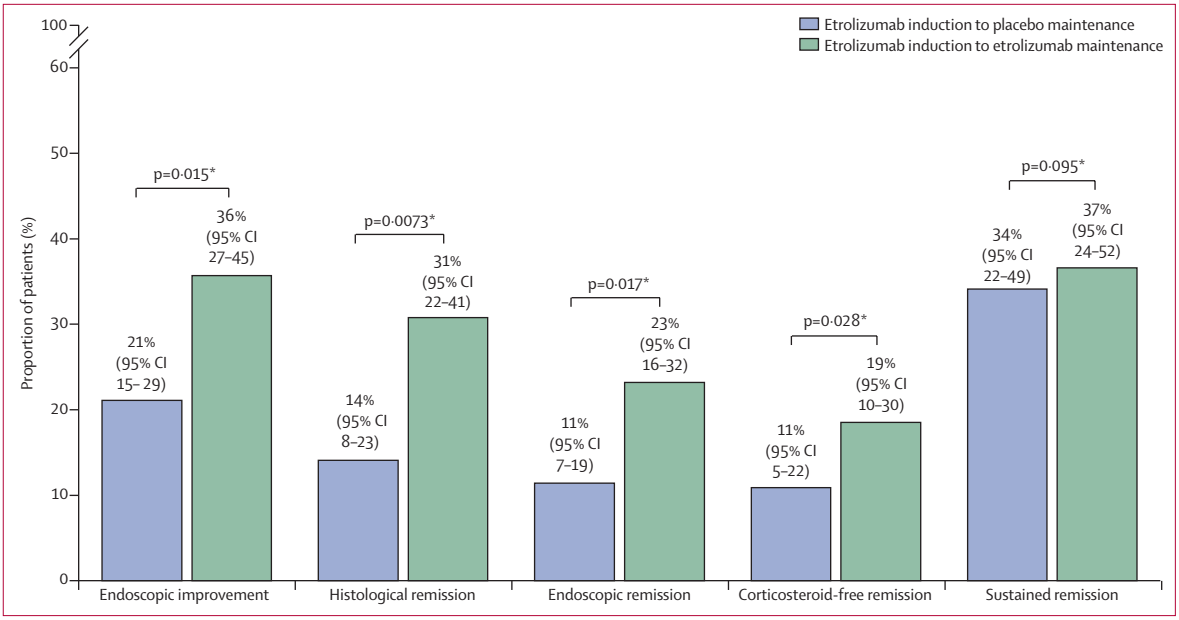

Figure 4: **Patients with moderately to severely active ulcerative colitis achieving secondary endpoints at week 66**
Endoscopic improvement was defined as a Mayo endoscopic subscore of no more than 1. Histological remission was defined as an NHI of no more than 1 in patients with baseline histological inflammation. Endoscopic remission was defined as a Mayo endoscopic subscore of 0. Corticosteroid-free remission was defined as remission (MCS of ≤2, with individual subscores of ≤1 and rectal bleeding subscore of 0) with no corticosteroid use for 24 weeks before week 66 among patients receiving corticosteroid at baseline. Sustained remission was defined as remission at week 66 among patients in remission at week 14. 95% CIs were constructed using the Wilson method. MCS=Mayo Clinic total score. NHI=Nancy histological index. *Nominal p values are based on analysis adjusting for stratification factors.

patients treated with etrolizumab versus placebo achieved corticosteroid-free remission at week 66 (defined as no corticosteroid use for at least 24 weeks before week 66), although this difference was not significant (ten [19%] of 54 versus six [11%] of 55; p=0·28). Finally, similar proportions of patients achieved sustained remission between the etrolizumab and placebo groups (15 [37%] of 41 *vs* 15 [34%] of 44; p=0·95). Results of additional secondary endpoints are included in the appendix (pp 6–7). In the maintenance population, six patients in the placebo group and 14 in the etrolizumab group had shifts from high to normal in faecal calprotectin (appendix p 8).

Among patients receiving etrolizumab for induction and maintenance, serum etrolizumab concentrations gradually increased from the induction phase to the maintenance phase. In these patients, the mean etrolizumab concentrations (2 weeks after administration) were 14·0 µg/mL (SD 6·12) at week 14 and 16·2 µg/mL (7·75) at week 66 (appendix p 4), more than ten times higher than the target exposure (1·3 µg/mL) associated with 90% peripheral β7 receptor occupancy.[19] Mean trough concentrations were 4·35 µg/mL (SD 2·41) at week 4, 9·55 µg/mL (5·24) at week 24, and 10·7 µg/mL (5·72) at week 44. The trough concentration during maintenance was more than seven times higher than the target exposure. For patients receiving etrolizumab for induction and placebo for maintenance, the mean concentration of etrolizumab decreased after week 14 and no measurable serum etrolizumab was observed after week 24.

Based on the total number of evaluable patients, the overall post-treatment incidence of anti-drug antibodies was 28 (25%) of 112 patients who received etrolizumab during both the induction and maintenance phases; six (5%) of 110 of these patients tested positive for anti-drug antibodies at baseline. Among patients who received etrolizumab during the induction phase and were subsequently randomly assigned to the placebo group, the post-treatment incidence of anti-drug antibodies was 35 (31%) of 114 patients; two (2%) of these 114 patients tested positive at baseline. There was no obvious impact of anti-drug antibodies on pharmacokinetic outcomes. The median concentrations of etrolizumab in anti-drug antibody-positive patients in the etrolizumab group were similar to those in anti-drug antibody-negative patients (appendix p 5).

Similar incidences of adverse events were reported between the etrolizumab and placebo groups, with most adverse events considered mild to moderate in severity in both study phases (table 2). In the induction phase, 253 (66%) of 384 patients in the etrolizumab group and 63 (66%) of 95 patients in the placebo group experienced one or more adverse event. In the maintenance phase, 98 (88%) of 112 patients in the etrolizumab group and 97 (85%) of 114 patients in the placebo group experienced at least one adverse event. Ulcerative colitis flares were the most common adverse event leading to treatment discontinuation in all groups, with similar incidence in patients receiving etrolizumab for induction and maintenance (seven [6%] of 112) and patients receiving

etrolizumab for induction and placebo for maintenance (nine [8%] of 114). The most frequently reported adverse events across both study groups and phases were ulcerative colitis flare, nasopharyngitis, abdominal pain, arthralgia, and headache. During the maintenance phase, a higher proportion of patients in the etrolizumab treatment group reported infections (58 [52%] of 112 for etrolizumab *vs* 44 [39%] of 114 for placebo); nasopharyngitis was the most frequently reported infection in all treatment groups.

In the induction phase, similar proportions of etrolizumab-treated and placebo-treated patients experienced serious adverse events; serious infections occurred with a similar frequency in both groups (five [1%] of 384 *vs* one [1%] of 95). In the maintenance phase, serious adverse events were slightly more common in patients receiving etrolizumab for induction and maintenance (11 [10%] of 112) than patients receiving etrolizumab for induction and placebo for maintenance (seven [6%] of 114); serious infections occurred with a similar frequency in both groups (etrolizumab to etrolizumab three [3%] of 112 *vs* etrolizumab to placebo three [3%] of 114). During induction, the most common serious adverse event was ulcerative colitis flare (etrolizumab ten [3%] of 384; placebo: two [2%] of 95). During maintenance, the most common serious adverse event in the etrolizumab to etrolizumab group was appendicitis (two [2%] of 112) and the most common serious adverse events in the etrolizumab to placebo group were ulcerative colitis flare (two [2%] of 114) and anaemia (two [2%] of 114). No deaths occurred during the study, and no cases of progressive multifocal leukoencephalopathy were reported.

	Induction (cohort 2)		Maintenance	
	Placebo (n=95)	Etrolizumab (n=384)	Etrolizumab to placebo (n=114)	Etrolizumab to etrolizumab (n=112)
Any adverse event	63 (66%)	253 (66%)	97 (85%)	98 (88%)
Any serious adverse event	5 (5%)	20 (5%)	7 (6%)	11 (10%)
One or more adverse event leading to treatment discontinuation	1 (1%)	12 (3%)	9 (8%)	10 (9%)
Infections	29 (31%)	100 (26%)	44 (39%)	58 (52%)
Serious infections	1 (1%)	5 (1%)	3 (3%)	3 (3%)
Deaths	0	0	0	0
Progressive multifocal leukoencephalopathy	0	0	0	0
Adverse events occurring in at least 5% of etrolizumab-treated patients				
Ulcerative colitis	12 (13%)	46 (12%)	48 (42%)	32 (29%)
Nasopharyngitis	7 (7%)	33 (9%)	17 (15%)	23 (21%)
Arthralgia	7 (7%)	33 (9%)	8 (7%)	19 (17%)
Abdominal pain	2 (2%)	13 (3%)	7 (6%)	10 (9%)
Headache	6 (6%)	22 (6%)	10 (9%)	10 (9%)
Injection site reactions	5 (5%)	4 (1%)	2 (2%)	8 (7%)
Rash	2 (2%)	7 (2%)	2 (2%)	8 (7%)
Diarrhoea	2 (2%)	10 (3%)	5 (4%)	6 (5%)
Hypertension	0	5 (1%)	2 (2%)	6 (5%)
Insomnia	1 (1%)	7 (2%)	2 (2%)	6 (5%)

Data are n (%). n represents individual patients, not individual events.

Table 2: **Adverse events (safety population)**

Discussion

The etrolizumab phase 3 ulcerative colitis study programme enrolled more than 2000 patients worldwide and consisted of five randomised studies with three head-to-head studies. In the present study, etrolizumab increased the proportion of patients in remission at week 14 compared with placebo, but did not improve the proportion of patients in remission at week 66 among clinical responders to etrolizumab at week 14. Etrolizumab treatment was generally well tolerated over 52 weeks, with a safety profile consistent with that previously reported for etrolizumab.[11] No new or unexpected safety signals occurred, and most adverse events were non-serious and low grade.

Endoscopic and histological examination of the colonic mucosa are reliable techniques to determine objective signs of inflammation in patients with ulcerative colitis and support claims of mucosal healing.[20] Objective measures such as these might serve as useful tools to evaluate efficacy signals in ulcerative colitis trials. In this study, the proportion of patients treated with etrolizumab who showed improvement in endoscopic appearance, endoscopic remission, and histological remission at the end of the study (week 66) was nominally statistically significantly higher than for those treated with placebo. The change from baseline to week 6 in rectal bleeding score was also significantly greater with etrolizumab versus placebo, further indicating early onset of treatment benefit with etrolizumab in this patient population.

Several factors might have influenced the results of this study. First, HICKORY was designed to provide more than 90% power to detect a 30% difference in remission rates between treatment groups for the primary endpoint at week 66 at a 5% significance level. However, this design assumed a remission rate of no more than 10% in the placebo group, which was much lower than the 20·2% observed during the study. In addition, the assumption of a 30% difference in maintenance remission rates in anti-TNF-experienced patients was high.

Second, the 105 mg dose of etrolizumab was chosen for this study based on results from the phase 2 EUCALYPTUS study, in which two dosing regimens were tested (a nominal 100 mg subcutaneous dose every 4 weeks [actual dose of 105 mg and a nominal 300 mg subcutaneous dose every 4 weeks following a loading dose [actual dose 315 mg]).[11] In that study, both doses were sufficient to maintain β7 receptor occupancy in both blood and colonic tissue during the entire 10-week dosing period. No apparent difference in the exposure–

response relationship was observed within approximately a four-times exposure range. However, the limited sample size from this phase 2 study (81 etrolizumab-treated patients with two-thirds from a TNF-experienced population) might have impacted assessment of the exposure–response relationship.

Pharmacokinetic analyses from this study confirmed that etrolizumab reached expected drug exposure in the systemic circulation; however, tissue-specific concentrations were not assessed. Initial examination of the exposure–response relationship in the phase 3 etrolizumab studies suggests that higher etrolizumab exposure in the early treatment phase during induction appears to be associated with improved clinical outcomes. However, the association between disease risk factors and exposure might result in overestimation of the exposure–response relationship, especially because only a single dose was tested in the phase 3 studies. Measures of etrolizumab exposure in this study confirmed that serum trough concentrations were at least seven times higher than needed to reach at least 90% β7 receptor occupancy; however, this study and other studies suggest that increasing the dose beyond full receptor occupancy in the peripheral circulation might provide additional benefit in this class of anti-integrin therapies.[21,22]

Third, the overall anti-drug antibody incidence rate observed in this study (25%) was higher than that observed during the phase 1 and 2 studies of etrolizumab (approximately 5%).[11,23] It is difficult to make direct comparisons of anti-drug antibody results between phase 3 and earlier studies as the patient population sizes and study designs were vastly different, and a different drug-tolerant assay was used in this study. The phase 3 clinical trials of etrolizumab used an ELISA with a relative sensitivity of 15·7 ng/mL, with drug tolerance established using 28 ng/mL of positive control monoclonal antibody in the presence of 50 µg/mL of etrolizumab. The electrochemiluminescent anti-drug antibody assay used in the phase 1 and 2 trials had a relative sensitivity of 29 ng/mL with a drug tolerance established using 500 ng/mL of positive control polyclonal antibody in the presence of 100 µg/mL etrolizumab. Nevertheless, a robust evaluation of the potential effect of anti-drug antibody response on etrolizumab exposure levels showed minimal impact both by between-patient and within-patient assessment (data not shown). Although we did not see any obvious correlation between etrolizumab anti-drug antibodies and pharmacokinetic measures in this study, subtle effects of anti-drug antibodies on efficacy or safety outcomes cannot be ruled out.

In conclusion, the HICKORY trial showed that etrolizumab was effective for induction of remission in anti-TNF-experienced patients. Although etrolizumab did not improve remission rates relative to placebo during the maintenance phase, objective evaluation of intestinal inflammation by endoscopy and histology suggests that etrolizumab has an objective anti-inflammatory effect as maintenance therapy. Etrolizumab also failed to meet its primary endpoint in LAUREL, a randomized, placebo-controlled, phase 3, maintenance study in patients naive to anti-TNFs.[24] Etrolizumab also did not meet its primary endpoint of superiority to infliximab in the randomised, phase 3 study GARDENIA.[25] Etrolizumab met the primary endpoint of induction of remission at week 10 versus placebo in one of the two HIBISCUS studies.[26] Data from the phase 3 etrolizumab clinical trial programme in ulcerative colitis and ongoing open-label extension programme (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.

Contributors

LP-B was involved in conceptualisation, investigation, methodology, resources (assisted with patient recruitment), visualisation, and writing (review and editing). AH was involved in conceptualisation, investigation, methodology, resources (assisted with patient recruitment), validation, visualisation, and writing (review and editing). PB was involved in investigation, resources (assisted with patient recruitment), validation, visualisation, and writing (review and editing). ML, MA, PJ, AA, and EVLJr were involved in investigation, resources (assisted with patient recruitment), validation, visualisation, and writing (review and editing). EO-S, AS, and YSO were involved in data curation, investigation, methodology, project administration, supervision, validation, visualisation, and writing (review and editing). ST and AC were involved in investigation, methodology, project administration, supervision, validation, visualisation, and writing (review and editing). JP was involved in statistical methodology, data analysis, data interpretation, and writing (review and editing). SL was involved in formal analysis, investigation, methodology, project administration, supervision, validation, visualisation, and writing (review and editing). WJS was involved in conceptualisation, investigation, methodology, resources (assisted with patient recruitment), validation, visualisation, and writing (review and editing). KC-J, AS, and YSO verified the underlying data. All authors had access to the data in the study and accept responsibility to submit for publication. All authors have contributed significantly to the work and have reviewed and approved the final version of the manuscript.

Declaration of interests

LP-B reports personal fees from AbbVie, Allergan, Alma, Amgen, Applied Molecular Transport, Arena, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Celltrion, Enterome, Enthera, Ferring, Fresenius, Gilead, Hikma, InDex Pharmaceuticals, Janssen, Lilly, Merck Sharp & Dohme, Mylan, Nestle, Norgine, Oppilan, OSE Immunotherapeutics, Pfizer, Pharmacosmos, Roche/Genentech, Samsung Bioepis, Sandoz, Sterna, Tillotts, Sublimity, Takeda, and Vifor; consultation fees from Clinical Trials Mobile Application; and grants from AbbVie, Merck Sharp & Dohme, and Takeda outside the submitted work. AH reports personal fees from AbbVie, Arena, Celgene, Celltrion, Falk, Ferring, Janssen, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Roche/Genentech, and Takeda, outside the submitted work. PB reports personal fees from AbbVie, Amgen, Arena Pharmaceuticals, Bristol Myers Squibb, Hospira, Janssen, Merck Sharp & Dohme, Mundipharma, Pentax, Pfizer, PSI-CRO, Roche/Genentech, Sandoz, and Takeda; and grants from AbbVie, Amgen, Janssen, Mundipharma, Mylan, Pfizer, and Takeda, outside the submitted work. ML reports personal fees from AbbVie, Bristol Myers Squibb, Gilead, Lilly, Janssen, Pfizer, Prometheus, Roche/Genentech, Salix, Takeda, Target PharmaSolutions, UCB, Valeant; and grants from Pfizer and Takeda, outside the submitted work. MA reports personal fees as a speaker from Ferring, Janssen, Pfizer, Roche/Genentech, Takeda, and Tillotts; personal fees for advisory boards from Amgen, Bristol Meyers Squibb, Celltrion, Janssen, Novartis, Roche/Genentech, and Pfizer; and grants from Janssen and Roche/Genentech. PJ has no conflicts to disclose. AA reports personal fees from AbbVie,

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Data sharing

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 online (https://vivli.org/members/ourmembers/). Further details on Roche's Global Policy on the Sharing of Clinical Information and information on how to request access to related clinical study documents are available online (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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