Etrolizumab versus infliximab for the treatment of moderately to severely active ulcerative colitis (GARDENIA): a randomised, double-blind, double-dummy, phase 3 study

Silvio Danese, Jean-Frederic Colombel*, Milan Lukas, Javier P Gisbert, Geert D'Haens, Bu'hussain Hayee, Remo Panaccione, Hyun-Soo Kim, Walter Reinisch, Helen Tyrrell, Young S Oh, Swati Tole, Akiko Chai, Kirsten Chamberlain-James, Meina Tao Tang, Stefan Schreiber, on behalf of the GARDENIA Study Group†*

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*Contributed equally

†Members are listed in the appendix (pp 8–13)

Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milan, Italy (Prof S Danese MD); Icahn School of Medicine, Mount Sinai, New York City, NY, USA (Prof J-F Colombel MD); Clinical and Research Centre for Inflammatory Bowel Diseases, ISCARE IVF Clinical Center Českomoravská, Prague, Czech Republic (Prof M Lukas, MD); Gastroenterology Unit, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa, Universidad Autónoma de Madrid and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Madrid, Spain (Prof J P Gisbert MD); Department of Gastroenterology, Imelda Hospital, Amsterdam University Medical Center, Amsterdam, Netherlands (Prof G D'Haens MD); King's College Hospital Denmark Hill London, London, UK (B Hayee PhD); University of Calgary, Calgary, AB, Canada (Prof R Panaccione MD); Department of Internal Medicine 20, Yonsei University, Wonju, South Korea (Prof H-S Kim MD); Medical University of Vienna, Vienna, Austria (W Reinisch MD); Roche, Welwyn Garden City, UK (H Tyrrell BSc, K Chamberlain-James MSc);

Summary

Background Etrolizumab is a gut-targeted anti-β7 integrin monoclonal antibody. In a previous phase 2 induction study, etrolizumab significantly improved clinical remission versus placebo in patients with moderately to severely active ulcerative colitis. We aimed to compare the safety and efficacy of etrolizumab with infliximab in patients with moderately to severely active ulcerative colitis.

Methods We conducted a randomised, double-blind, double-dummy, parallel-group, phase 3 study (GARDENIA) across 114 treatment centres worldwide. We included adults (age 18–80 years) 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) who were naive to tumour necrosis factor inhibitors. Patients were required to have had 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. Participants were randomly assigned (1:1) to receive subcutaneous etrolizumab 105 mg once every 4 weeks or intravenous infliximab 5 mg/kg at 0, 2, and 6 weeks and every 8 weeks thereafter for 52 weeks. Randomisation was stratified by baseline concomitant treatment with corticosteroids, concomitant treatment with immunosuppressants, and baseline disease activity. All participants and study site personnel were masked to treatment assignment. The primary endpoint was the proportion of patients who had both clinical response at week 10 (MCS ≥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) and clinical remission at week 54 (MCS ≤2, with individual subscores ≤1); efficacy was analysed using a modified intention-to-treat population (all randomised patients who received at least one dose of study drug). GARDENIA was designed to show superiority of etrolizumab over infliximab for the primary endpoint. This trial is registered with ClinicalTrials.gov, NCT02136069, and is now closed to recruitment.

Findings Between Dec 24, 2014, and June 23, 2020, 730 patients were screened for eligibility and 397 were enrolled and randomly assigned to etrolizumab (n=199) or infliximab (n=198). 95 (48%) patients in the etrolizumab group and 103 (52%) in the infliximab group completed the study through week 54. At week 54, 37 (18·6%) of 199 patients in the etrolizumab group and 39 (19·7%) of 198 in the infliximab group met the primary endpoint (adjusted treatment difference –0·9% [95% CI –8·7 to 6·8]; p=0·81). The number of patients reporting one or more adverse events was similar between treatment groups (154 [77%] of 199 in the etrolizumab group and 151 [76%] of 198 in the infliximab group); the most common adverse event in both groups was ulcerative colitis (55 [28%] patients in the etrolizumab group and 43 [22%] in the infliximab group). More patients in the etrolizumab group reported serious adverse events (including serious infections) than did those in the infliximab group (32 [16%] *vs* 20 [10%]); the most common serious adverse event was ulcerative colitis (12 [6%] and 11 [6%]). There was one death during follow-up, in the infliximab group due to a pulmonary embolism, which was not considered to be related to study treatment.

Interpretation To our knowledge, this trial is the first phase 3 maintenance study in moderately to severely active ulcerative colitis to use infliximab as an active comparator. Although the study did not show statistical superiority for the primary endpoint, etrolizumab performed similarly to infliximab from a clinical viewpoint.

Funding F Hoffmann-La Roche.

Introduction

Ulcerative colitis is a chronic relapsing-remitting inflammation of the bowel with long-term adverse effects on patient quality of life.[1–4] Current treatments for moderately to severely active ulcerative colitis include corticosteroids, immunosuppressants, and targeted therapies, including tumour necrosis factor (TNF) inhibitors, vedolizumab, ustekinumab, and

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 we included trials 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 who were admitted to hospital were excluded). We found that etrolizumab was one of 19 therapies that have entered or completed phase 2 and phase 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. In this Article we report the results from GARDENIA, a randomised head-to-head study comparing etrolizumab with infliximab in patients with moderately to severely active ulcerative colitis who had not previously received tumour necrosis factor inhibitors. Etrolizumab did not show superiority to infliximab. A similar proportion of patients in each group had both a clinical response at week 10 and clinical remission at week 54 after randomisation. Broadly similar proportions were also seen for several secondary clinical and endoscopic endpoints. No unexpected safety signals were identified.

Implications of all the available evidence

Gut-targeted therapies, such as etrolizumab, have the potential to effectively mitigate inflammatory bowel disease 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 mixed, 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).

Genentech, South San Francisco, CA, USA (Y S Oh MD, S Tole MD, A Chai MS, M T Tang PhD); **Christian-Albrechts University, Kiel, Germany** (Prof S Schreiber MD)

Correspondence to: Prof Stefan Schreiber, Christian-Albrechts University, Kiel 24105, Germany
s.schreiber@mucosa.de

See **Online** for appendix

tofacitinib. Despite these treatment options, a large proportion of patients do not maintain a durable response to therapy.[4–6]

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. By contrast with 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 previous phase 2 study, the etrolizumab induction regimen was well tolerated and provided significantly higher rates of clinical remission than placebo in patients with moderately to severely active ulcerative colitis.[11]

Head-to-head trials are the gold standard in treatment comparisons and have the potential to guide treatment decisions and position therapies within treatment algorithms.[12,13] However, only one study has directly compared the efficacy and safety of biological therapies for ulcerative colitis. The first head-to-head study of biological therapies in ulcerative colitis (VARSITY) compared an anti-integrin therapy (vedolizumab) with an anti-TNF therapy (adalimumab) in patients with ulcerative colitis.[14] GARDENIA, reported here, is the second head-to-head study directly comparing biological therapies in ulcerative colitis, and it is the first study to use infliximab (a standard of care in moderately to severely active ulcerative colitis) as the primary comparator. Etrolizumab was compared with adalimumab in the identical phase 3 induction studies HIBISCUS I and HIBISCUS II, reported by Rubin and colleagues.[15] HIBISCUS I achieved the primary endpoint of superiority of etrolizumab over placebo for remission at week 10, and HIBISCUS II did not. Etrolizumab was not shown to be superior to adalimumab; however, similar numerical results were observed in both groups for several clinical and endoscopic endpoints at week 10.

The etrolizumab ulcerative colitis study programme consisted of five studies, including the three head-to-head studies, assessing the safety and efficacy of etrolizumab in patients with moderately to severely active ulcerative colitis. In this study, we aimed to compare the safety and efficacy of etrolizumab with infliximab in anti-TNF-naive patients with moderately to severely active ulcerative colitis.

Methods

Study design

We conducted a randomised, double-blind, double-dummy, parallel-group, head-to-head, phase 3 study

(GARDENIA) across 114 treatment centres in 19 countries worldwide. This study consisted of a double-blind treatment period of 54 weeks (induction phase up to week 10; maintenance phase from week 10 to week 54), and a 12-week safety follow-up period. 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 or phase 3 studies.

This trial was done in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants. The trial protocols, informed consent forms, and other relevant information were approved by the Istituto Clinico Humanitas (Milan, Italy) and the institutional review board and ethics committee at each study site (appendix pp 14–17).

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, a rectal bleeding subscore of ≥1, and a stool frequency subscore of ≥1). Patients were required to have had an established diagnosis of ulcerative colitis for at least 3 months, corroborated by both clinical and endoscopic evidence and a histopathology report, and evidence of disease extending at least 20 cm from the anal verge. Patients must not have received previous anti-TNF treatment and must have had an inadequate response, loss of response, or intolerance to previous immunosuppressant or corticosteroid treatment, or both. Patients receiving stable doses of oral 5-aminosalicylates were eligible if the dose had been stable for at least 4 weeks before randomisation; likewise for oral corticosteroids (prednisolone ≤30 mg per day) if the dose was stable for at least 4 weeks before randomisation (≥2 weeks if corticosteroids were being tapered), and immunosuppressants, such as azathioprine, 6-mercaptopurine, or methotrexate, if the dose had been stable for at least 8 weeks before randomisation.

Patients who received treatment with corticosteroid enemas or suppositories or topical (rectal) 5-aminosalicylate preparations within 2 weeks before randomisation were not eligible. Patients with previous exposure to any anti-TNF therapy, anti-integrin therapy (including vedolizumab and natalizumab), or anti-adhesion molecule therapy were excluded. Patients who received any investigational treatment within five half-lives of the investigational agent or within 28 days (whichever was greater) before randomisation were excluded. Additional exclusion criteria included planned surgery for ulcerative colitis or previous extensive colonic resection, colectomy, ileostomy, or colostomy; diagnosis of indeterminate colitis; past or present fistula or abdominal abscess; colonic mucosal dysplasia; history of toxic megacolon within 12 months before screening; colonic stricture; history or evidence of adenomatous colonic polyps that had not been removed; and an increased risk of infection (ie, congenital or acquired immune deficiency, HIV, hepatitis B virus, hepatitis C virus, cytomegalovirus, tuberculosis, or history of other opportunistic infections or organ transplantation). Eligibility criteria are described in full in the protocol (appendix pp 65–71).

Randomisation and masking

Participants were randomly assigned via an interactive voice or web-based response system (IxRS; Paraxel International, Newton, MA, USA) into parallel treatment groups to receive either etrolizumab or infliximab. 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* ≥10). A permuted block randomisation method ensured an approximately 1:1 ratio between treatment groups and within each stratum. During the 54-week double-blind treatment period and the infliximab washout period, the IxRS made etrolizumab or etrolizumab dummy kit assignments. The IxRS also made infliximab or infliximab dummy treatment assignments at weeks 0, 2, and 6 and then at 8-week intervals until week 46. All patients, study site personnel, and the funder of the study were masked to treatment assignment throughout the 54-week treatment period.

Procedures

Participants assigned to the etrolizumab group received subcutaneous etrolizumab 105 mg once every 4 weeks, plus an intravenous dummy infliximab treatment of 250 mL saline placebo at weeks 0, 2, and 6, then every 8 weeks thereafter, until week 54. Patients assigned to the infliximab group received intravenous infliximab 5 mg/kg at weeks 0, 2, and 6, then every 8 weeks, plus a subcutaneous dummy etrolizumab treatment of 0·7 mL placebo once every 4 weeks, until week 54. Dose escalation or dose reduction was not allowed in either treatment group. Patients could enrol in the COTTONWOOD open-label extension study if they received permitted rescue treatment, completed 54 weeks of the study, or experienced disease worsening between weeks 10 and 54 (defined as an increase in partial MCS of ≥3 points from week 10, an absolute partial MCS of ≥5, and an endoscopic subscore of ≥2, or an absolute partial MCS of ≥7 and an endoscopy subscore of ≥2). 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 screening, week 10, week 30, and week 54.

The dose of corticosteroids was kept stable during the induction phase. Patients entering the maintenance phase at week 10 underwent a mandatory corticosteroid tapering regimen (patients receiving >10 mg per day prednisone or equivalent reduced the dose by 5 mg per week until 10 mg per day was reached and patients receiving ≤10 mg per day prednisone or equivalent reduced the dose by 2·5 mg per 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 2 weeks after this increase. Baseline doses of immunosuppressant therapy were kept stable throughout the study.

Serum concentrations of etrolizumab were measured at weeks 2, 10, 30, and 54 (2 weeks after etrolizumab administration). Serum concentrations were also measured pre-etrolizumab administration (trough) at weeks 4 and 12. 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.[16] 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 7). Neither pharmacokinetics nor anti-drug antibodies were assessed in the infliximab treatment group.

Safety was assessed by 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 could 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

The primary efficacy endpoint was both clinical response at week 10 and clinical remission at week 54. Clinical response was defined as at least a 3-point decrease and at least a 30% reduction in MCS from baseline, plus at least a 1-point decrease in rectal bleeding subscore or an absolute rectal bleeding score of 0 or 1. Clinical remission was defined as an MCS of 2 or less with individual subscores of 1 or less. Key secondary efficacy endpoints were: endoscopic improvement at week 54 (defined as Mayo endoscopic subscore of ≤1), endoscopic remission at week 54 (defined as Mayo endoscopic subscore of 0), clinical remission at week 54 (defined as MCS of ≤2 with individual subscores ≤1), corticosteroid-free clinical remission at week 54 (defined as clinical remission with no corticosteroid use for 24 weeks before week 54 among patients receiving corticosteroids at baseline), clinical remission at week 10, clinical remission at week 54 among patients with a clinical response at week 10, and sustained clinical remission (defined as clinical remission at both week 10 and week 54). Additional secondary efficacy endpoints were: endoscopic improvement at week 10, sustained endoscopic improvement (defined as endoscopic improvement at both week 10 and week 54), clinical response at week 10, sustained clinical response (defined as clinical response at both week 10 and week 54), and the change from baseline in patient-reported health-related quality of life at weeks 10, 30, and 54 (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. Additional endpoints are defined in the protocol (appendix 63–65).

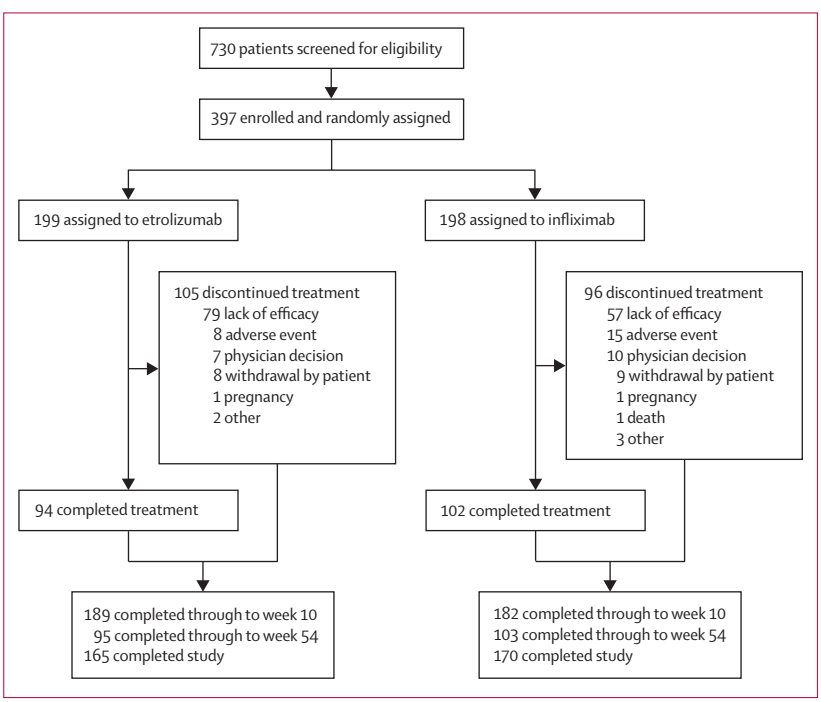

Figure 1: **Trial profile**
Patients who completed treatment are those who received all doses of study treatment specified by the protocol. Patients who completed the study are all patients who either enrolled into the open-label extension study or completed 12 weeks of safety follow-up, following treatment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

	Etrolizumab group (n=199)	Infliximab group (n=198)
Age in years, median (range)	37 (18–76)	37 (18–70)
Sex		
Female	81 (41%)	66 (33%)
Male	118 (59%)	132 (67%)
Body-mass index in kg/m², median (range)	23·9 (15·4–40·9)	23·8 (15·6–44·7)
Duration of disease in years, median (range)	3·3 (0·3–49·0)	4·1 (0·3–33·7)
MCS category*		
≤9	141 (71%)	142 (72%)
≥10	58 (29%)	56 (28%)
Corticosteroid use at baseline*		
No	108 (54%)	104 (53%)
Yes	91 (46%)	94 (47%)
Immunosuppressant use at baseline*		
No	131 (66%)	130 (66%)
Yes	68 (34%)	68 (34%)
MCS, mean (SD)	8·60 (1·53)	8·59 (1·52)
Mayo endoscopic subscore, mean (SD)	2·60 (0·49)	2·61 (0·50)
Faecal calprotectin in µg/g, median (IQR)	1303 (502–2834)	1466 (473–3562)
C-reactive protein in mg/L, median (IQR)	3·55 (1·23–9·68)	4·34 (1·26–9·18)
Disease location		
Left-sided colitis	124 (62%)	127 (64%)
Extensive colitis	31 (16%)	20 (10%)
Pancolitis	44 (22%)	51 (26%)
Baseline treatment		
5-aminosalicylic acid	158 (79%)	168 (85%)
No corticosteroid or immunosuppressant	75 (38%)	76 (38%)
Corticosteroid, no immunosuppressant	59 (30%)	56 (28%)
Immunosuppressant, no corticosteroid	40 (20%)	36 (18%)
Corticosteroid and immunosuppressant	25 (13%)	30 (15%)

Data are n (%) unless otherwise stated. MCS=Mayo Clinic total score.
*Stratification factors were MCS category (≤9 *vs* ≥10), corticosteroid use (yes *vs* no), and immunosuppressant use (yes *vs* no).

Table 1: **Baseline characteristics**

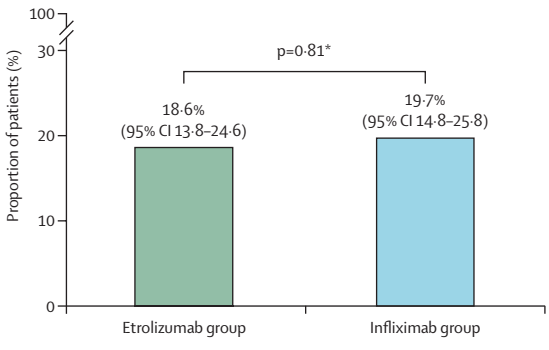

Figure 2: **Proportion of patients who had clinical response at week 10 and clinical remission at week 54 (primary endpoint)**
Clinical response was defined as MCS with at least a 3-point decrease and 30% reduction from baseline, plus at least a 1-point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1. Clinical remission was defined as MCS of 2 or less with individual subscores of 1 or less. 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.

Statistical analysis

The planned sample size of 390 patients (195 patients per treatment group) was expected to provide approximately 80% power to detect superiority of etrolizumab over infliximab for the primary endpoint, with a target difference between treatment groups of 12% (expected treatment effect: infliximab 18%; etrolizumab 30%) via two-sided χ^2 test at the 5% significance level.[17,18] Statistical hypotheses for the primary and key secondary endpoints were tested with a multistage gatekeeping procedure using truncated Holm,[19] to ensure an overall type I error probability of 5% or less, with the primary endpoint tested first at a two-sided significance of p of less than 0·05. Non-inferiority was assessed for a single endpoint, clinical remission at week 10, which was evaluated with a margin of 12·5% and should be compared against a one-sided significance level of 0·025. 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 on the basis of clinical importance, before unmasking. Hierarchal testing began with family one, and at least one endpoint in each family must have been considered significant after multiplicity adjustment to continue testing in subsequent families (appendix pp 1, 197–198). The primary endpoint was compared between the etrolizumab and infliximab groups using the Cochran-Mantel-Haenszel test statistic, adjusted for stratification factors (MCS [≤9 *vs* ≥10], corticosteroid use [yes *vs* no], and immunosuppressant use [yes *vs* no]), to test the null hypothesis that the proportion of patients reaching the primary endpoint was the same in each group. A strata-adjusted proportion difference was obtained by weighted average of stratum-specific proportion differences.[20]

Efficacy was analysed using a modified intention-to-treat population, defined as all randomised patients who received at least one dose of study drug. Patients who had missing data, who were non-evaluable for efficacy at a particular timepoint, who began concomitant medications not permitted with etrolizumab or infliximab, 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. All analyses were done using SAS version 9.4. This study is registered with ClinicalTrials.gov, NCT02136069.

Role of the funding source
The funder 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, and writing of the report, in collaboration with the study authors.

Results
Between Dec 24, 2014, and June 23, 2020, 730 patients were screened for eligibility and 397 were enrolled and randomly assigned to receive etrolizumab (n=199) or infliximab (n=198; figure 1). Most patients in both treatment groups completed the study through week 10 (189 [95%] in the etrolizumab group and 182 [92%] in the infliximab group), and approximately half of the patients in both groups completed through week 54 (95 [48%] and 103 [52%]). The most common reason for treatment discontinuation in both groups was lack of efficacy (79 [40%] in the etrolizumab group and 57 [29%] in the infliximab group).

Baseline characteristics were generally balanced between the treatment groups, except for a greater proportion of men in the infliximab group (table 1). Mean MCS at baseline was 8·60 (SD 1·52) for both treatment groups combined.

In the modified intention-to-treat population, 37 (18·6%) of 199 patients in the etrolizumab group and 39 (19·7%) of 198 in the infliximab group met the primary endpoint of clinical response at week 10 and clinical remission at week 54 (figure 2). Etrolizumab was not found to be superior to infliximab, with an adjusted treatment difference of –0·9% (95% CI –8·7 to 6·8; p=0·81). Because the primary endpoint was not met, secondary endpoints were not formally compared as per the conditions of the prespecified hierarchical testing, and interpretation of all nominal p values reported for these comparisons should be considered exploratory.

No significant differences between the etrolizumab and infliximab groups were observed in the proportion of patients who had endoscopic remission (35 [18%] of 199 in the etrolizumab group *vs* 45 [23%] of 198 in the infliximab group; p=0·22), endoscopic improvement (54 [27%] *vs* 64 [32%]; p=0·28), or clinical remission (40 [20%] *vs* 47 [24%]; p=0·41) at week 54 (figure 3).

Non-inferiority at a 0·025 one-sided significance level was not met for clinical remission at week 10 for etrolizumab compared with infliximab (41 [21%] of 199 patients in the etrolizumab group *vs* 65 [33%] of 198 in the infliximab group; non-inferiority p=0·13; figure 4). Numerically similar rates of corticosteroid-free clinical remission were observed at week 54 in the etrolizumab and infliximab groups (13 [15%] of 84 patients *vs* 15 [17%] of 86; p=0·89). Among patients who had clinical response at week 10, a numerically similar proportion of patients reached clinical remission at week 54 in the etrolizumab and infliximab groups (37 [38%] of 98 *vs* 39 [33%] of 117; p=0·42; figure 4). There was no significant difference in

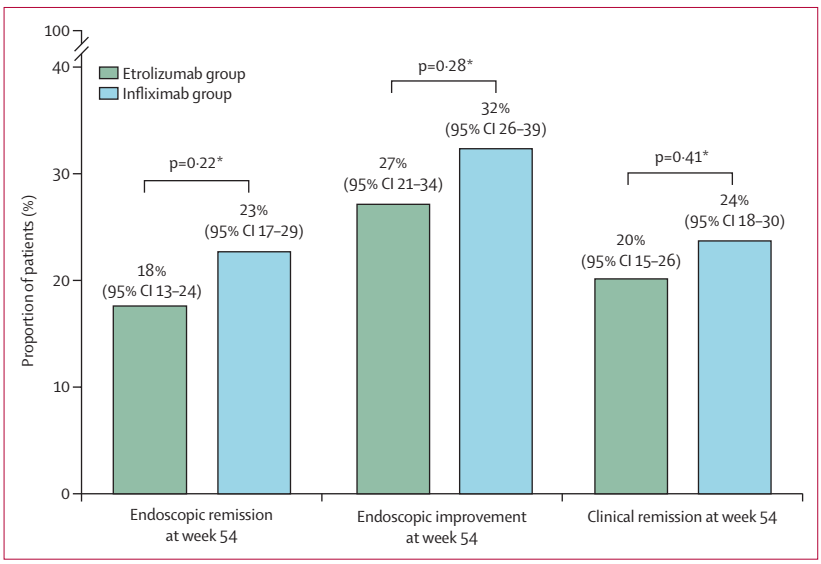

Figure 3: **Proportion of patients who had endoscopic remission, endoscopic improvement, or clinical remission at week 54**
Endoscopic remission was defined as Mayo endoscopic subscore of 0. Endoscopic improvement was defined as Mayo endoscopic subscore of 1 or less. Clinical remission was defined as MCS of 2 or less with individual subscores of 1 or less. 95% CIs were constructed using the Wilson method. MCS=Mayo Clinic total score. *Nominal p values were constructed using the Cochran-Mantel-Haenszel method, adjusting for stratification factors, not adjusted for multiplicity.

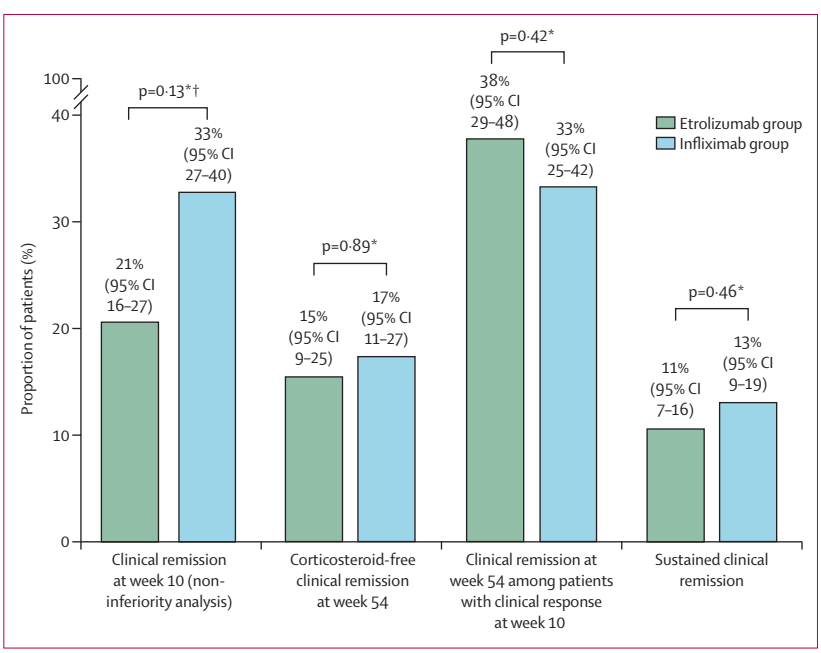

Figure 4: **Proportion of patients who met secondary clinical endpoints**
Clinical remission was defined as MCS of 2 or less with individual subscores of 1 or less. Corticosteroid-free clinical remission was defined as clinical remission with no corticosteroid use for 24 weeks before week 54 among patients receiving corticosteroids at baseline. Clinical response was defined as MCS with at least a 3-point decrease and 30% reduction from baseline, plus at least a 1-point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1. Endoscopic remission was defined as Mayo endoscopic subscore of 0. Sustained clinical remission was defined as clinical remission at weeks 10 and 54. 95% CIs were constructed using the Wilson method. MCS=Mayo Clinic total score. *Nominal p values were constructed using the Cochran-Mantel-Haenszel method, adjusting for stratification factors, not adjusted for multiplicity. †Should be compared against a one-sided significance level of 0·025.

	Etrolizumab group (n=199)	Infliximab group (n=198)
Any adverse event	154 (77%)	151 (76%)
Any serious adverse event	32 (16%)	20 (10%)
At least one adverse event leading to treatment discontinuation	29 (15%)	25 (13%)
Infection	69 (35%)*	61 (31%)
Serious infection	11 (6%)*	3 (2%)
Anal abscess	3 (2%)	0
Appendicitis	2 (1%)	0
Cytomegalovirus colitis	1 (1%)	1 (1%)
Bacteraemia	1 (1%)	0
Lower respiratory tract infection	0	1 (1%)
Meningitis listeria	0	1 (1%)
Orchitis	1 (1%)	0
Pneumonia	1 (1%)	0
Pyelonephritis	1 (1%)	0
Sepsis	1 (1%)	0
Stitch abscess	1 (1%)	0
Viral upper respiratory tract infection	1 (1%)	0
Death	0	1 (1%)†
Progressive multifocal leukoencephalopathy	0	0
Adverse events occurring in ≥5% of any treatment group		
Ulcerative colitis	55 (28%)	43 (22%)
Nasopharyngitis	22 (11%)	23 (12%)
Headache	22 (11%)	19 (10%)
Arthralgia	21 (11%)	15 (8%)
Anaemia	10 (5%)	7 (4%)
Abdominal pain	12 (6%)	5 (3%)
Diarrhoea	11 (6%)	4 (2%)
Nausea	10 (5%)	4 (2%)
Serious adverse events occurring in ≥1% of any treatment group		
Ulcerative colitis	12 (6%)	11 (6%)
Anal abscess	3 (2%)	0
Abdominal pain	2 (1%)	0
Appendicitis	2 (1%)	0
Renal colic	2 (1%)	0

Data are n (%); n represents individual patients, not individual events.
*One patient (male, aged 71 years) experienced three serious infections (sepsis, orchitis, and bacteraemia) during the study; all of these resolved before study completion. †Cause of death was pulmonary embolism; deemed not related to treatment by the investigator.

Table 2: **Adverse events**

the proportion of patients who had sustained clinical remission in the etrolizumab and infliximab groups (21 [11%] of 199 *vs* 26 [13%] of 198; p=0·46; figure 4). Among patients who were receiving concomitant immunosuppressants at baseline, both treatment groups had numerically higher rates of clinical response at week 10 and clinical remission at week 54 than among patients who were not receiving immunosuppressants (17 [26%] of 65 patients *vs* 20 [15%] of 134 in the etrolizumab group; 18 [27%] of 66 *vs* 21 [16%] of 132 in the infliximab group). The magnitude of this difference was similar between the etrolizumab and infliximab groups. Results of additional secondary endpoints are included in the appendix (pp 4–5). At week 54, one patient in the infliximab group and none in the etrolizumab group had shifts in faecal calprotectin from normal to high, compared with 18 and 22 patients respectively who had shifts from high to normal (appendix p 6).

In patients receiving etrolizumab, serum etrolizumab concentrations gradually increased at weeks 2, 10, and 30 (2 weeks after etrolizumab administration) and remained steady until week 54 (appendix p 2). The mean etrolizumab concentration at week 10 was 12·0 µg/mL (SD 4·63) and at week 54 was 13·2 µg/mL (5·68), which was more than nine times higher than the target exposure (1·3 µg/mL) associated with 90% peripheral β7 receptor occupancy.[21] The mean trough serum concentration of etrolizumab at week 12 was 6·9 µg/mL (SD 3·18), more than five times higher than the target exposure.

Based on the total number of evaluable patients, 69 (35%) of 196 patients in the etrolizumab group had anti-drug antibodies after treatment; ten (5%) patients tested positive for anti-drug antibodies at baseline. There was no obvious effect of anti-drug antibodies on pharmacokinetic outcomes. The median concentrations of etrolizumab in patients with anti-drug antibodies in the etrolizumab group were similar to those in patients without anti-drug antibodies (appendix p 3).

Similar incidences of adverse events were reported between the etrolizumab and infliximab groups; 154 (77%) of 199 patients in the etrolizumab group and 151 (76%) of 198 in the infliximab group had one or more adverse events (table 2). Most adverse events were mild to moderate in severity. The most common adverse event in both treatment groups was ulcerative colitis (55 [28%] patients in the etrolizumab group; 43 [22%] in the infliximab group). Ulcerative colitis flares were also the most common adverse event leading to treatment discontinuation in both groups, although this was more common in the etrolizumab group (21 [11%] patients) than in the infliximab group (seven [4%]). The incidence of infections was similar between groups (69 [35%] patients in the etrolizumab group; 61 [31%] in the infliximab group); however, gastrointestinal infections were more common in the etrolizumab group (15 [8%]) than in the infliximab group (seven [4%]).

Serious adverse events, including serious infections, were numerically higher in the etrolizumab group (32 [16%] patients) than in the infliximab group (20 [10%]; table 2). The most common serious adverse event was ulcerative colitis, experienced by 12 (6%) patients in the etrolizumab group and 11 (6%) in the infliximab group (table 2). Most of the serious infections were considered unrelated to etrolizumab treatment, and only one serious

infection (cytomegalovirus colitis) led to treatment discontinuation in the etrolizumab group.

The most common serious infection was anal abscess (three [2%] patients) in the etrolizumab group (table 2). Each of these patients was receiving a concomitant corticosteroid or immunosuppressant, and two cases were considered by the investigators to be unrelated to etrolizumab treatment. There were two cases of appendicitis in the etrolizumab group, which were considered unrelated to study treatment. Anti-drug antibodies had no effect on safety outcomes. There were no deaths in the etrolizumab group. One death (due to a pulmonary embolism) occurred in the infliximab group but was not considered to be related to study treatment. No cases of progressive multifocal leukoencephalopathy were identified in either treatment group.

Discussion

The etrolizumab phase 3 ulcerative colitis study programme enrolled more than 2000 patients worldwide and consisted of five randomised controlled studies, including three head-to-head studies. In this double-blind, double-dummy, parallel-group, head-to-head study, etrolizumab was not superior to infliximab in terms of the primary endpoint of both clinical response at week 10 combined with clinical remission at week 54 in anti-TNF-naive patients with moderately to severely active ulcerative colitis. However, the proportion of patients who met the primary endpoint with etrolizumab treatment was numerically similar (although not powered to show non-inferiority) to that observed with infliximab treatment.

The primary endpoint in GARDENIA (clinical response at week 10 and clinical remission at week 54), in combination with the treat-through design, was designed to mimic clinical practice, where patients who initially have a clinical response to a particular treatment might go on to have clinical remission at a later timepoint. Of note, histological endpoints were not included in GARDENIA, but were included in other randomised, placebo-controlled, phase 3 studies of etrolizumab.[15,22,23] Etrolizumab was well tolerated, with a safety profile consistent with previous results from the phase 2 study.[11] Nonetheless, incidences of serious infections and gastrointestinal infections were numerically higher in the etrolizumab group than in the infliximab group, although no clinically significant patterns were observed except for anal abscess (three cases) and appendicitis (two cases).

Several factors might have influenced the results of this study. GARDENIA was designed to provide approximately 80% power to detect a difference of 12% (18% *vs* 30%) between treatment groups for the primary efficacy endpoint at a 5% significance level. Here, 19% of patients in the etrolizumab group and 20% in the infliximab group met the primary endpoint, suggesting that infliximab performed as expected in this study, but etrolizumab did not. In addition, treat-through study designs, such as the one used in GARDENIA, are associated with higher withdrawal rates.[17] Only around half of the patients in both treatment groups completed the study through week 54 (for assessment of the primary endpoint), which might have affected the study results.

The 105 mg dose of etrolizumab was chosen for this study on the basis of the results from the phase 2 EUCALYPTUS study, where two dosing regimens were tested (a nominal 100 mg subcutaneous dose every 4 weeks [actual dose 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-fold exposure range. However, the small sample size in the phase 2 study (81 patients treated with etrolizumab, with only a third TNF-naive) might have affected the 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. Because dose optimisation was not done in this study, we cannot rule out the possibility that etrolizumab was underdosed. It is also worth noting that infliximab was front-loaded with three starter doses of 5 mg/kg at weeks 0, 2, and 6, whereas etrolizumab was not. 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 more than five 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 benefits in this class of anti-integrin therapies.[24,25]

The anti-drug antibody incidence rate observed in this study (35% in patients treated with etrolizumab) is higher than that observed during the phase 1 and phase 2 studies of etrolizumab (about 5%).[11,26] It is difficult to make direct comparisons of anti-drug antibody results between phase 3 and earlier studies as the patient population size 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 antidrug 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, robust evaluation of the potential effect of anti-drug antibody response on etrolizumab exposure levels showed minimal effect both by between-patient and within-patient assessments (data not shown). Although we did not see any obvious correlation between etrolizumab anti-drug antibodies and pharmacokinetic measures in this study, that does not rule out subtle effects of anti-drug antibodies on efficacy or safety outcomes.

Etrolizumab was not shown to be superior to infliximab in anti-TNF-naive patients with moderately to severely active ulcerative colitis. Data from the phase 3 etrolizumab clinical trial programme in ulcerative colitis and the 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 patient population.

Contributors

SD, J-FC, and ML contributed to study conceptualisation, investigation, methodology, resources (assisted with patient recruitment), data validation, data visualisation, and writing (review and editing) of the manuscript. JPG, GD'H, BH, RP, H-SK, and WR contributed to investigation, resources (assisted with patient recruitment), data validation, data visualisation, and writing (review and editing) of the manuscript. HT contributed to study conceptualisation, data curation, investigation, methodology, project administration, supervision, data validation, data visualisation, and writing (review and editing) of the manuscript. YSO contributed to data curation, investigation, methodology, project administration, supervision, data validation, data visualisation, and writing (review and editing) of the manuscript. ST and AC contributed to investigation, methodology, project administration, supervision, data validation, data visualisation, and writing (review and editing) of the manuscript. KC-J contributed to data curation, formal analysis, investigation, software, data validation, visualisation, and writing (review and editing) of the manuscript. MTT contributed to study conceptualisation, data curation, investigation, methodology, project administration, resources, supervision, data validation, data visualisation, and writing (review and editing) of the manuscript. SS contributed to study conceptualisation, investigation, methodology, resources (assisted with patient recruitment), data validation, data visualisation, and writing (review and editing) of the manuscript. HT, YSO, and KC-J accessed and verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

SD reports consultation fees from AbbVie, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Enthera, Ferring Pharmaceuticals, Gilead, Hospira, Inotrem, Janssen, Johnson & Johnson, Merck Sharp & Dohme, Mundipharma, Mylan, Pfizer, Roche/Genentech, Sandoz, Sublimity Therapeutics, Takeda, TiGenix, UCB, and Vifor, outside of the submitted work. J-FC reports research grants from AbbVie, Janssen Pharmaceuticals, and Takeda, lecture fees from AbbVie, Amgen, Allergan, Ferring Pharmaceuticals, Shire, and Takeda, consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Ferring Pharmaceuticals, Galmed Research, GlaxoSmithKline, Janssen Pharmaceuticals, Kaleido Biosciences, Imedex, Immunic, Iterative Scopes, Merck, Microba, Novartis, PBM Capital, Pfizer, Roche/Genentech, Sanofi, Takeda, TiGenix, and Vifor, and holding stock options in Intestinal Biotech Development, outside of the submitted work. ML has served as a speaker, consultant, and advisory member for AbbVie, Celltrion, Janssen Pharmaceuticals, Pfizer, Roche/Genentech, and Takeda, outside of the submitted work. JPG has served as speaker, consultant, and advisory member for, or has received research funding from, AbbVie, Biogen, Casen Fleet, Celgene, Chiesi, Dr Falk Pharmaceuticals, Faes Farma, Ferring, Gebro Pharmaceuticals, Hospira, Janssen, Kern Pharmaceuticals, Otsuka Pharmaceutical, Pfizer, Roche/Genentech, Sandoz, Shire Pharmaceuticals, Takeda, Tillotts Pharmaceuticals, and Vifor, outside of the submitted work. GD'H reports personal fees from AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb, Boehringer Ingelheim, Celltrion, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Gossamer Bio, Immunic, Johnson & Johnson, Kintai, Takeda, Mitsubishi, Nextbiotics, Pfizer, ProDigest, Procise Diagnostics, Prometheus Laboratories, Progenity, Protagonist Therapeutics, RedHill, Robarts Clinical Trials, Roche/Genentech, and Tillotts, and grants from Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Medtronic, Pfizer, Procise, Prometheus Laboratories, Progenity Diagnostics, Robarts Clinical Trials, and Takeda, outside of the submitted work. RP reports personal fees from AbbVie, Abbott, Alimentiv (formerly Robarts Clinical Trials), Amgen, Arena Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Eli Lilly, Ferring, Galapagos, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Merck, Mylan, Oppilan Pharma, Pandion Therapeutics, Pfizer, Progenity, Protagonist Therapeutics, Roche/Genentech, Satisfai Health, Sandoz, Schering-Plough, Shire, Sublimity Therapeutics, Theravance Biopharma, UCB, and Takeda Pharmaceuticals, outside of the submitted work. H-SK is one of the principal investigators for an ongoing clinical trial for Allergan, Bristol Myers Squibb, GlaxoSmithKline, Eli Lilly, Roche/Genentech, Takeda, and Theravance. WR has served as a speaker for AbbVie, Celltrion, Falk Pharma, Janssen, Mitsubishi Tanabe Pharma Corporation, Pfizer, Shire, and Takeda, as a consultant for AbbVie, Algernon Pharmaceuticals, Amgen, AM Pharma, AMT, AOP Orphan, Arena Pharmaceuticals, Astellas, Roland Berger, Bioclinica, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Covance, Eli Lilly, Falk Pharma, Galapagos, Gilead, Grünenthal, ICON, InDex Pharmaceuticals, Inova, Intrinsic Imaging, Janssen, Johnson & Johnson, LivaNova, Mallinckrodt, Mitsubishi Tanabe Pharma Corporation, Merck Sharp & Dohme, Nash Pharmaceuticals, OMass Therapeutics, Parexel, Peri Consulting, Pharmacosmos, Prometheus, Protagonist Therapeutics, Provention Bio, Roche/Genentech, Robarts Clinical Trial, Sandoz, Seres Therapeutics, Setpoint Medical, Sigmoid Pharma, Sublimity, Takeda, Therakos, Theravance, TiGenix, and Zealand Pharma, and as an advisory board member for AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Galapagos, Grünenthal, Inova, Janssen, Johnson & Johnson, Mitsubishi Tanabe Pharma Corporation, Merck Sharp & Dohme, Pharmacosmos, Pfizer, Prometheus, Roche/Genentech, Sandoz, Takeda, Therakos, TiGenix, and Zealand Pharma, outside of the submitted work. HT, AC, and KC-J are employees of Roche/Genentech and receive Roche stocks as a part of their compensation. MTT, YSO, and ST were employees of Roche/Genentech at the time of this work, and received salary and stock options during the conduct of this study. SS reports personal fees from AbbVie, Arena, Bristol Myers Squibb, Biogen, Celltrion, Celgene, Falk, Fresenius, Gilead, I-MAB, Janssen, Merck Sharp & Dohme, Mylan, Pfizer, ProventionBio, Protagonist Therapeutics, Takeda, and Theravance, outside of the submitted work. BH declares no competing interests.

Data sharing

Qualified researchers can request access to individual patient-level data through the clinical study data request platform available at https://vivli.org/. Further details on Roche's criteria for eligible studies are available at https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see 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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