Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial

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Summary

Background Despite the introduction of new monoclonal antibodies and oral therapies for the treatment of ulcerative colitis, clinical remission rates remain low, underscoring the need for innovative treatment approaches. We assessed whether guselkumab plus golimumab combination therapy was more effective for ulcerative colitis than either monotherapy.

Methods We did a randomised, double-blind, controlled, proof-of-concept trial at 54 hospitals, academic medical centres, or private practices in nine countries. Eligible adults (aged ≥18 to 65 years) had a confirmed diagnosis of ulcerative colitis at least 3 months before screening and moderately-to-severely active ulcerative colitis (Mayo score 6–12) with a centrally-read baseline endoscopy subscore of 2 or higher. Patients were randomly assigned (1:1:1) using a computer-generated randomisation schedule to combination therapy (subcutaneous golimumab 200 mg at week 0, subcutaneous golimumab 100 mg at weeks 2, 6, and 10, and intravenous guselkumab 200 mg at weeks 0, 4, and 8, followed by subcutaneous guselkumab monotherapy 100 mg every 8 weeks for 32 weeks), golimumab monotherapy (subcutaneous golimumab 200 mg at week 0 followed by subcutaneous golimumab 100 mg at week 2 and every 4 weeks thereafter for 34 weeks), or guselkumab monotherapy (intravenous guselkumab 200 mg at weeks 0, 4, and 8, followed by subcutaneous guselkumab 100 mg every 8 weeks thereafter for 32 weeks). The primary endpoint was clinical response at week 12 (defined as a ≥30% decrease from baseline in the full Mayo score and a ≥3 points absolute reduction with either a decrease in rectal bleeding score of ≥1 point or a rectal bleeding score of 0 or 1). Efficacy was analysed in the modified intention-to-treat population up to week 38, which included all randomly assigned patients who received at least one (partial or complete) study intervention dose. Safety was analysed up to week 50, according to study intervention received among all patients who received at least one (partial or complete) dose of study intervention. This trial is complete and is registered with ClinicalTrials.gov, NCT03662542.

Findings Between Nov 20, 2018, and Nov 15, 2021, 358 patients were screened for eligibility, of whom 214 patients were randomly assigned to combination therapy (n=71), golimumab monotherapy (n=72), or guselkumab monotherapy (n=71). Of the 214 patients included, 98 (46%) were women and 116 (54%) were men and the mean age was 38·4 years (SD 12·0). At week 12, 59 (83%) of 71 patients in the combination therapy group had achieved clinical response compared with 44 (61%) of 72 patients in the golimumab monotherapy group (adjusted treatment difference 22·1% [80% CI 12·9 to 31·3]; nominal p=0·0032) and 53 (75%) of 71 patients in the guselkumab monotherapy group (adjusted treatment difference 8·5% [–0·2 to 17·1; nominal p=0·2155). At week 50, 45 (63%) of 71 patients in the combination therapy group, 55 (76%) of 72 patients in the golimumab monotherapy group, and 46 (65%) of 71 patients in the guselkumab monotherapy group had reported at least one adverse event. The most common adverse events were ulcerative colitis, upper respiratory tract infection, headache, anaemia, nasopharyngitis, neutropenia, and pyrexia. No deaths, malignancies, or cases of tuberculosis were reported during the combination induction period. One case of tuberculosis was reported in the combination therapy group and one case of colon adenocarcinoma was reported in the guselkumab monotherapy group; both occurred after week 12. Two deaths were reported after the final dose of study intervention (poisoning in the combination therapy group and COVID-19 in the guselkumab monotherapy group).

Interpretation Data from this proof-of-concept study suggest that combination therapy with guselkumab and golimumab might be more effective for ulcerative colitis than therapy with either drug alone. These findings require confirmation in larger trials.

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed from database inception to July 15, 2021, for articles published in English, using the search terms "ulcerative colitis," "combination therapy," and "biologic therapy." Our search yielded 393 articles, including the 2021 American Gastroenterology Association clinical practice guidelines and 2022 European Crohn's and Colitis Organisation Guidelines on Therapeutics in Ulcerative Colitis that reported evidence from the SONIC and UC-SUCCESS trials. The trials reported superiority of combination azathioprine plus infliximab versus either drug alone for inducing corticosteroid-free clinical remission in patients with Crohn's disease (SONIC) and ulcerative colitis (UC-SUCCESS). One randomised control trial studied the use of adalimumab plus thiopurine combination therapy compared with adalimumab monotherapy for the induction of clinical remission in patients naive to both therapies. In the trial, combination therapy was not superior to adalimumab monotherapy for inducing clinical remission. Combination therapy was associated with endoscopic improvement at week 26, although no difference was identified at 1 year. No clinical trials comparing combination therapy with biological monotherapy for maintenance of remission for patients with ulcerative colitis were identified. Furthermore, combination treatment with tumour necrosis factor (TNF) antagonists has been associated with increased toxicity (mainly infections) and malignancy, such as lymphoproliferative disease. Risk needs to be individualised since specific patient groups, such as older adults (aged >65 years), might be at higher risk for infections or lymphoma and young men might be at higher risk for specific complications, such as hepatosplenic T-cell lymphoma. This toxicity could potentially be reduced by using lower doses of immunosuppressive drugs, a strategy that has been shown to be equally potent in reducing immunogenicity.

Added value of this study

In the VEGA trial, after induction treatment, 83% of patients in the combination therapy group, 61% of patients in the golimumab group, and 75% of patients in the guselkumab group achieved clinical response. When the therapeutic target of clinical remission, a more stringent and regulatory accepted endpoint was evaluated, a larger treatment effect was observed at week 12 between combination therapy and guselkumab monotherapy than for clinical response at week 12. The observed treatment effect was numerically greater for combination therapy across multiple objective endpoints, including faecal biomarkers, endoscopy, and histopathology. The magnitude of the differences observed were consistent with the hypothesis derived from a murine model that the combination of the two drugs might have additive efficacy through effects on both shared and unique molecular pathways involved in the pathogenesis of inflammatory bowel disease.

Implications of all the available evidence

The VEGA randomised, controlled proof-of-concept study provides early evidence that combination therapy with a TNF antagonist and a interleukin (IL)-23p19 antagonist monoclonal antibody could yield improvements in clinical efficacy compared with the respective monotherapies. If confirmed in larger ongoing studies of induction and maintenance combination therapy in ulcerative colitis and Crohn's disease (NCT05242484 and NCT05242471), these findings could shift the treatment framework for inflammatory bowel disease towards combinations of advanced biologic and small molecule therapies.

Introduction

The introduction of new monoclonal antibody and oral treatments including tumour necrosis factor (TNF), interleukin (IL)-12/23, integrin antagonists, Janus kinase inhibitors, and a sphingosine-1-phosphate receptor modulator in the past two decades has revolutionised the management of ulcerative colitis.[1–6] Transformational efficacy similar to that observed with IL-23p19 or IL-17 antagonist therapy for psoriasis has not been realised in the treatment of patients with inflammatory bowel disease.[7,8] Despite the availability of these biologic and advanced small molecule monotherapies, more than half of patients with inflammatory bowel disease do not achieve clinical remission after 1 year.[1–6] Approximately 25% of clinically asymptomatic patients have active disease that is observable during endoscopy.[9] The efficacy plateau observed with advanced monotherapies underscores the need for innovative treatment approaches.

Guselkumab (Tremfya; Janssen Biotech, Horsham, PA, USA), an IL-23 antagonist monoclonal antibody, is approved for the treatment of psoriasis and psoriatic arthritis.[10] Phase 2 studies have demonstrated efficacy in moderately-to-severely active ulcerative colitis[11] and Crohn's disease.[12] Golimumab (Simponi; Janssen Biotech), a TNF-antagonist monoclonal antibody, is approved for moderately-to-severely active ulcerative colitis, rheumatoid arthritis in combination with methotrexate, psoriatic arthritis (alone or in combination with methotrexate), and ankylosing spondylitis.[13] Preclinical studies suggest that combination therapy could have higher efficacy than observed with each monotherapy.[14] We aimed to compare the efficacy and safety of guselkumab plus golimumab combination therapy with either monotherapy in patients with ulcerative colitis.

Methods

Study design and participants

We did a randomised, double-blind, controlled, phase 2, proof-of-concept trial (VEGA) at 54 sites, including hospitals, academic medical centres, and

private practices across nine countries (appendix p 4). Eligible adults (aged ≥18 to 65 years) had a confirmed diagnosis of ulcerative colitis at least 3 months before screening and moderately-to-severely active ulcerative colitis (Mayo score 6–12; appendix p 8)[15,16] with a centrally read baseline endoscopy subscore of 2 or higher. Patients had to have discontinued immunosuppressants (mercaptopurine, methotrexate, or azathioprine) at least 2 weeks before the first study dose.

Patients had no previous treatment with TNF, IL-12/23, or IL-23p19 antagonists, with inadequate response or intolerance to oral or intravenous corticosteroids or immunosuppressants. Previous treatment with vedolizumab (if discontinued for ≥18 weeks) or tofacitinib (if discontinued for ≥4 weeks or five half-lives, whichever was longer) was permitted. Oral aminosalicylates and corticosteroids (prednisone or equivalent ≤20 mg per day) at stable doses for ulcerative colitis were permitted.

Key exclusion criteria included imminent colectomy, potentially confounding gastrointestinal conditions, cancer, active infections, and previous active or latent tuberculosis. Full inclusion and exclusion criteria are in the appendix (pp 86–95).

Written informed consent was obtained from all patients before commencing the study. The study protocol (appendix p 38) was approved by relevant ethics committees or institutional review boards and conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulations.

Randomisation and masking

Patients were randomly assigned (1:1:1) to combination guselkumab plus golimumab induction therapy, followed by guselkumab maintenance monotherapy (hereafter referred to as combination therapy), guselkumab monotherapy, or golimumab monotherapy. Patients were randomly assigned using an interactive web response system generated by an independent vendor (Bracket, Wayne, PA, USA) under the supervision of the Janssen Research and Development biostatistics group before patient enrolment began. Randomisation was balanced using permuted blocks and stratified by baseline corticosteroid use (yes *vs* no). Placebo administrations (intravenous or subcutaneous) were administered to maintain masking (appendix p 27). Study participants, study personnel who administered interventions, study personnel who conducted outcome assessments, and study personnel who analysed data were masked to treatment group assignment.

Procedures

Patients in the combination therapy group received intravenous guselkumab 200 mg and subcutaneous golimumab 200 mg at week 0, subcutaneous golimumab 100 mg at weeks 2, 6, and 10, and intravenous guselkumab 200 mg at weeks 4 and 8, followed by subcutaneous guselkumab 100 mg every 8 weeks until week 32. Patients in the golimumab monotherapy group received subcutaneous golimumab 200 mg at week 0, followed by subcutaneous golimumab 100 mg at week 2 and every 4 weeks thereafter until week 34. Patients in the guselkumab monotherapy group received intravenous guselkumab 200 mg at weeks 0, 4, and 8, followed by subcutaneous guselkumab 100 mg every 8 weeks until week 32. No dose adjustment of study drugs was permitted during the study. Corticosteroid tapering beginning at week 6 was mandatory unless not medically feasible; the recommended tapering schedule is shown in the appendix (p 7).

Among demographic characteristics collected, sex was self-reported (female, male, unknown, undifferentiated). The full Mayo score (0–12; a higher score indicates more severe disease), a composite disease activity index calculated as the sum of stool frequency, rectal bleeding, endoscopic findings, and physician's global assessment subscores (each scored 0–3; appendix p 8) and modified Mayo score (excluding physician's global assessment) were assessed at weeks 0, 12, and 38. Disease-specific quality of life was assessed with the Inflammatory Bowel Disease Questionnaire (IBDQ),[17] at weeks 0, 6, 12, 24, and 38. Faecal calprotectin concentrations were measured at weeks 0, 2, 4, 8, 12, 24, and 38. C-reactive protein concentrations were measured at the same timepoints as those for faecal calprotectin, and at weeks 6, 10, 16, and 32.

Video endoscopies for endoscopic endpoints and colonic biopsies for histological endpoints were obtained at screening, weeks 12 and 38, or early discontinuation (appendix p 13). Video endoscopies were assessed by central reviewers and biopsies were assessed by a gastrointestinal pathologist who were masked to treatment, results, and timepoint. Central reviewers were masked to the endoscopy subscore assigned by the local endoscopist. If there was a discrepancy between the local endoscopist and the central reader endoscopy subscores, the video endoscopy was submitted to a second central reader (designated for adjudication). The median score of the three completed reads (ie, local read, central read 1, and central read 2 designated for adjudication) was the final reported endoscopy subscore.

Safety was monitored until week 50 (16 weeks after final administration of study intervention at week 34), including haematology and blood chemistry values. Blood samples for drug concentrations were collected at all induction visits and weeks 14, 16, 24, 32, 34, and 38. Blood samples for anti-drug antibodies were collected at weeks 2, 4, 8, 12, 16, 24, 32, and 38.

Outcomes

The primary endpoint was clinical response at week 12 (defined as ≥30% decrease from baseline in the full Mayo score and a decrease of ≥3 points with either a decrease in rectal bleeding score of ≥1 point or a rectal bleeding score of 0 or 1). The major secondary endpoint was clinical remission at week 12 (defined as a full Mayo score of ≤2 with no individual subscore of >1).

Additional prespecified endpoints were modified Mayo score-based definitions of clinical remission (defined as a rectal bleeding subscore of 0, stool frequency subscore of 0 or 1 with no increase in stool frequency from baseline, and endoscopy subscore of 0 or 1 with no friability present), 7-day and 60-day corticosteroid-free clinical remission, symptomatic remission (defined as stool frequency subscore of 0 or 1 with no increase from baseline and rectal bleeding subscore of 0), endoscopic improvement (defined as Mayo endoscopy subscore of 0 or 1 with no friability) and normalisation (defined as Mayo endoscopy subscore of 0), histological remission, and composite histological-endoscopic remission and normalisation, C-reactive protein concentrations, faecal calprotectin concentrations, IBDQ scores, change in IBDQ scores from baseline, and IBDQ response (≥16 point increase from baseline in IBDQ score) and remission (IBDQ score ≥170). Other prespecified endpoints related to the Ulcerative Colitis Index of Endoscopic Severity, the 29-item Patient-Reported Outcomes Measurement Information System (PROMIS), PROMIS fatigue 7-item short form, Bristol Stool Form Scale, Patient's Global Impression of Change of Severity of Ulcerative Colitis, and medical resource utilisation will be presented elsewhere. More detailed pharmacokinetic and immunogenicity, and biomarker analyses will also be presented elsewhere (appendix pp 9–11). Although baseline C-reactive protein concentrations were used to evaluate potential differences in inflammatory burden between groups, change from baseline in C-reactive protein concentrations is not a reliable marker of changes in disease activity in patients with ulcerative colitis,[18] and thus the results have not been presented.

Safety was assessed through the collection of adverse events and serious adverse events including infections (as determined by the investigator), adverse events of special interest (ie, malignancy or tuberculosis), and death. Definitions of adverse events, serious adverse events, attributions, and severity criteria are provided in the protocol (appendix p 154). Vital signs and clinical laboratory values were monitored until the final safety visit at week 50.

Statistical analysis

On the basis of previous studies,[2,19] we assumed a clinical response rate of 55% for golimumab monotherapy at week 12.[2,19] No previous data were available on guselkumab treatment for ulcerative colitis, therefore we assumed the same clinical response rate for guselkumab monotherapy and 75% for combination therapy. On the basis of a two-sided α level of 0·20, a sample size of 210 patients (70 patients per group) provided approximately 80% power to detect a 20% difference in the primary endpoint between the combination group and each monotherapy group. The study was considered positive if comparisons of guselkumab and golimumab combination therapy versus both guselkumab monotherapy and golimumab monotherapy achieved statistical significance at the two-sided significance level of 0·2 for the primary endpoint.

Efficacy outcomes were analysed in the modified intention-to-treat population, which included all randomly assigned patients who received at least one (partial or complete) study intervention dose. Safety was analysed according to study intervention received among all patients who received at least one (partial or complete) dose of study intervention. Analyses were performed using SAS (version 9·4 M6).

In the efficacy analyses, patients who had undergone an ostomy or colectomy, had a prohibited change in concomitant ulcerative colitis medication, or had discontinued study treatment due to poor efficacy or an adverse event of worsening of ulcerative colitis were considered, from the time of the event onward, as not achieving the binary endpoint and as having no change from baseline for continuous endpoints. Patients who discontinued study treatment due to COVID-19-related reasons (excluding COVID-19 infection; eg, inability to get to the site due to pandemic restrictions) were considered, from the time of the event onward, as having missing data (ie, data were excluded from analyses).

Dichotomous endpoints were compared between the combination therapy group and each monotherapy group with a two-sided Cochran–Mantel–Haenszel test adjusted for baseline corticosteroid use. We used non-responder imputation for missing data.

Continuous endpoints were analysed using a mixed model for repeated measures with explanatory variables including corticosteroid use at baseline (yes, no), visit, baseline score for a specific variable, and an interaction term of visit with treatment group. An unstructured covariance matrix for repeated measures within a participant was used.

No adjustment was made for multiple comparisons; nominal p values are presented. The widths of 80% CIs were not adjusted for multiplicity; thus, CIs should not be used in place of hypothesis testing.

The treatment effect for clinical response at week 12 was assessed for subgroups of patients based on demographic and baseline disease characteristics, baseline concomitant ulcerative colitis medication use, and history of ulcerative colitis-related medications (appendix p 14). For each subgroup, odds ratios of the combination therapy group versus each monotherapy group and the associated 80% CI were obtained from a logistic regression model. The logistic regression model

included treatment group and corticosteroid use at baseline as the factors. For subgroup analyses of corticosteroid use at baseline, treatment group was the only factor in the model.

Role of the funding source

The study funder was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Nov 20, 2018, and Nov 15, 2021, 358 patients were screened for eligibility, of whom 214 patients were randomly assigned: 71 were assigned to the combination therapy group, 72 to the golimumab monotherapy group, and 71 to the guselkumab monotherapy group. Fewer than 2% of patients in any treatment group missed study intervention administrations. One patient in the golimumab monotherapy group and

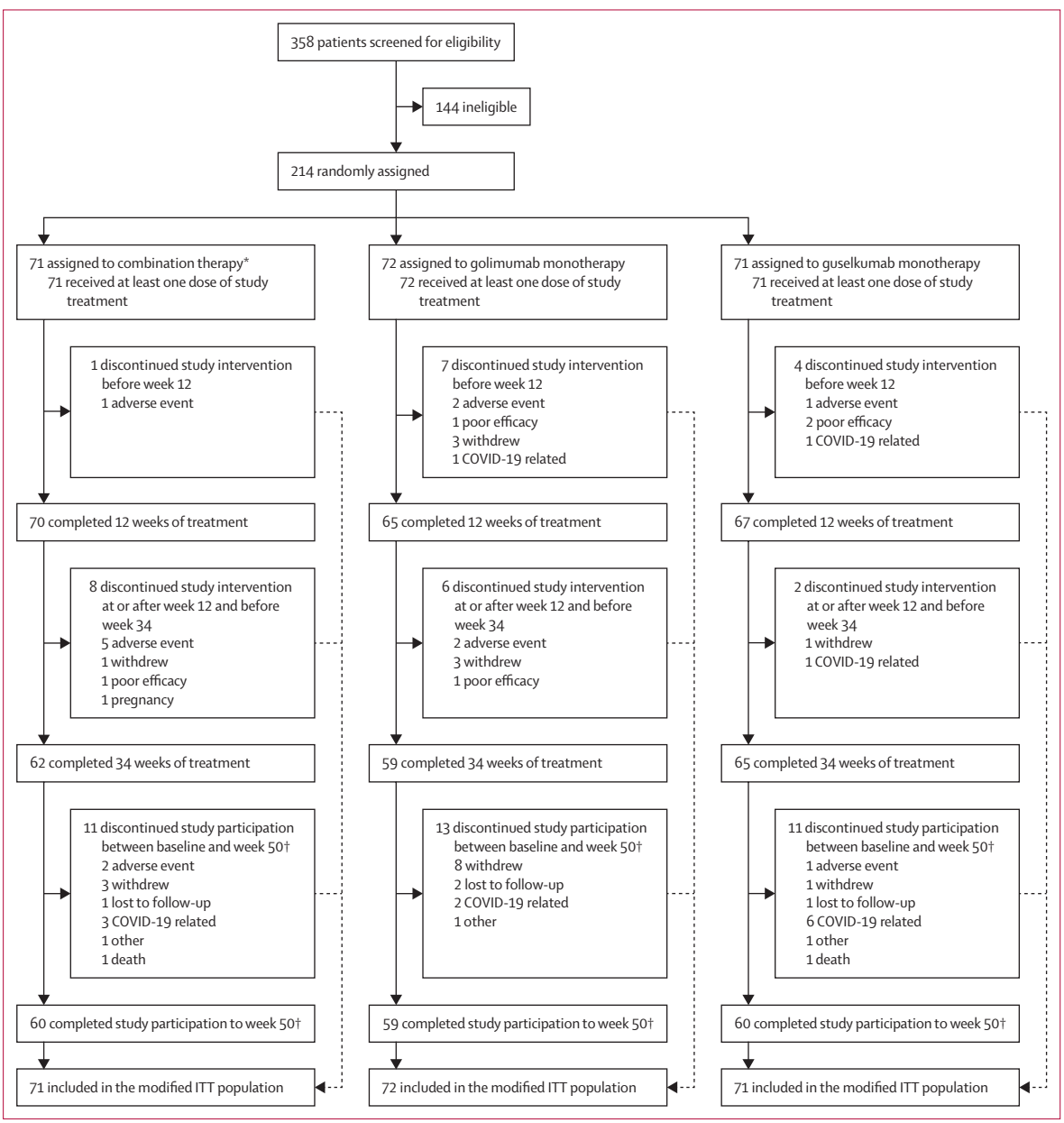

Figure 1: **Trial profile**

The final dose of study intervention was administered at week 34. A patient was considered to have completed study participation if they completed the final safety follow-up visit at week 50, regardless of whether they discontinued study intervention. ITT=intention-to-treat. *Patients in the combination group switched to guselkumab monotherapy after week 12. †Not mutually exclusive; patients who discontinued study intervention might have continued study participation and assessments to week 50, and thus, could have been included in both the number of patients who discontinued study intervention and the number who discontinued study participation.

	Combination therapy (n=71)	Golimumab monotherapy (n=72)	Guselkumab monotherapy (n=71)
Sex			
Male	34 (48%)	42 (58%)	40 (56%)
Female	37 (52%)	30 (42%)	31 (44%)
Age, years	37·8 (11·69)	38·1 (10·47)	39·1 (13·67)
Ethnicity			
Hispanic or Latino	5 (7%)	4 (6%)	6 (8%)
Other	66 (93%)	68 (94%)	65 (92%)
Race			
White	70 (99%)	67 (93%)	71 (100%)
Black or African American	1 (1%)	3 (4%)	0
American Indian or Alaska Native	0	2 (3)	0
Bodyweight, kg	69·8 (18·79)	73·9 (17·11)	69·6 (16·72)
Ulcerative colitis duration, years	4·6 (4·61)	4·7 (4·48)	5·4 (5·70)
Full Mayo score (0–12)*	8·8 (1·37)	8·7 (1·44)	8·9 (1·33)
Modified Mayo score (0–9)*	6·7 (1·14)	6·5 (1·26)	6·7 (1·14)
Moderately active ulcerative colitis (Mayo score 6–10)	62 (87%)	63 (88%)	64 (90%)
Endoscopy subscore (0–3)			
2 (moderate)	28 (39%)	35 (49%)	24 (34%)
3 (severe)	43 (61%)	37 (51%)	47 (66%)
Disease limited to left side of colon	50 (70%)	38 (53%)	36 (51%)
IBDQ score (32–224)	117·4 (32·78)	115·2 (31·24)	117·7 (36·63)
CRP concentration, mg/L†	3·9 (1·1–13·5)	2·5 (1·2–7·7)	3·4 (1·0–12·1)
Faecal calprotectin concentration, mg/kg‡	1577·0 (605·0–3577·0)	1588·0 (421·0–3224·0)	1511·0 (495·0–4166·0)
Albumin, g/L	42·1 (4·65)	43·3 (4·01)	42·6 (4·00)
Extra-intestinal manifestations			
Any	13 (18%)	11 (15%)	15 (21%)
Arthralgia	10 (14%)	6 (8%)	13 (18%)
Arthritis	7 (10%)	3 (4%)	1 (1%)
Aphthous stomatitis	1 (1%)	1 (1%)	2 (3%)
Pyoderma gangrenosum	1 (1%)	0	0
Erythema nodosum	0	0	2 (3%)
Iritis	0	0	1 (1%)
Sclerosing cholangitis	0	1 (1%)	0
Uveitis	0	1 (1%)	0
Medication history			
Corticosteroids§	68 (96%)	72 (100%)	70 (99%)
Immunosuppressants¶	37 (52%)	24 (33%)	28 (39%)
Aminosalicylates	70 (99%)	69 (96%)	71 (100%)
Vedolizumab	5 (7%)	0	3 (4%)
Tofacitinib	2 (3%)	1 (1%)	1 (1%)
Concomitant medications at baseline			
Corticosteroids§	29 (41%)	31 (43%)	28 (39%)
Aminosalicylates	67 (94%)	63 (88%)	63 (89%)
History of inadequate response, intolerance, or dependence to corticosteroids, mercaptopurine, or azathioprine	71 (100%)	72 (100%)	71 (100%)
Corticosteroids	60 (85%)	65 (90%)	64 (90%)
Immunosuppressants¶	32 (45%)	19 (26%)	24 (34%)

Data are n (%), mean (SD), or median (IQR). IBDQ=Inflammatory Bowel Disease Questionnaire. *Full Mayo score ranges from 0 to 12, with higher scores indicating more active disease; modified Mayo score ranges from 0 to 9, with higher scores indicating more active disease. †Data were missing for one patient in the guselkumab monotherapy group. ‡Data were missing for four patients in the combination therapy group, three patients in the golimumab monotherapy group, and four patients in the guselkumab monotherapy group. §Including budesonide and beclomethasone dipropionate. ¶Immunosuppressants included azathioprine, mercaptopurine, or methotrexate.

Table 1: **Demographic and disease characteristics at baseline**

two patients in the guselkumab monotherapy group discontinued study intervention due to COVID-19-related events.

Among 214 randomly assigned patients, 28 (13%) prematurely discontinued treatment before the last administration of study intervention (week 34) and 35 (16%) prematurely discontinued the study before the safety follow-up visit (between week 30 and week 50; figure 1; appendix p 17).

Overall, 98 (46%) women and 116 (54%) men participated and the mean age was 38·4 years (SD 12·0) (table 1). Demographic and baseline disease characteristics were similar among groups; however, 43 (61%) of 71 patients in the combination therapy group and 47 (66%) of 71 patients in the guselkumab monotherapy group had endoscopic severe disease at baseline compared with 37 (51%) of 72 patients in the golimumab monotherapy group. Disease limited to the left side of colon was higher among patients in the combination therapy group (50 [70%] of 71 patients) than those in the golimumab (38 [53%] of 72 patients) or guselkumab (36 [51%] of 71 patients) monotherapy groups.

At week 12, 59 (83%) of 71 patients in the combination therapy group had clinical response compared with 44 (61%) of 72 patients in the golimumab monotherapy group (adjusted treatment difference 22·1% [80% CI 12·9 to 31·3]; nominal p=0·0032) and 53 (75%) of 71 patients in the guselkumab monotherapy group (adjusted treatment difference 8·5% [–0·2 to 17·1;

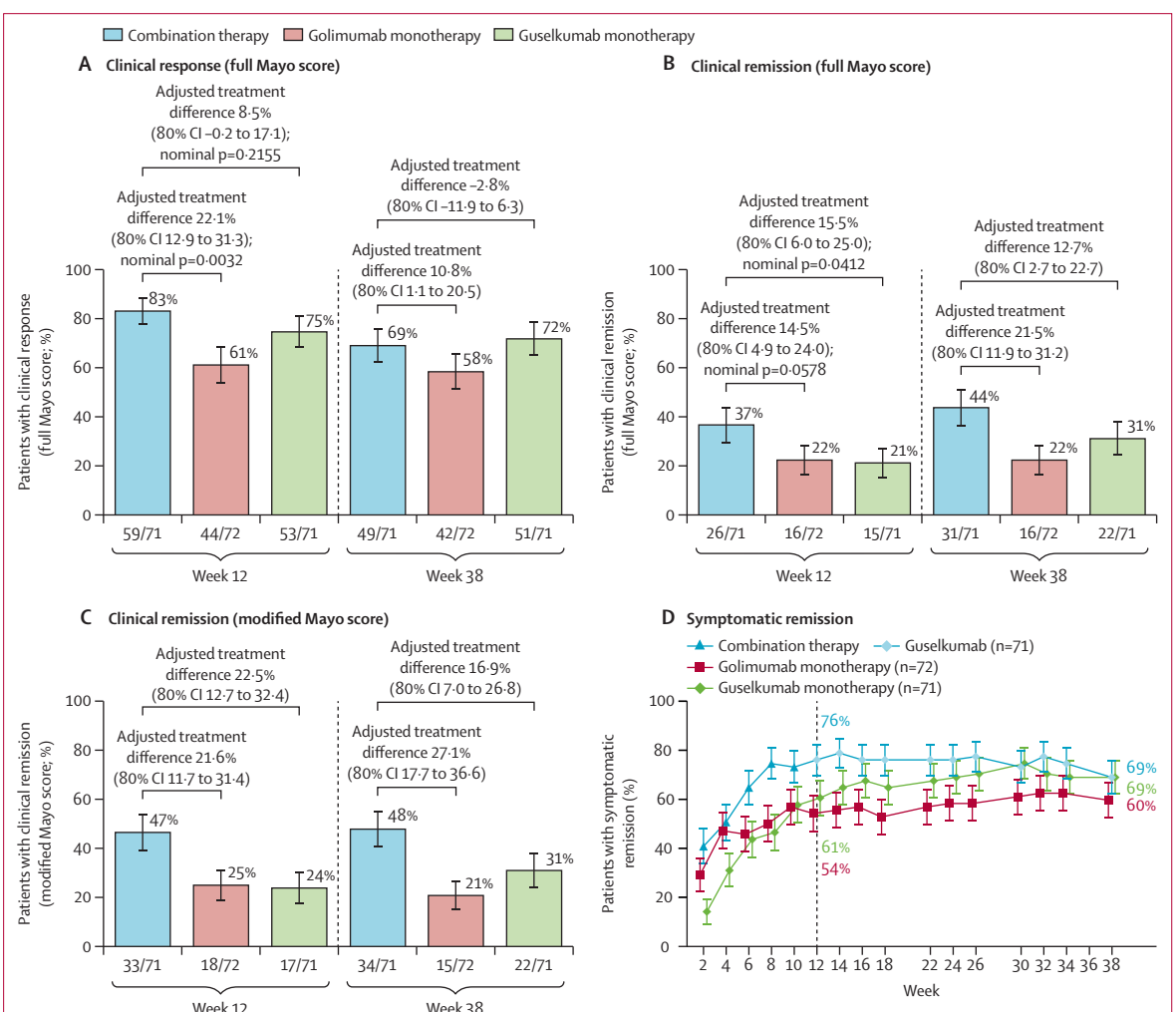

Figure 2: **Proportion of patients with clinical response and clinical remission at weeks 12 and 38 and symptomatic remission over time**
The proportion of patients who had achieved a clinical response (A) and clinical remission (B) according to the full Mayo score, and the proportion of patients who had achieved clinical remission according to the modified Mayo score (C) at weeks 12 and 38. (D) The proportion of patients who had achieved symptomatic remission over time. Patients in the combination group switched to guselkumab monotherapy after week 12. Error bars show 80% CIs; CIs for the dichotomous endpoint in each treatment group were based on the Wald statistic. The adjusted treatment difference between the combination therapy and the monotherapy groups and the 80% CIs were based on the Wald statistic with the Cochran-Mantel-Haenszel weight. Nominal p values were based on the two-sided Cochran-Mantel-Haenszel χ^2 test, stratified by corticosteroid use at baseline (yes or no).

nominal p=0·2155; figure 2A). Statistical significance was not achieved between the combination therapy group and both monotherapy groups, thus the primary efficacy endpoint was not met.

At week 12, 26 (37%) of 71 patients in the combination therapy group had achieved clinical remission compared with 16 (22%) of 72 patients in the golimumab monotherapy group (adjusted treatment difference 14·5% [80% CI 4·9–24·0]; nominal p=0·0578) and 15 (21%) of 71 patients in the guselkumab monotherapy group (adjusted treatment difference 15·5% [6·0–25·0]; nominal p=0·0412; figure 2B).

At week 12, 33 (47%) of 71 patients in the combination therapy group, 18 (25%) of 72 patients in the golimumab monotherapy group, and 17 (24%) of 71 patients in the guselkumab monotherapy group had achieved clinical remission according to the modified Mayo score (figure 2C).

At week 2, 29 (41%) of 71 patients in the combination therapy group had achieved symptomatic remission compared with 21 (29%) of 72 patients in the golimumab monotherapy group and ten (14%) of 71 patients in the guselkumab monotherapy group (figure 2D).

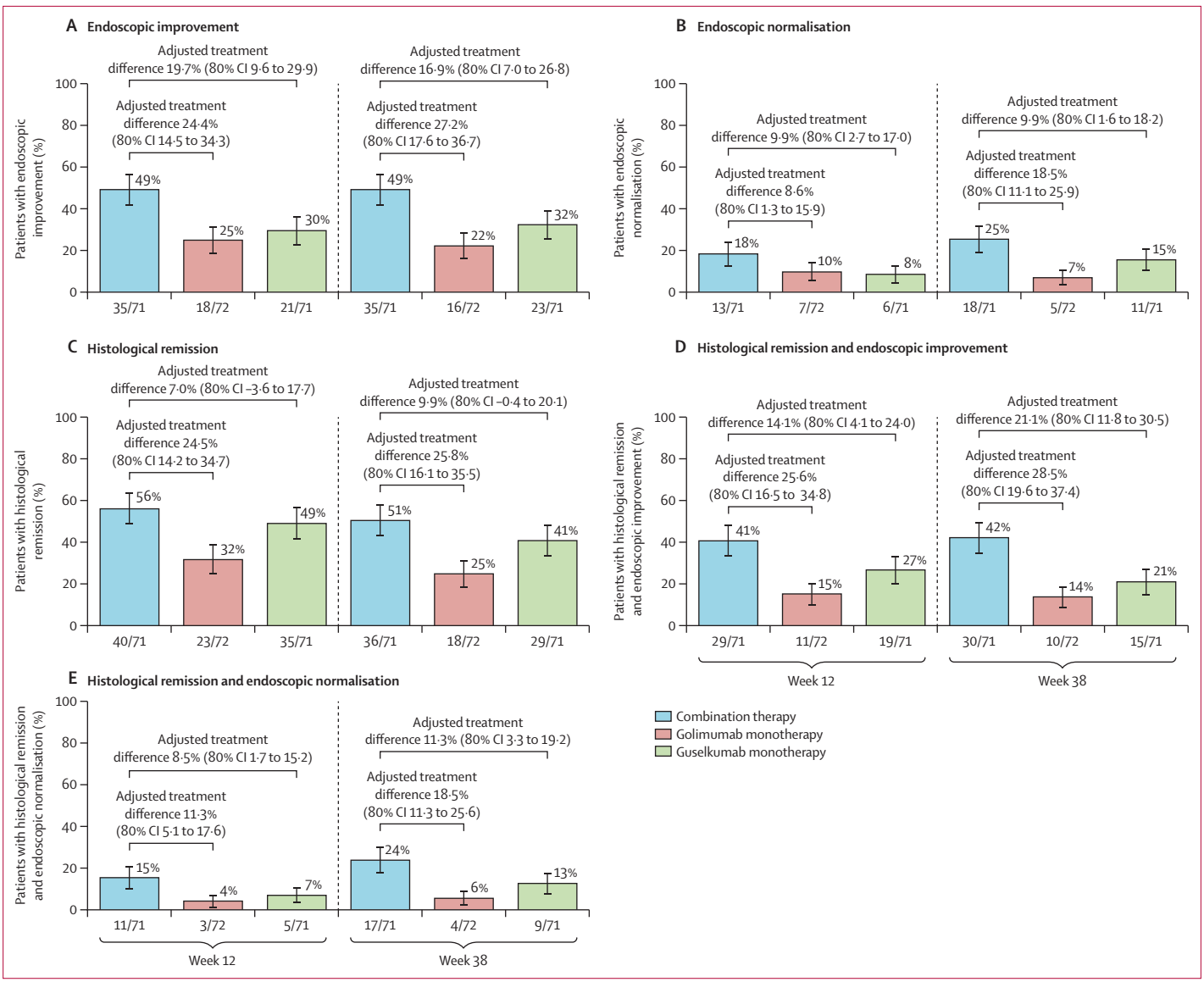

Figure 3: **Individual and composite endoscopy and histology outcomes at weeks 12 and 38**
Proportion of patients who had achieved endoscopic improvement (A), endoscopic normalisation (B), histological remission (C), composite histological remission and endoscopic improvement (D), and composite histological remission and endoscopic normalisation (E) at week 12 and 38. Error bars show 80% CIs; CIs for achieving the dichotomous endpoint in each treatment group were based on the Wald statistic. The adjusted treatment difference between the combination therapy vsersus the monotherapy groups and the CI were based on the Wald statistic with the Cochran-Mantel-Haenszel weight.

	Week 12					Week 38				
	Combination therapy (n=71)	Golimumab monotherpay (n=72)	Guselkumab monotherpay (n=71)	Treatment difference (combination therapy *vs* golimumab monotherapy), (80% CI*)	Treatment difference (combination therapy *vs* guselkumab monotherapy; 80% CI*)	Combination therapy (n= 71)	Golimumab monotherapy (n=72)	Guselkumab monotherapy (n=71)	Treatment difference (combination therapy *vs* golimumab monotherapy; 80% CI*)	Treatment difference (combination therapy *vs* guselkumab monotherapy; 80% CI*)
7-day corticosteroid-free clinical remission (full Mayo score)†	22 (31%)	15 (21%)	14 (20%)	10·2% (1·2 to 19·3)	11·3% (2·3 to 20·2)	31 (44%)	16 (22%)	21 (30%)	21·5% (11·9 to 31·2)	14·1% (4·2 to 24·0)
60-day corticosteroid-free clinical remission (full Mayo score)†	NA	NA	NA	NA	NA	31 (44%)	16 (22%)	21 (30%)	21·5% (11·9 to 31·2)	14·1% (4·2 to 24·0)
60-day corticosteroid-free among patients in clinical remission (full Mayo score)†	NA	NA	NA	NA	NA	31/31 (100%)	16/16 (100%)	21/22 (95%)	..	..
Least-squares mean change from baseline in IBDQ (80% CI) ‡§	57·9 (52·6 to 63·1)	49·0 (43·7 to 54·3)	53·3 (48·0 to 58·6)	8·9 (1·5 to 16·3)	4·5 (−2·9 to 11·9)	63·4 (57·4 to 69·4)	50·3 (44·2 to 56·4)	59·4 (53·4–65·4)	13·1 (4·6 to 21·6)	3·9 (−4·5 to 12·4)
IBDQ response†¶	61 (86%)	50 (69%)	56 (79%)	16·5% (7·8 to 25·2)	7·0% (−1·1 to 15·2)	55 (77%)	47 (65%)	54 (76%)	12·3% (2·9 to 21·7)	1·4% (−7·5 to 10·3)
IBDQ remission†¶	42 (59%)	38 (53%)	43 (61%)	6·5% (−4·0 to 16·9)	−1·4% (−11·9 to 9·1)	49 (69%)	39 (54%)	44 (62%)	14·9% (4·8 to 25·0)	7·0% (−2·9 to 17·0)
Least-squares mean change from baseline in faecal calprotectin (80% CI) ‡§**	−2650·1 (−3425·8 to −1874·4)	−2263·2 (−3047·5 to −1478·9)	−1532·2 (−2305·8 to −758·5)	−386·8 (−1489·7 to 716·0)	−1117·9 (−2212·5 to −23·2)	−2595·3 (−3101·8 to −2088·8)	−1919·1 (−2449·6 to −1388·7)	−2815·6 (−3318·4 to −2312·8)	−676·2 (−1409·0 to 56·6)	220·2 (−492·1 to 932·6)

Data are n (%) or n/N (%), unless stated otherwise. IBDQ=Inflammatory Bowel Disease Questionnaire. NA=not applicable. *The adjusted treatment difference between the combination therapy versus the monotherapy groups and the 80% CIs were based on the Wald statistic with the Cochran-Mantel-Haenszel weight. †Patients who had a missing dichotomous endpoint status at the designated analysis timepoint were considered to not have achieved the dichotomous endpoint at that timepoint. ‡A mixed-effect model repeated measure was used to account for missing data under the assumption of missing at random. The explanatory variables of the mixed-effect model repeated measure model included treatment group, corticosteroid use at baseline (yes or no), visit, baseline score for a specific variable, and an interaction term of visit with treatment group. §The least-squares mean and CI for each treatment group and the least-squares mean difference and CI between the combination therapy versus each monotherapy group were based on the mixed-effect model repeated measure.¶IBDQ response was defined as a ≥16-point improvement from baseline; IBDQ remission was defined as IBDQ score of ≥170. **Data for faecal calprotectin were available for 181 patients at week 12: 60 in the combination therapy group, 60 in the golimumab monotherapy group, and 61 in the guselkumab monotherapy group, and 179 patients at week 38: 61 in the combination therapy group, 55 in the golimumab monotherapy group, and 63 in the guselkumab monotherapy group.

Table 2: **Efficacy outcomes at weeks 12 and 38**

	Combination therapy induction until week 12			Therapy until week 50		
	Combination therapy (n=71)	Golimumab monotherapy (n=72)	Guselkumab monotherapy (n=71)	Combination therapy (n=71)	Golimumab monotherapy (n=72)	Guselkumab monotherapy (n=71)
Duration of follow-up, weeks	12·4 (0·84)	12·0 (0·92)	12·1 (1·74)	48·8 (9·70)	45·8 (12·91)	48·6 (9·00)
Any adverse event	29 (41%)	38 (53%)	31 (44%)	45 (63%)	55 (76%)	46 (65%)
Common adverse events*						
Ulcerative colitis	4 (6%)	9 (13%)	1 (1%)	10 (14%)	17 (24%)	4 (6%)
Upper respiratory tract infection	1 (1%)	4 (6%)	5 (7%)	6 (8%)	5 (7%)	6 (8%)
Headache	4 (6%)	2 (3%)	3 (4%)	5 (7%)	4 (6%)	6 (8%)
Anaemia	4 (6%)	5 (7%)	6 (8%)	4 (6%)	7 (10%)	10 (14%)
Nasopharyngitis	2 (3%)	3 (4%)	2 (3%)	4 (6%)	5 (7%)	3 (4%)
Neutropenia	2 (3%)	2 (3%)	4 (6%)	3 (4%)	3 (4%)	5 (7%)
Pyrexia	1 (1%)	2 (3%)	0	2 (3%)	5 (7%)	1 (1%)
Infections†	10 (14%)	16 (22%)	10 (14%)	22 (31%)	23 (32%)	17 (24%)
Opportunistic infections	0	0	0	2 (3%)	0	0
Serious adverse events	1 (1%)	1 (1%)	2 (3%)	4 (6%)	4 (6%)	4 (6%)
Serious infections†	1 (1%)	0	0	2 (3%)	2 (3%)	2 (3%)
Adverse events leading to discontinuation of study treatment	2 (3%)	3 (4%)	1 (1%)	7 (10%)	4 (6%)	1 (1%)
Malignancies	0	0	0	0	0	1 (1%)
Deaths	0	0	0	1 (1%)	0	1 (1%)
Adverse events associated with an injection site reaction	1 (1%)	0	1 (1%)	1 (1%)	0	1 (1%)
Adverse events temporally associated with an infusion	1 (1%)	2 (3%)	2 (3%)	1 (1%)	2 (3%)	2 (3%)
Adverse events associated with COVID-19 infection	1 (1%)	0	0	2 (3%)	2 (3%)	3 (4%)

Data are mean (SD) or n (%). *Reported by at least 5% of patients in any group. †As assessed by the investigator.

Table 3: **Adverse events**

The effects of combination therapy relative to golimumab and guselkumab were consistent in prespecified patient subgroups (appendix pp 28–35).

At week 12, the proportion of patients who had achieved endoscopic improvement, endoscopic normalisation, histological remission, and composite histological-endoscopic endpoints was higher in the combination therapy group than either monotherapy group (figure 3A–E).

At week 12, the proportion of patients who had achieved 7-day corticosteroid-free clinical remission following induction therapy was higher in the combination therapy group than either monotherapy group (table 2).

At week 12, mean IBDQ scores increased in all three treatment groups (appendix p 36). A higher proportion of patients in the combination therapy group (86% [61 of 71 patients]) had an IBDQ response (ie, ≥16-point improvement from baseline in the IBDQ score) at week 12 than did patients in the golimumab monotherapy group (50 [69%] of 72 patients) or guselkumab monotherapy group (56 [79%] of 71 patients). At week 12, 42 (59%) of 71 patients in the combination therapy group, 38 (53%) of 72 patients in the golimumab monotherapy group, and 43 (61%) of 71 patients in the guselkumab monotherapy group achieved IBDQ remission (IBDQ score ≥170).

At week 12, median faecal calprotectin concentration was lower in the combination therapy group (117·5 mg/kg [IQR 15·0–654·0]) than in the golimumab monotherapy group (505·0 mg/kg [182·0–1572·0]) and the guselkumab monotherapy group (397·5 mg/kg [113·0–1117·5]; appendix p 37).

At week 38, clinical response and remission rates were largely sustained with guselkumab maintenance in the group that initially received combination therapy. At week 38, 49 (69%) of 71 patients in the combination therapy group had clinical response compared with 42 (58%) of 72 patients in the golimumab monotherapy group (adjusted treatment difference 10·8% [80% CI 1·1 to 20·5]) and 51 (72%) of 71 patients in the guselkumab monotherapy group (adjusted treatment difference –2·8% [–11·9 to 8·3]; figure 2A). At week 38, 31 (44%) of 71 patients in the combination therapy group had achieved clinical remission compared with 16 (22%) of 72 patients in the golimumab monotherapy group (adjusted treatment difference 21·5% [11·9 to 31·2]) and 22 (31%) of 71 patients in the guselkumab monotherapy group (adjusted treatment difference 12·7% [2·7 to 22·7]; figure 2B). At week 38, 34 (48%) of 71 patients in the combination therapy group, 15 (21%) of 72 patients in the golimumab monotherapy group, and 22 (31%) of 71 patients in the guselkumab group had clinical remission according to the modified Mayo score and

49 (69%) patients in the combination therapy group, 43 (60%) patients in the golimumab monotherapy group, and 49 (69%) patients in the guselkumab monotherapy group had achieved symptomatic remission (figure 2C–D).

At week 38, the proportion of patients with endoscopic improvement, endoscopic normalisation, histological remission, composite histological remission and endoscopic improvement, and composite histological remission and endoscopic normalisation was higher in the combination therapy group than either monotherapy group (figure 3A–E).

At week 38, the proportion of patients who had achieved 60-day corticosteroid-free clinical remission was higher in the combination therapy group than either monotherapy group (table 2). Nearly all patients who achieved clinical remission at week 38 were corticosteroid-free for at least 60 days (table 2). At week 38, the proportion of patients who had achieved an IBDQ response was similar in the combination therapy group and the guselkumab monotherapy group and lower in the golimumab monotherapy group (table 2). At week 38, 49 (69%) of 71 patients in the combination therapy group, 39 (54%) of 72 patients in the golimumab monotherapy group, and 44 (62%) of 71 patients in the guselkumab monotherapy group had achieved IBDQ remission (table 2).

Median faecal calprotectin concentrations remained stable following induction and were numerically lower at week 38 in the combination therapy group (118·0 mg/kg [IQR 15·0–816·0]) than in the golimumab monotherapy group (326·0 mg/kg [87·5–1566·6]) and guselkumab monotherapy group (260·0 mg/kg [45·0–1245·0]; appendix p 37).

At week 12, 29 (41%) of 71 patients in the combination therapy group, 38 (53%) of 72 patients in the golimumab monotherapy group, and 31 (44%) of 71 patients in the guselkumab monotherapy group had reported at least one adverse event. Infections occurred in ten (14%) of 71 patients in the combination therapy group and guselkumab monotherapy group, and in 16 (22%) of 72 patients in the golimumab monotherapy group (table 3). Serious adverse events occurred in one (1%) of 71 patients in the combination therapy group (concurrent sepsis and influenza B), one (1%) of 72 patients in the golimumab monotherapy group (ulcerative colitis exacerbation), and in two (3%) of 71 patients in the guselkumab monotherapy group (intestinal obstruction and atrial fibrillation). No deaths, malignancies, or cases of tuberculosis or opportunistic infections were reported during the combination therapy induction period until week 12.

At week 50, 45 (63%) of 71 patients in the combination therapy group, 55 (76%) of 72 patients in the golimumab monotherapy group, and 46 (65%) of 71 patients in the guselkumab monotherapy group had experienced at least one adverse event (table 3). Serious infections were the most frequently reported serious adverse events and frequency was similar among treatment groups (table 3).

Two deaths occurred between weeks 34 (final dose of study intervention) and 50. One patient in the combination therapy group died of poisoning from an unknown substance, and one patient in the guselkumab monotherapy group died of COVID-19. One patient in the combination therapy group assigned at a site in Russia developed tuberculosis (week 18) and one patient in the same treatment group was diagnosed with cytomegalovirus colitis (week 14). One patient in the guselkumab monotherapy group had a malignant colon adenocarcinoma identified at week 38. More information about serious adverse events are included the appendix (p 15). Results of the pharmacokinetic, immunogenicity, and biomarker analyses are shown in the appendix (pp 18, 37).

Discussion

The proportion of patients who achieved a clinical response at week 12 was higher in the combination therapy group than either monotherapy group; however, the prespecified criterion for statistical significance relative to guselkumab monotherapy was not met. At week 12, more patients in the combination therapy (37%) group met the more stringent clinical remission endpoint than did those in the golimumab monotherapy (22%) or guselkumab monotherapy (21%) groups. The proportion of patients who met other objective endpoints, including endoscopic, histological, and composite histologic-endoscopic endpoints was numerically higher among the combination therapy group than either monotherapy at weeks 12 and 38. The proportion of patients who had met clinical, endoscopic, and histological endpoints was numerically higher among the guselkumab monotherapy group than the golimumab monotherapy group.

Multidrug regimens are superior to monotherapy in prostate cancer,[20] HIV,[21] and hepatitis C.[22] Combination therapy is already well accepted in the clinical management of inflammatory bowel disease. Studies have shown that patients treated with a combination of infliximab and azathioprine are more likely to achieve corticosteroid-free remission than those treated with either monotherapy alone.[23,24]

There has been increasing interest in the potential of combination advanced therapy in inflammatory bowel disease from various sponsors and independent investigators; however, to date, most of the reported data have been uncontrolled and limited by sample size.[25,26] A systematic review and meta-analysis of the safety and effectiveness of advanced combination therapy (dual biologics or biologic and oral small-molecule [eg, tofacitinib] drugs in combination) in patients with refractory inflammatory bowel disease showed combination therapy might be a treatment option in patients with refractory inflammatory bowel disease at specialised centres.[27]

Preclinical data from an acute colitis murine model and in silico evaluation suggested that dual blockade of

IL-23 and TNF can affect complementary and unique pathways in inflammatory bowel disease pathogenesis.[14] In the anti-CD40 agonistic antibody murine colitis model, the anti-TNF and anti-IL-23p19 antibody combination more effectively inhibited local intestinal inflammation than either therapy alone. Colonic gene signatures of anti-TNF, anti-IL-23p19, and combination treatment were generated from the mice and the human orthologues of these genes were mapped onto a human inflammatory bowel disease network to generate unique treatment subnetworks for anti-TNF and anti-IL-23p19 that were enriched for myeloid and intestinal epithelial genes, respectively. The combination of anti-TNF and anti-IL-23p19 uniquely impacted a wound repair and mucosal healing gene network, suggesting the potential for synergy with this combination. Taken together, the clinical and preclinical data suggest that combination therapy might potentially break through the efficacy barrier observed with monotherapies as reviewed by Danese and colleagues.[28]

In the VEGA proof-of-concept trial, golimumab plus guselkumab combination therapy had greater efficacy than either monotherapy for a number of clinically important endpoints. After induction treatment, 83% of patients in the combination therapy group, 61% of patients in the golimumab monotherapy group, and 75% of patients in the guselkumab monotherapy group achieved clinical response. However, the prespecified criteria for statistical significance relative to guselkumab was not met. For the therapeutic target of clinical remission, a more stringent and regulatory accepted endpoint, there was a numerically greater effect with combination therapy than with the monotherapies. Notably, the magnitude of the differences observed were consistent with the hypothesis derived from a murine model that the combination of the two drugs would yield additive efficacy through effects on overlapping and non-overlapping molecular pathways involved in inflammatory bowel disease pathogenesis.[14] Similar results were observed for clinical endpoints (eg, symptomatic remission) based on patient-reported outcomes of stool frequency and rectal bleeding. This conclusion is further supported by analyses of endoscopy and histology measures that are less susceptible to expectation bias than symptom-based measures. Median faecal calprotectin concentrations at week 38 were 118 mg/kg in the combination therapy group, but were greater than the upper limit of normal (>250 mg/kg) in both monotherapy groups. Collectively, these results suggest that the efficacy of golimumab plus guselkumab combination therapy might be greater than either monotherapy and support the conduct of large-scale efficacy and safety studies. Combination therapy was limited to the 12-week induction period for safety evaluation reasons. Potential safety concerns for combination therapy use include increased risk of serious infection and neoplasia. Although this study was relatively small and of short duration, the frequency of adverse events, serious adverse events, and infections were not appreciably different among groups. Previous studies of TNF-antagonist and IL-1-antagonist and TNF and cytotoxic T-lymphocyte-associated antigen-4-antagonist combination therapy in patients with rheumatoid arthritis suggested these drugs might increase serious infections. Accordingly, the investigative community concluded that an unacceptable benefit–risk ratio exists for combining monoclonal antibodies.[29,30] However, it is unclear whether this assessment is broadly valid considering the imprecise data available and the inherent differences in mechanism of action for the drugs previously evaluated and those studied in VEGA.

A study strength was the observed treatment effect favouring combination therapy across a number of outcome measures, including endoscopic and histological outcomes. Inclusion of a maintenance phase generated exploratory data that suggest there might be a benefit of induction combination therapy despite withdrawal of golimumab. Although the study was conducted during the COVID-19 pandemic, the pandemic did not affect the study results.

This study had limitations. The small sample size precluded comprehensive determination of potential safety risks of combination therapy. The study was not powered to show differences in clinical remission rates, the accepted endpoint for regulatory approval. Additionally, a two-sided α error of 0·20 was used in this proof-of-concept study, and no adjustments were done for multiple comparisons, which raises the probability of type I errors occurring. All presented p values are considered nominal. The optimal duration of combination therapy requires further evaluation considering that efficacy of combination treatment was not assessed beyond week 10 when golimumab was withdrawn. The intent of this study was to evaluate the benefit–risk ratio of short-term combination therapy before exposing patients to combination therapy of longer duration. Because of these findings, larger studies of induction and maintenance combination therapy in ulcerative colitis and Crohn's disease are ongoing (ClinicalTrials.gov NCT05242484 and NCT05242471).

The results from this proof-of-concept trial suggest that combination therapy with guselkumab and golimumab could be a more effective treatment for ulcerative colitis than either drug alone. Larger randomised controlled trials are required to confirm these findings.

Contributors

BGF, BES, WJS, MG, MV, JS, SS, JJ, and JP were involved in data acquisition. MV, SS, and JJ verified the underlying data. All authors had full access to all the data in the study and accept responsibility to submit for publication. SS and JJ analysed the data. All authors drafted the article or revised it critically for important intellectual content with the assistance of a professional medical writer employed by Janssen Scientific Affairs. All authors agreed to be accountable for all aspects

of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

BGF reports consulting fees from AbbVie, AbolerIS, AgomAB Therapeutics, Allianthera, Amgen, AnaptysBio, Applied Molecular Transport, Arena Pharma, Avoro Capital Advisors, Atomwise, BioJamp, Biora Therapeutics, Boehringer-Ingelheim, Boxer, Celsius Therapeutics, Celgene/Bristol-Myers Squibb, Connect BioPharma, Cytoki, Disc Medicine, Duality, EcoR1, Eli Lilly, Equillium, Ermium, First Wave, First Word Group, Galapagos, Galen Atlantica, Genentech/Roche, Gilead, Gossamer Pharma, GlaxoSmithKline, Hinge Bio, Hot Spot Therapeutics, Index Pharma, Imhotex, Immunic Therapeutics, JAKAcademy, Janssen, Japan Tobacco, Kaleido Biosciences, Landos Biopharma, Leadiant, LEK Consulting, LifeSci Capital, Lument AB, Millennium, MiroBio, Morphic Therapeutics, Mylan, OM Pharma, Origo BioPharma, Orphagen, Pandion Therapeutics, Pendopharm, Pfizer, Prometheus Therapeutics and Diagnostics, Play to Know AG, Progenity, Protagonist, PTM Therapeutics, Q32 Bio, Rebiotix, REDX, Roche, Sandoz, Sanofi, Seres Therapeutics, Silverback Therapeutics, Surrozen, Takeda, Teva, Thelium, Tigenix, Tillotts, Ventyx Biosciences, VHSquared, Viatris, Ysios, Ysopia, and Zealand Pharma; is a member of the speakers bureau for AbbVie, Janssen, Takeda, and Boehringer-Ingelheim; has received payment for expert testimony from Morgan Lewis and Lenczner Slaght; has received support for attendance at meetings or travel from Janssen, AbbVie, Pfizer, Takeda, and Boehringer-Ingelhein; has participated on a Data Safety Monitoring Board or Advisory Board from AbbVie, Amgen, AMT, AnaptysBio, Boehringer-Ingelheim, Celgene/Bristol-Myers Squibb, Eli Lilly, Genentech/Roche, Janssen, MiroBio, Origo BioPharma, Pfizer, Prometheus, RedX Pharma, Sanofi, Takeda, Tillotts Pharma, Teva, Progenity, Index, Ecor1Capital, Morphic, GlaxoSmithKline, and Axio Research; and holds stock or stock options in Gossamer Pharma. 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Data sharing

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available online. Requests for access to the study data can be submitted through Yale Open Data Access.

For the **data sharing policy of Janssen Pharmaceutical Companies** see https://www.janssen.com/clinical-trials/transparency

For the **Yale Open Data Access project site** see http://yoda.yale.edu

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