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Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial

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Summary

Background The global prevalence of ulcerative colitis is increasing, and induction and maintenance of remission is a crucial therapeutic goal. We assessed the efficacy and safety of filgotinib, a once-daily, oral Janus kinase 1 preferential inhibitor, for treatment of ulcerative colitis.

Methods This phase 2b/3, double-blind, randomised, placebo-controlled trial including two induction studies and one maintenance study was done in 341 study centres in 40 countries. Eligible patients were aged 18–75 years with moderately to severely active ulcerative colitis for at least 6 months before enrolment (induction study A: inadequate clinical response, loss of response to or intolerance to corticosteroids or immunosuppressants, naive to tumour necrosis factor [TNF] antagonists and vedolizumab [biologic-naive]; induction study B: inadequate clinical response, loss of response to or intolerance to any TNF antagonist or vedolizumab, no TNF antagonist or vedolizumab use within 8 weeks before screening [biologic-experienced]). Patients were randomly assigned 2:2:1 to receive oral filgotinib 200 mg, filgotinib 100 mg, or placebo once per day for 11 weeks. Patients who had either clinical remission or a Mayo Clinic Score response at week 10 in either induction study entered the maintenance study. Patients who received induction filgotinib were rerandomised 2:1 to continue their induction filgotinib regimen or to placebo. Patients who received induction placebo continued receiving placebo. The primary endpoint was clinical remission by Mayo endoscopic, rectal bleeding, and stool frequency subscores at weeks 10 and 58. For the induction studies, efficacy was assessed in all randomised patients who received at least one dose of study drug or placebo within that study. For the maintenance study, efficacy was assessed in all patients randomised to any filgotinib treatment group in the induction studies who received at least one dose of study drug or placebo in the maintenance study. Patients who received placebo throughout the induction and maintenance study were not included in the full analysis set for the maintenance study. Safety was assessed in all patients who received at least one dose of the study drug or placebo within each study. This trial is registered with ClinicalTrials.gov, NCT02914522.

Findings Between Nov 14, 2016, and March 31, 2020, we screened 2040 patients for eligibility. 659 patients enrolled in induction study A were randomly assigned to receive filgotinib 100 mg (n=277), filgotinib 200 mg (n=245), or placebo (n=137). 689 patients enrolled into induction study B were randomly assigned to receive filgotinib 100 mg (n=285), filgotinib 200 mg (n=262), or placebo (n=142). 34 patients in induction study A and 54 patients in induction study B discontinued the study drug before week 10. After efficacy assessment at week 10, 664 patients entered the maintenance study (391 from induction study A, 273 from induction study B). 93 patients continued to receive placebo. 270 patients who had received filgotinib 100 mg in the induction study were randomly assigned to receive filgotinib 100 mg (n=179) or placebo (n=91). 301 patients who had received filgotinib 200 mg in the induction study were randomly assigned to receive filgotinib 200 mg (n=202) or placebo (n=99). 263 patients discontinued treatment in the maintenance study. At week 10, a greater proportion of patients given filgotinib 200 mg had clinical remission than those given placebo (induction study A 26·1% *vs* 15·3%, difference 10·8%; 95% CI 2·1–19·5, p=0·0157; induction study B 11·5% *vs* 4·2%, 7·2%; 1·6–12·8, p=0·0103). At week 58, 37·2% of patients given filgotinib 200 mg had clinical remission versus 11·2% in the respective placebo group (difference 26·0%, 95% CI 16·0–35·9; p<0·0001). Clinical remission was not significantly different between filgotinib 100 mg and placebo at week 10, but was significant by week 58 (23·8% *vs* 13·5%, 10·4%; 0·0–20·7, p=0·0420). The incidence of serious adverse events and adverse events of interest was similar between treatment groups. In the induction studies, serious adverse events occurred in 28 (5·0%) of 562 patients given filgotinib 100 mg, 22 (4·3%) of 507 patients given filgotinib 200 mg, and 13 (4·7%) of 279 patients given placebo. In the maintenance study, serious adverse events were reported in eight (4·5%) of 179 patients given filgotinib 100 mg, seven (7·7%) of 91 patients in the respective placebo group, nine (4·5%) of 202 patients in the filgotinib 200 mg group, and no patients in the respective placebo group. No deaths were reported during either induction study. Two patients died during the maintenance study; neither was related to treatment.

Interpretation Filgotinib 200 mg was well tolerated, and efficacious in inducing and maintaining clinical remission compared with placebo in patients with moderately to severely active ulcerative colitis.

Funding Gilead Sciences.

Introduction

The global prevalence of ulcerative colitis is rapidly increasing.[1,2] Ulcerative colitis is an immune-mediated disease characterised by chronic inflammation of the colon leading to bloody diarrhoea, frequent bowel movements, and tenesmus. The pathogenesis of ulcerative colitis is multifactorial and includes immune, genetic, environmental, and microbial components.[1] Available treatments for moderately to severely active ulcerative colitis include corticosteroids, immunosuppressants such as thiopurines and ciclosporin, tumour necrosis factor (TNF) antagonists, the anti-integrin vedolizumab, the interleukin-12/23 antagonist ustekinumab, and the Janus kinase (JAK) inhibitor tofacitinib.[3] A crucial therapeutic goal is the induction and maintenance of remission,[1] defined as both resolution of symptoms and objective evidence of improvement in the endoscopic appearance of the colonic mucosa.[4] Long-term aims include minimisation of the risks associated with corticosteroid exposure, colectomy, and colorectal cancer.[1,5] Despite the advent of targeted treatments, a substantial proportion of patients do not respond to treatment, lose response over time, or have adverse events,[6] and additional therapeutic options are therefore needed.

JAK–signal transducers and activators of transcription pathways are implicated in the pathogenesis of ulcerative colitis,[7–9] and JAK inhibition is effective for the treatment of ulcerative colitis.[10] Filgotinib, an oral JAK1 preferential inhibitor,[11] is in development for the treatment of inflammatory diseases including ulcerative colitis and Crohn's disease. Filgotinib preferentially inhibits JAK1 over JAK2, JAK3, and tyrosine kinase 2,[12] and could thereby confer an improved safety profile.[13–15] Filgotinib has been evaluated in several randomised controlled trials in patients with rheumatoid arthritis,[16–18] psoriatic arthritis,[19] and ankylosing spondylitis.[20] In patients with Crohn's disease, filgotinib 200 mg was superior to placebo for induction of clinical remission in the phase 2 FITZROY trial.[21] In the phase 2b/3 SELECTION trial, we aimed to assess the efficacy and safety of filgotinib in inducing and maintaining remission in patients with moderately to severely active ulcerative colitis.

Methods

Study design

This phase 2b/3 double-blind, randomised, placebo-controlled trial included two induction studies and one maintenance study in adults with moderately to severely active ulcerative colitis from 341 study centres (clinics, research centres, community centres, and academic hospitals) in 40 countries (Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, France, Georgia, Germany, Greece, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, South Korea, Romania, Russia, Serbia, Singapore, Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Ukraine, the UK, and the USA).

Research in context

Evidence before this study

The global prevalence of ulcerative colitis is increasing, and the field of inflammatory bowel disease is advancing rapidly. However, despite some available therapies, including one pan-Janus kinase (JAK) inhibitor, tofacitinib, there remains a substantial unmet need for effective, well tolerated treatments for ulcerative colitis. We searched PubMed with the terms "ulcerative colitis", "treatment", and "moderate to severe" to identify articles in English published from Jan 1, 2016, to Nov 1, 2020. We found 592 articles describing the treatment of ulcerative colitis. The efficacy and safety of once-daily oral JAK1 preferential inhibitor filgotinib has been investigated in a randomised controlled trial in Crohn's disease.

Added value of this study

SELECTION was the first randomised, placebo-controlled, combined phase 2b–3 trial to evaluate the efficacy and safety of filgotinib for induction and maintenance of remission in patients with moderately to severely active ulcerative colitis. Efficacy relative to placebo was shown for filgotinib 200 mg once per day for induction and maintenance of remission. Filgotinib was well tolerated and the incidence of serious adverse events was not different to placebo.

Implications of all the available evidence

The SELECTION trial provides evidence for the efficacy of filgotinib in patients with moderately to severely active ulcerative colitis. Filgotinib could represent a new treatment option for patients with moderately to severely active ulcerative colitis who are either naive to biologic therapy or have had previous treatment with biologics.

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The final protocol and five amendments were reviewed and approved by the Independent Ethics Committee or Institutional Review Board at each study site. The study was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. A copy of the protocol can be found in the appendix (p 4).

See Online for appendix

Participants

Eligible patients were aged 18–75 years at screening and had a diagnosis of ulcerative colitis with endoscopic and histopathologic evidence of ulcerative colitis for at least 6 months before enrolment. Patients had moderately to severely active ulcerative colitis (Mayo endoscopy subscore ≥2, rectal bleeding subscore ≥1, stool frequency subscore ≥1, physician's global assessment subscore ≥2; total Mayo Clinic Score [MCS] 6–12). Full details of inclusion and exclusion criteria for all studies are provided in the appendix (p 4).

Eligible patients were enrolled into one of two induction studies (A and B) based on their experience with TNF antagonists or vedolizumab. Eligible patients who had an inadequate clinical response, loss of response to or intolerance to corticosteroids or immunosuppressants, and were naive to TNF antagonists and vedolizumab (biologic-naive) were enrolled in induction study A. Eligible patients who had an inadequate clinical response, loss of response to or intolerance to any TNF antagonist or vedolizumab, and had not used any TNF antagonist or vedolizumab within 8 weeks before screening (biologic-experienced) were enrolled in induction study B. Patients who had previously received any JAK inhibitor were not eligible for either induction study, following an amendment to the protocol.

Concomitant medications permitted during the studies were oral 5-aminosalicylic acid, azathioprine, 6-mercaptopurine, methotrexate (if the dose was stable for 4 weeks before and 10 weeks after randomisation), and prednisone at a dose of up to 30 mg/day or budesonide at a dose of up to 9 mg/day (if the dose was stable for 2 weeks before and 14 weeks after randomisation). Starting at week 14, corticosteroids had to be tapered according to a predefined schedule. Corticosteroids could be increased in dose or restarted at doses up to and including the baseline dose if symptoms returned, according to the investigator's judgment. Treatment was considered to have failed for patients who received corticosteroids at a dose higher than their baseline dose, but these patients were permitted to remain in the study.

Randomisation and masking

Patients in induction studies A and B were randomly assigned (2:2:1) to receive filgotinib or matched placebo. Efficacy was assessed at week 10, and patients who had either clinical remission or MCS-defined response were rerandomised 2:1 at week 11 to continue their induction filgotinib regimen or to receive placebo to week 58 (maintenance study). Placebo responders continued to receive placebo in the maintenance study. Patients who did not have either clinical remission or MCS response at week 10 had the option to enter a separate, long-term extension study (SELECTIONLTE, NCT02914535). Patients who met disease worsening criteria in the maintenance study were discontinued from treatment and offered open-label filgotinib in SELECTIONLTE (appendix p 7). Patients who completed week 58 were also eligible for enrolment in SELECTIONLTE.

Patients were stratified by use of oral systemic corticosteroids on day 1 and use of immunosuppressants (6-mercaptopurine, azathioprine, and methotrexate) on day 1 (induction study A); by the same factors as induction study A and by previous exposure to one versus more than one biologic agent (induction study B); and by the same factors as induction study A and by participation in induction study A or B in the maintenance study. Randomisation was done via an interactive web response system. All people directly involved in the conduct and analysis of the trial (including patients, investigators, and study personnel) were fully masked to treatment allocation before the week 58 database lock. To maintain masking, study drug appearance, packaging, and labels were identical irrespective of treatment.

Procedures

Participants were randomly assigned to receive oral filgotinib (Mayne Pharma, NC, USA, or Rottendorf Pharma, Ennigerloh, Germany) 200 mg, filgotinib 100 mg, or placebo, once daily for 11 weeks. Doses were based on the results of the phase 2 FITZROY study in Crohn's disease.[21] Because of concerns from regulatory agencies in the USA and South Korea about the potential effect of filgotinib on semen, men from these countries for whom two biologic therapies (a TNF antagonist and vedolizumab) had not failed were randomised (2:1) to receive filgotinib 100 mg or placebo. Only men for whom both therapies had failed were randomly assigned to filgotinib 200 mg or placebo.

Patients recorded symptoms of rectal bleeding and stool frequency daily in an eDiary. A colonoscopy or flexible sigmoidoscopy with biopsy was done at baseline, week 10, and week 58, and centrally read for assessment of endoscopy and histopathology. Methods pertaining to central reading are included in the appendix (p 7). Blood samples for pharmacokinetic assessments were obtained at weeks 4, 10, 26, and 58, and used to determine plasma concentrations of filgotinib and its primary metabolite, GS-829845. Patients who gave their consent to take part in the optional pharmacokinetic substudy had additional pharmacokinetic samples obtained before treatment and at 30 min and 1, 2, 3, 4, and 6 h after supervised dosing in the clinic visit between week 2 and week 10. Plasma

concentrations of filgotinib and GS-829845 were determined as described previously.[22,23]

Outcomes

Definitions of efficacy endpoints are provided in the panel. The primary outcome was clinical remission at week 10 and week 58. Clinical remission was defined by use of the Mayo endoscopic, rectal bleeding, and stool frequency subscores (the three-component version of MCS, distinct to the four-component total MCS) in accordance with regulatory feedback at the time of study design.[25,26]

Key secondary objectives of the induction studies were MCS remission, endoscopic remission, histologic remission, and MCS remission (alternative definition) at week 10 in induction studies A and B, and at week 58. 6-month corticosteroid-free clinical remission and sustained clinical remission were also assessed at week 58 in the maintenance study. Exploratory efficacy endpoints included MCS response and endoscopic improvement at week 10 and week 58. Exploratory endpoints included MCS response, endoscopic improvement, and health-related quality of life measures. Details of these measures and post hoc analyses on speed of onset of action and corticosteroid-related measures will be reported separately.

Safety assessments included adverse events, concomitant medications, laboratory analyses, vital signs, electrocardiograms, and physical examinations (intervals differed between variables). The severity of adverse events and clinical laboratory results were graded by use of the modified Common Terminology Criteria for Adverse Events, version 4.03.

Statistical analysis

We estimated that a sample size of 130 in the placebo group and 260 in each filgotinib group (650 in each induction study) would provide 90% power for each filgotinib dose group comparison with placebo at a two-sided significance level of 0·025, to detect a difference of 15% in clinical remission rate (25% for filgotinib *vs* 10% for placebo). Assuming a response rate of 55% in patients assigned to filgotinib 200 mg or 100 mg in the induction studies, approximately 285 patients from each filgotinib dose group from induction study A and B combined were needed for rerandomisation into the maintenance study. A sample size of 190 patients in each filgotinib group and 95 patients in each respective placebo group in the maintenance study would provide more than 85% power for each filgotinib dose group comparison with placebo at a two-sided significance level of 0·025, to detect a difference of 20% in clinical remission rate (40% for filgotinib *vs* 20% for placebo).

Efficacy endpoints were analysed by use of the full analysis sets. For the induction studies, these included all randomised patients who received at least one dose of study drug within that study. For the maintenance study, the full analysis set included all patients randomised to either filgotinib treatment group in the induction studies who had clinical remission or an MCS response at week 10, were rerandomised in the maintenance study, and who received at least one dose of study drug in the maintenance period. Patients who received placebo throughout the induction and maintenance study were not included in the full analysis set for the maintenance study. Safety endpoints were analysed by use of data from all patients who received at least one dose of the study drug or placebo within each study.

***Panel:* Efficacy endpoint definitions**

Primary endpoint

Clinical remission

- Mayo endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1 point decrease in stool frequency from induction baseline for a subscore of 0 or 1

Key secondary endpoints

Mayo Clinic Score (MCS) remission

- A total MCS of 2 or less and no single subscore higher than 1

MCS remission (alternative definition)

- Rectal bleeding, stool frequency, and physician's global assessment subscores of 0 and an endoscopic subscore of 0 or 1; overall MCS of 1 or 0

Endoscopic remission

- Mayo endoscopic subscore of 0

Histologic remission

- Based on the Geboes Scale. No or mild increase in chronic inflammatory infiltrate in lamina propria, no neutrophils in lamina propria or epithelium, and no erosion, ulceration, or granulation tissue (Grade 0 of ≤0·3, Grade 1 of ≤1·1, Grade 2a of ≤2A·3, Grade 2b of 2B·0, Grade 3 of 3·0, Grade 4 of 4·0, and Grade 5 of 5·0)[24]

6-month corticosteroid-free remission

- Clinical remission with no corticosteroid use for the indication of ulcerative colitis for at least 6 months before week 58 in patients who were on corticosteroids at baseline of the maintenance study

Sustained clinical remission

- Clinical remission at both week 10 and week 58

Exploratory endpoints

MCS response

- A reduction of 3 or more points in MCS and at least 30% from induction baseline with an accompanying decrease in rectal bleeding subscore of 1 point or more, or an absolute rectal bleeding subscore of 0 or 1

Endoscopic improvement

- Mayo endoscopic subscore of 0 or 1

Health-related quality of life (HRQoL)

- Change from baseline in HRQoL scores; HRQoL measures comprised the 36-Item Short Form Survey, the Work Productivity and Activity Impairment Questionnaire, the European Quality of Life 5-Dimension Questionnaire, and the Inflammatory Bowel Disease Questionnaire

Post hoc analyses

Mucosal healing

- Endoscopic improvement and histologic remission in the same patient

The hypothesis testing procedures for the induction studies and the maintenance study are outlined in the appendix (p 9). A graphical approach to sequentially rejective test procedures was used to control a family-wise type I error rate at 5% (α=0·05) for each individual study. A Bonferroni approach with equal α allocation of 0·025 (two-sided) to each filgotinib dose group comparison with placebo was used to control the overall study-wide type I error rate at 0·05 within each study. Because of the unblinded interim futility analysis for each induction study, an α of 0·00001 was spent for each filgotinib dose group comparison with placebo within each induction study. Accordingly, a nominal p<0·02499 (two-sided) was needed to declare statistical significance for the final primary analysis of each filgotinib dose group when compared with placebo in each induction study. Given that no interim analysis was planned, the significance level for the final primary analysis in the maintenance study was set as 0·025 (two-sided) for each filgotinib dose group versus placebo.

Primary, key secondary, and binary exploratory efficacy endpoints were analysed by use of stratified Cochran-Mantel-Haenszel tests. A non-responder imputation approach was used to impute missing values. Separate comparisons were done between the filgotinib 200 mg

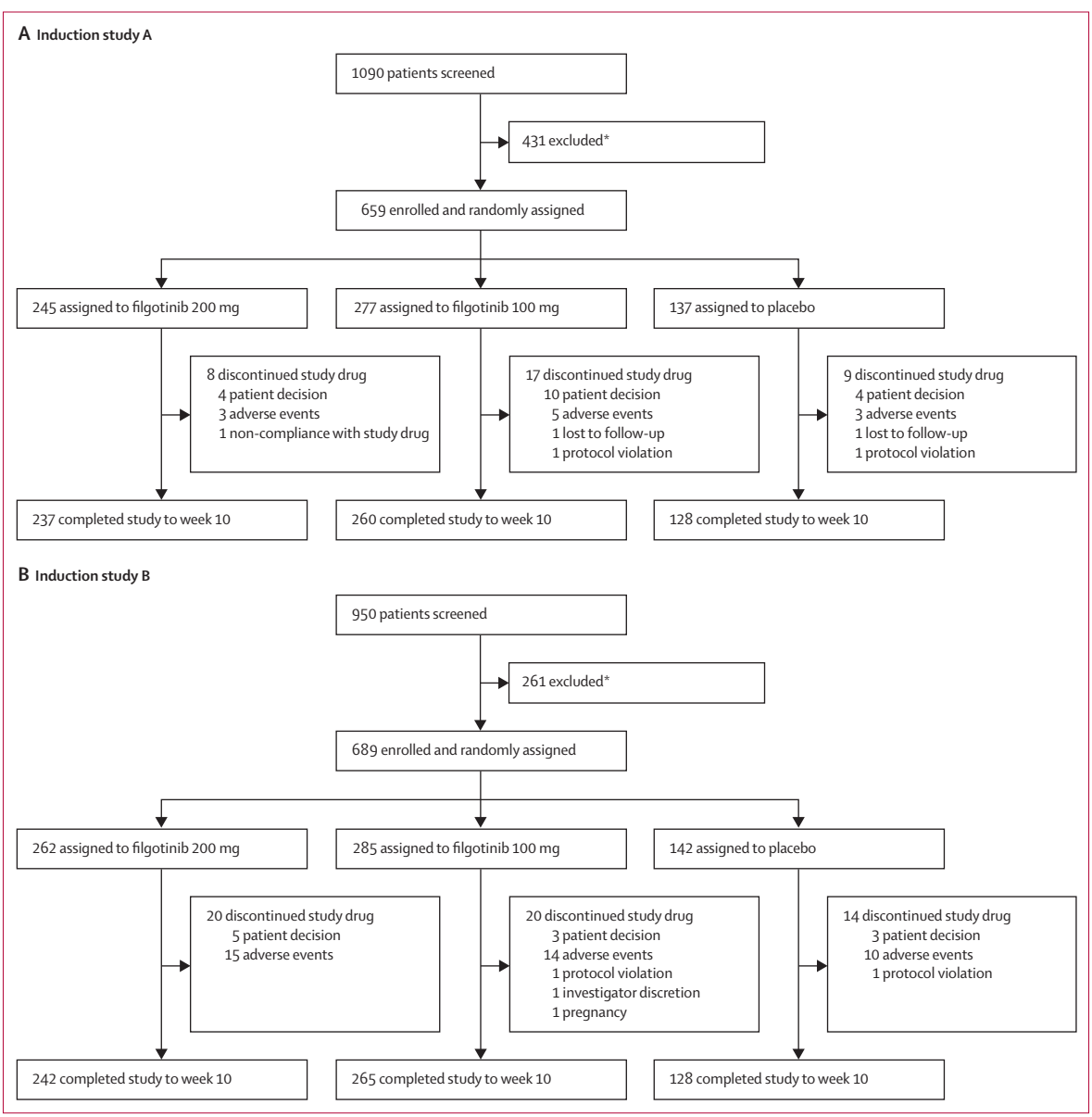

Figure 1: **Trial profile**
*Validated output for patients who failed screening were not available.

	Induction study A: biologic-naive patients			Induction study B: biologic-experienced patients		
	Placebo (n=137)	Filgotinib 100 mg (n=277)	Filgotinib 200 mg (n=245)	Placebo (n=142)	Filgotinib 100 mg (n=285)	Filgotinib 200 mg (n=262)
Age, years	41 (12·9)	42 (13·3)	42 (13·1)	44 (14·9)	43 (14·3)	43 (14·2)
Sex						
Female	50 (36·5%)	120 (43·3%)	122 (49·8%)	56 (39·4%)	99 (34·7%)	114 (43·5%)
Male	87 (63·5%)	157 (56·7%)	123 (50·2%)	86 (60·6%)	186 (65·3%)	148 (56·5%)
Duration of ulcerative colitis, years	6·4 (7·4)	6·7 (7·4)	7·2 (6·9)	10·2 (8·2)	9·7 (7·2)	9·8 (7·6)
Total Mayo Clinic Score	8·7 (1·3)	8·6 (1·4)	8·6 (1·3)	9·3 (1·4)	9·3 (1·3)	9·2 (1·4)
Mayo endoscopy subscore of 3	76 (55·5%)	159 (57·4%)	133 (54·3%)	111 (78·2%)	222 (77·9%)	203 (77·5%)
C-reactive protein, mg/L	5·8 (7·6)	7·8 (17·4)	8·6 (16·3)	14·0 (24·3)	11·7 (18·0)	12·2 (14·9)
Faecal calprotectin, µg/g	2231 (2917)	2001 (3448)	2059 (2639)	2479 (3571)	2236 (3095)	2845 (4077)
Concomitant use of systemic corticosteroids*	34 (24·8%)	67 (24·2%)	54 (22·0%)	51 (35·9%)	103 (36·1%)	94 (35·9%)
Concomitant use of immunosuppressants*†	33 (24·1%)	63 (22·7%)	53 (21·6%)	21 (14·8%)	34 (11·9%)	34 (13·0%)
Concomitant use of systemic corticosteroids and immunosuppressants	8 (5·8%)	19 (6·9%)	20 (8·2%)	11 (7·7%)	28 (9·8%)	28 (10·7%)
Prednisone-equivalent dose, mg/day	20·0 (15·0–30·0)	15·0 (10·0–25·0)	20·0 (10·0–25·0)	20·0 (10·0–20·0)	20·0 (10·0–20·0)	15·0 (10·0–20·0)
Number of previous biologic agents‡						
0	137 (100·0%)	275 (99·3%)	245 (100·0%)	3 (2·1%)	2 (0·7%)	3 (1·1%)
1	..	1 (0·4%)	..	46 (32·4%)	98 (34·4%)	80 (30·5%)
2	..	1 (0·4%)	..	45 (31·7%)	109 (38·2%)	90 (34·4%)
≥3	..	..	..	48 (33·8%)	76 (26·7%)	89 (34·0%)
Previous use of at least one TNF antagonist	..	2 (0·7%)	..	130 (91·5%)	266 (93·3%)	242 (92·4%)
Previous use of vedolizumab	..	1 (0·4%)	..	85 (59·9%)	145 (50·9%)	164 (62·6%)
Previous use of at least one TNF antagonist and vedolizumab	..	1 (0·4%)	..	76 (53·5%)	128 (44·9%)	147 (56·1%)
Previous failure of a TNF antagonist and vedolizumab	..	1 (0·4%)	..	64 (45·1%)	113 (39·6%)	120 (45·8%)

Data are n (%), mean (SD), or median (IQR). TNF=tumour necrosis factor. *Corticosteroids or immunosuppressants, but not both. †6-mercaptopurine, azathioprine, and methotrexate. ‡Patients who received biologic agents in induction study A and patients who did not receive biologic agents in induction study B were ineligible.

Table 1: **Baseline demographics and characteristics of patients in induction studies A and B**

and placebo group, and between the filgotinib 100 mg and placebo group in induction studies A and B and between the filgotinib 200 mg and the respective placebo group, and the filgotinib 100 mg and the respective placebo group in the maintenance study. Continuous exploratory efficacy endpoints were either summarised by descriptive statistics or by an analysis of covariance model adjusting for stratification factors and baseline values. A last observation carried forward approach was used to impute the missing values for continuous endpoints in the model. Baseline demographics and characteristics, safety data, and pharmacokinetic data were summarised by descriptive statistics. Pharmacokinetic analyses were done by use of non-compartmental analyses in conjunction with a non-linear mixed-effects population modelling approach. Statistical analyses were done by use of SAS version 9.4. This study is registered with ClinicalTrials.gov, NCT02914522.

Role of the funding source

The funder of the study was involved in the study design and the data collection and analysis. The study funder provided funding for medical writing assistance with manuscript preparation.

Results

Between Nov 14, 2016, and March 31, 2020, we screened 2040 patients for eligibility into the induction studies. 1090 patients were screened for eligibility into induction study A, of whom 659 biologic-naive patients were enrolled and randomly assigned to receive filgotinib 100 mg (n=277), filgotinib 200 mg (n=245), or placebo (n=137). 950 patients were screened for eligibility into induction study B, of whom 689 biologic-experienced patients were enrolled and randomly assigned to receive filgotinib 100 mg (n=285), filgotinib 200 mg (n=262), or placebo (n=142; figure 1). Following the efficacy assessment at week 10, 664 patients entered the maintenance

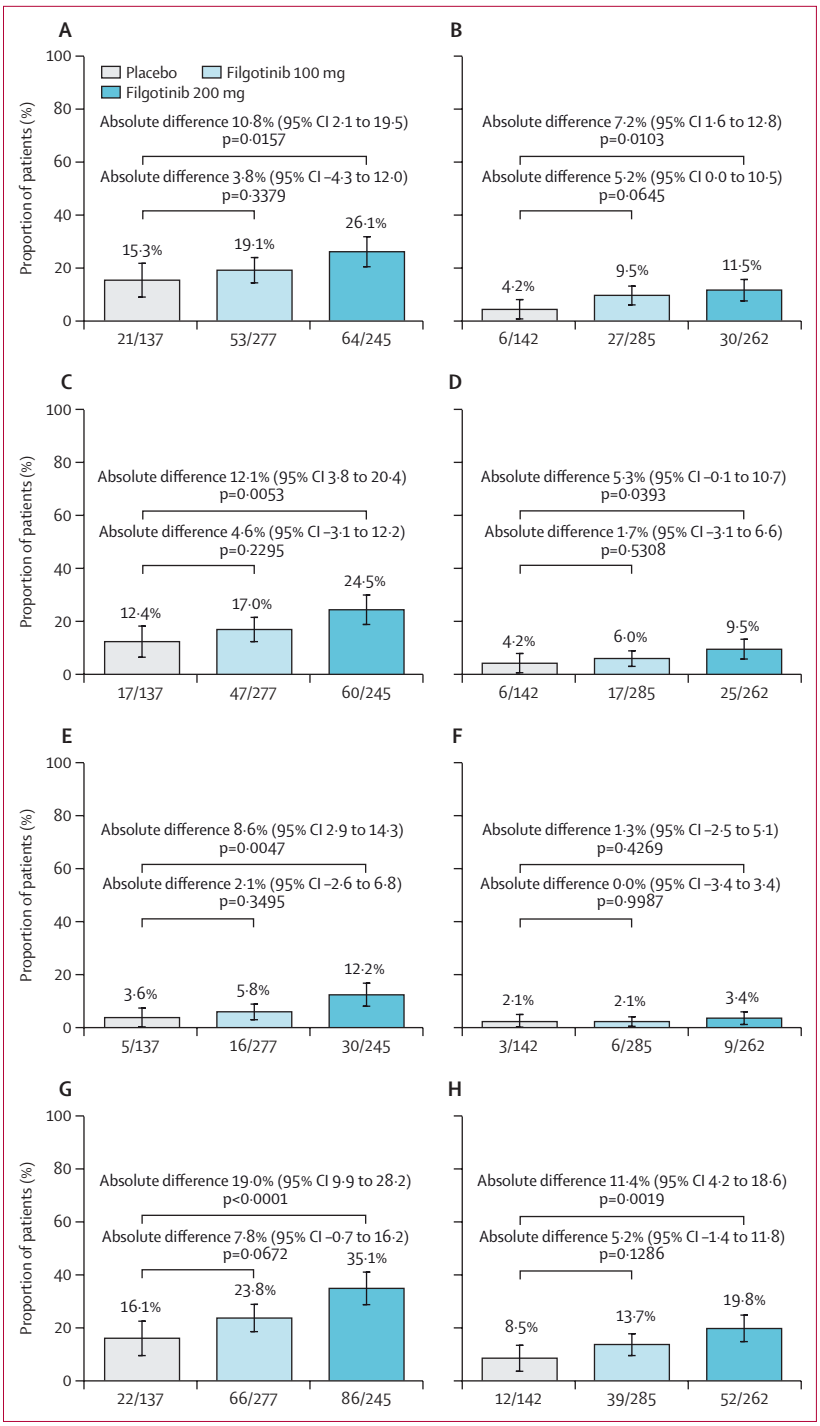

Figure 2: **Remission and key secondary endpoints at week 10 in patients given filgotinib or placebo for ulcerative colitis (induction studies)**

(A) Clinical remission in biologic-naive patients. (B) Clinical remission in biologic-experienced patients. (C) MCS remission in biologic-naive patients. (D) MCS remission in biologic-experienced patients. (E) Endoscopic remission in biologic-naive patients. (F) Endoscopic remission in biologic-experienced patients. (G) Histological remission in biologic-naive patients. (H) Histological remission in biologic-experienced patients. Error bars indicate 95% CI. MCS=Mayo Clinic Score.

study (391 [58·9%] of 664 patients were from induction study A and 273 [41·1%] were from induction study B). 93 patients who had responded while receiving placebo in the induction study were assigned to continue placebo. 270 patients who had received filgotinib 100 mg in the induction study were randomly assigned to receive filgotinib 100 mg (n=179) or placebo (n=91). 301 patients who had received filgotinib 200 mg in the induction study were randomly assigned to receive filgotinib 200 mg (n=202) or placebo (n=99). Full details of the groups in the maintenance study, including patient discontinuations, can be found in the appendix (p 11).

Baseline characteristics were similar between treatment groups in each induction study (table 1). 55·8% of biologic-naive patients (induction study A) and 77·8% of biologic-experienced patients (induction study B) had a Mayo endoscopic subscore of 3. Median baseline prednisone-equivalent dose was 20·0 mg/day in both induction trials. 30·7% of biologic-naive patients were receiving systemic corticosteroids at baseline compared with 45·7% of biologic-experienced patients. 43·1% of biologic-experienced patients had failure of both a TNF antagonist and vedolizumab. The baseline characteristics of patients who participated in the maintenance study were similar across treatment groups (appendix p 16).

In induction study A, 34 patients discontinued treatment (17 patients assigned to filgotinib 100 mg [ten patient decisions, five adverse events, one lost to follow-up, one protocol violation]; eight patients assigned to filgotinib 200 mg [four patient decisions, three adverse events, one non-compliance with study drug]; and nine patients assigned to placebo [four patient decisions, three adverse events, one loss to follow-up, one protocol violation]). 625 patients from induction study A completed study drug or placebo to week 10. In induction study B, 54 patients discontinued treatment (20 patients assigned to filgotinib 100 mg [14 adverse events, three patient decisions, one protocol violation, one investigator's decision, one pregnancy]; 20 patients assigned to filgotinib 200 mg [15 adverse events, five patient decisions]; and 14 patients assigned to placebo [ten adverse events, three patient decisions, one protocol violation]). 635 patients from induction study B completed study drug or placebo to week 10. In the maintenance study, 263 patients discontinued treatment (75 patients assigned to filgotinib 100 mg, 52 patients assigned to filgotinib 200 mg, and 136 patients assigned to placebo). 401 patients completed the maintenance study to week 58. The most common reason for study drug discontinuation in the maintenance study for all treatment groups was disease worsening (for full details see appendix p 11).

In induction study A, 64 (26·1%) of 245 biologic-naive patients given filgotinib 200 mg had clinical remission at week 10, compared with 21 (15·3%) of 137 patients given placebo (absolute difference 10·8%, 95% CI 2·1–19·5; p=0·0157, figure 2A). In induction study B, 30 (11·5%) of

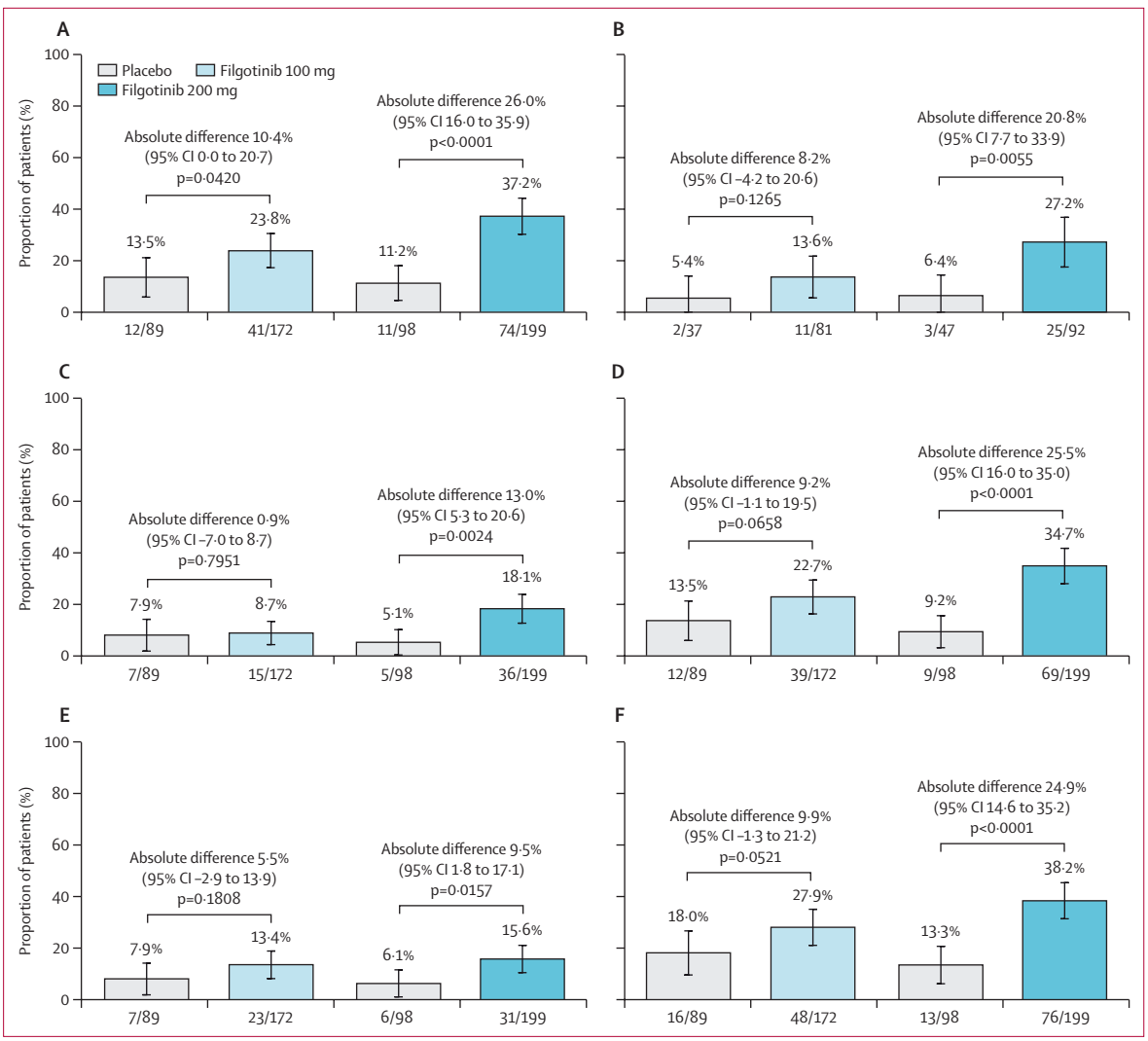

Figure 3: **Proportion of patients with clinical remission and key secondary efficacy endpoints at week 58 in patients given filgotinib or placebo for ulcerative colitis (maintenance study)**

(A) Clinical remission. (B) 6-month corticosteroid-free remission. (C) Sustained clinical remission. (D) MCS remission. (E) Endoscopic remission. (F) Histological remission. Error bars indicate 95% CI. MCS=Mayo Clinic Score.

262 biologic-experienced patients given filgotinib 200 mg had clinical remission at week 10, compared with six (4·2%) of 142 patients given placebo (absolute difference 7·2%, 95% CI 1·6–12·8; p=0·0103, figure 2B). The differences in clinical remission between filgotinib 100 mg and placebo were not statistically significant at week 10 in either induction study (biologic-naive filgotinib 100 mg *vs* placebo p=0·3379, biologic-experienced filgotinib 100 mg *vs* placebo p=0·0645; figure 2A).

In the maintenance study, 74 (37·2%) of 199 patients in the filgotinib 200 mg group had clinical remission at week 58, compared with 11 (11·2%) of 98 patients assigned to placebo (absolute difference 26·0%, 95% CI 16·0–35·9; p<0·0001, figure 3A). 41 (23·8%) of 172 patients assigned to filgotinib 100 mg had clinical remission at week 58 compared with 11 (13·5%) of 81 patients assigned to placebo, and this difference was statistically significant (absolute difference 10·4%, 95% CI 0·0–20·7; p=0·0420, figure 3A).

36 (62·1%) of 58 patients given filgotinib 200 mg and five (13·9%) of 36 patients given placebo were in clinical remission at both week 10 and week 58. 15 (27·8%) of 54 patients in the filgotinib 100 mg group and seven (29·2%) of 24 patients in the placebo group were in clinical remission at both timepoints.

The treatment effect of filgotinib 200 mg on clinical remission relative to placebo at week 58 was consistent across the prespecified subgroups (biologic-naive *vs* biologic-experienced patients, TNF antagonist failure status, vedolizumab failure status, and dual refractory status [failure of both a TNF antagonist and vedolizumab]; appendix p 12).

	Placebo (n=279)	Filgotinib 100 mg (n=562)	Filgotinib 200 mg (n=507)
Total duration of study drug exposure, weeks	10·7 (1·93)	10·8 (1·91)	10·8 (1·58)
Treatment-emergent adverse events			
Adverse events	157 (56·3%)	283 (50·4%)	272 (53·6%)
Serious adverse events	13 (4·7%)	28 (5·0%)	22 (4·3%)
Adverse events leading to study drug discontinuation	14 (5·0%)	20 (3·6%)	23 (4·5%)
Deaths	0	0	0
Adverse events of interest			
Infections	39 (14·0%)	82 (14·6%)	92 (18·1%)
Serious infections	3 (1·1%)	6 (1·1%)	3 (0·6%)
Herpes zoster	0	1 (0·2%)	3 (0·6%)
Opportunistic infections	0	0	1 (0·2%)
Malignancies*	0	1 (0·2%)	1 (0·2%)
Non-melanoma skin cancer	1 (0·4%)	0	2 (0·4%)
Gastrointestinal perforation	1 (0·4%)	0	0
Venous thrombosis excluding pulmonary embolism	0	0	0
Pulmonary embolism	0	0	1 (0·2%)
Arterial thrombosis	0	0	0
Cerebrovascular events	1 (0·4%)	0	0
Abnormal laboratory test results†			
Haemoglobin <8g/dL	8 (2·9%)	10 (1·8%)	10 (2·0%)
WBC <2000/mm³	1 (0·4%)	1 (0·2%)	3 (0·6%)
Neutrophils <1000/mm³	2 (0·7%)	7 (1·3%)	3 (0·6%)
Lymphocytes <500/mm³	6 (2·2%)	10 (1·8%)	11 (2·2%)
AST >5 × ULN	0	1 (0·2%)	1 (0·2%)
ALT >5 × ULN	2 (0·7%)	0	1 (0·2%)
CK >5 × ULN	0	4 (0·7%)	7 (1·4%)
Triglycerides >500 mg/dL	0	2 (0·4%)	1 (0·2%)

Data are n (%) or mean (SD). ALT=alanine aminotransferase. AST=aspartate aminotransferase. CK=creatine kinase. ULN=upper limit of normal. WBC=white blood cells. *Excluding non-melanoma skin cancer. †A treatment-emergent laboratory abnormality was defined as an increase of at least one grade from baseline at any post-baseline timepoint up to the maintenance first dose date or 30 days after the induction last dose date, whichever was earlier.

Table 2: **Summary of safety outcomes in induction studies A and B combined**

A greater proportion of biologic-naive patients given filgotinib 200 mg than those given placebo had MCS remission, endoscopic remission, histologic remission, and MCS remission (alternative definition) at week 10 (figure 2; appendix p 13). There were no statistically significant differences in these key secondary endpoints for filgotinib 100 mg relative to placebo in biologic-naive patients. In biologic-experienced patients, differences in prespecified secondary endpoints between patients given filgotinib (either dose) and patients given placebo were not statistically significant at week 10 (figure 2).

At week 58, a greater proportion of patients who received filgotinib 200 mg had 6-month corticosteroid-free clinical remission, sustained clinical remission, MCS remission, endoscopic remission, histologic remission, and MCS remission (alternative definition) than those who received placebo (figure 3; appendix p 13). There were no significant differences in the proportion of patients with these endpoints between patients given filgotinib 100 mg and those given placebo (figure 3; appendix p 13).

In both induction studies and the maintenance study, a greater proportion of patients in the filgotinib 200 mg and 100 mg groups had an MCS response and endoscopic improvement than in the placebo group (appendix p 14). Changes from baseline were greater in the filgotinib 200 mg group than the placebo group in the total and all four domain scores of the Inflammatory Bowel Disease Questionnaire, 36-Item Short Form Survey mental component summary and physical component summary (appendix p 17). We recorded greater improvements in the filgotinib 200 mg group than the placebo group in the presenteeism, work productivity loss, and activity impairment domains of the Work Productivity and Activity Impairment questionnaire, and the European Quality of Life 5-Dimension questionnaire visual analogue scale.

The treatment effect of filgotinib 200 mg compared with placebo in all key secondary endpoints was consistent between biologic-naive and biologic-experienced patients at week 58 (appendix p 29). Greater proportions of patients in the filgotinib 200 mg group than in the respective placebo group had mucosal healing in all studies (appendix p 15).

In the induction studies, the proportion of patients who had treatment-emergent adverse events was similar between the placebo, filgotinib 100 mg, and filgotinib 200 mg groups (table 2). In the maintenance study, adverse events were reported for a similar proportion of patients in the placebo groups and filgotinib 100 mg and filgotinib 200 mg groups. In all three studies, most adverse events were mild or moderate in severity. The most frequent adverse events in the induction studies were nasopharyngitis, headache, and ulcerative colitis (data not shown). The most frequent adverse events in the maintenance study were worsening of ulcerative colitis, nasopharyngitis, arthralgia, headache, abdominal pain, and upper respiratory tract infections (appendix p 31). The proportion of patients who discontinued treatment owing to adverse events was similar across treatment groups in the induction and maintenance studies (tables 2, 3).

In the induction studies, serious adverse events occurred in 28 (5·0%) of 562 patients given filgotinib 100 mg, 22 (4·3%) of 507 patients given filgotinib 200 mg, and 13 (4·7%) of 279 patients given placebo (table 2). In the maintenance study, serious adverse events were reported in eight (4·5%) of 179 patients given filgotinib 100 mg and seven (7·7%) of 91 patients in the respective placebo group, by nine (4·5%) of 202 patients in the filgotinib 200 mg group, and no patients in the respective placebo group (table 3). Exposure-adjusted incidence rates of serious adverse events were similar across treatment groups in the induction and maintenance studies (appendix p 31).

The incidence of infections and serious infections was similar between treatment groups in all three studies

(tables 2, 3). The exposure-adjusted incidence rate of infections and serious infections was also similar between patients who received placebo, filgotinib 100 mg, and filgotinib 200 mg in all three studies (appendix p 33). Six patients from all studies had herpes zoster infections, none of which were serious or complicated (multidermatomal, disseminated, ophthalmic, or with CNS involvement), or resulted in discontinuation of the study drug. The exposure-adjusted incidence rate of herpes zoster was similar across treatment groups in all three studies (appendix p 33). One patient in induction study A who received filgotinib 200 mg had an opportunistic infection of mild oesophageal candidiasis that resolved with treatment.

One patient with hypothyroidism and pulmonary symptoms of unknown origin who was taking prednisone and who received filgotinib 200 mg had pulmonary embolism in induction study B. No patients who received filgotinib 100 mg or 200 mg had venous thromboses or pulmonary embolism in the maintenance study. Two patients who received placebo in the induction study and then in the maintenance study had venous thromboses.

Non-melanoma skin cancers occurred in three patients in the induction studies and one patient in the maintenance study. All patients with non-melanoma skin cancer had been previously treated with thiopurines. Malignancies were reported in three patients (one colon cancer in induction study A, filgotinib 100 mg [diagnosed during the maintenance study based on findings in the induction phase]; one breast cancer in induction study B, filgotinib 200 mg; one malignant melanoma in the maintenance study, filgotinib 200 mg). Other adverse events of interest are reported in tables 2 and 3.

No deaths were reported during either induction study. Two patients died during the maintenance study (one left ventricular failure, one asthma), neither death was deemed related to the study treatment by the investigator (appendix p 10).

The proportion of patients with treatment-emergent laboratory abnormalities (an increase of at least one grade) was similar across studies and treatment groups (tables 2, 3). In the induction studies, a small increase in lipids (total cholesterol, LDL, and HDL) was observed in the filgotinib groups (appendix p 34). In the maintenance study, lipid concentrations remained stable in the filgotinib groups. The proportion of patients with abnormal creatine kinase increase was higher in the filgotinib groups than in the placebo groups in all three studies, but no rhabdomyolysis associated with increased creatine kinase was reported in patients who received filgotinib.

Data from 41 patients who participated in the pharmacokinetic substudy suggested that the pharmacokinetics of filgotinib and GS829845 were similar in biologic-naive and biologic-experienced patients. Filgotinib and GS829845 exposures were approximately dose proportional from 100 mg to 200 mg (appendix p 35). The median concentration at the end of the dosing interval was similar between patients in the induction and maintenance studies. Filgotinib and GS829845 exposures overlapped substantially between patients who met the primary endpoint in either the induction or maintenance phase and those who did not for both dose regimens. Filgotinib exposures were similar for patients who reported the most common adverse events or

	Placebo* (n=93)	Placebo† (n=91)	Filgotinib 100 mg (n=179)	Placebo‡ (n=99)	Filgotinib 200 mg (n=202)
Total duration of study drug exposure, weeks	38·1 (15·2)	29·2 (18·6)	34·5 (16·8)	28·8 (17·7)	39·4 (14·3)
Treatment-emergent adverse events					
Adverse events	57 (61·3%)	60 (65·9%)	108 (60·3%)	59 (59·6%)	135 (66·8%)
Serious adverse events	4 (4·3%)	7 (7·7%)	8 (4·5%)	0	9 (4·5%)
Adverse events leading to study drug discontinuation	3 (3·2%)	4 (4·4%)	10 (5·6%)	2 (2·0%)	7 (3·5%)
Deaths	0	0	0	0	2 (1·0%)
Adverse events of interest					
Infections	21 (22·6%)	27 (29·7%)	46 (25·7%)	25 (25·3%)	71 (35·1%)
Serious infections	1 (1·1%)	2 (2·2%)	3 (1·7%)	0	2 (1·0%)
Herpes zoster	0	1 (1·1%)	0	0	1 (0·5%)
Opportunistic infections	0	0	0	0	0
Malignancies§	0	0	1 (0·6%)	0	1 (0·5%)
Non-melanoma skin cancer	0	0	1 (0·6%)	0	0
Gastrointestinal perforation	0	0	0	0	0
Venous thrombosis excluding pulmonary embolism	2 (2·2%)	0	0	0	0
Pulmonary embolism	0	0	0	0	0
Arterial thrombosis¶	0	0	1 (0·6%)	0	0
Cerebrovascular events¶	0	0	1 (0·6%)	0	0
Abnormal laboratory test results‖					
Haemoglobin <8 g/dL	0	1 (1·1%)	1 (0·6%)	1 (1·0%)	3 (1·5%)
WBC <2000/mm³	0	1 (1·1%)	0	0	1 (0·5%)
Neutrophils <1000/mm³	0	2 (2·2%)	3 (1·7%)	2 (2·1%)	0
Lymphocytes <500/mm³	1 (1·1%)	1 (1·1%)	3 (1·7%)	1 (1·0%)	5 (2·5%)
AST >5 × ULN	1 (1·1%)	1 (1·1%)	1 (0·6%)	1 (1·0%)	1 (0·5%)
ALT >5 × ULN	1 (1·1%)	2 (2·2%)	3 (1·7%)	0	1 (0·5%)
CK >5 × ULN	1 (1·1%)	1 (1·1%)	2 (1·1%)	2 (2·1%)	8 (4·0%)
Triglycerides >500 mg/dL	0	1 (1·3%)	1 (0·7%)	1 (1·2%)	0
Total cholesterol >400 mg/dL	0	0	0	0	1 (0·5%)

Data are n (%) or mean (SD). ALT=alanine aminotransferase. AST=aspartate aminotransferase. CK=creatine kinase. ULN=upper limit of normal. WBC=white blood cells. *Patients who responded with placebo in the induction studies and continued to receive placebo in the maintenance study. †Patients who responded with filgotinib 100 mg in the induction studies and were randomly assigned to placebo in the maintenance study. ‡Patients who responded with filgotinib 200 mg in the induction studies and were randomly assigned to placebo in the maintenance study. §Excluding non-melanoma skin cancer. ¶Transient ischaemic attack was reported in one patient and was reported as both arterial thrombosis and a cerebrovascular event. ‖A treatment-emergent laboratory abnormality was defined as an increase of at least one grade from maintenance baseline at any maintenance post-baseline timepoint up to 30 days after the last maintenance study drug dose date. Denominator for laboratory abnormality was patients who received at least one dose of drug with at least one post-baseline value for the variable under evaluation.

Table 3: **Summary of safety outcomes in the maintenance study**

grade 3 or 4 laboratory abnormalities and those who did not.

Discussion

This is the first investigation of filgotinib, a once-daily, oral JAK1 preferential inhibitor, for the treatment of patients with moderately to severely active ulcerative colitis. 200 mg filgotinib was consistently efficacious for both induction and maintenance treatment, with the primary efficacy endpoint being met in all three studies. Filgotinib was well tolerated at both 100 mg and 200 mg, with serious adverse events and adverse events of interest occurring with similar incidence to placebo.

Filgotinib was efficacious in both biologic-naive and biologic-experienced patients, all of whom had non-response to other therapies and high inflammatory burden at baseline. In particular, the proportion of patients with severe endoscopic disease was 77·8% in induction study B, which studied patients who had had previous TNF antagonist or vedolizumab treatment, indicating that this was a difficult population to treat. 43·1% of patients in induction study B had failure of both drug classes, which could also indicate poor prognosis. The low placebo remission rate of 4·2% observed at week 10 also suggests that these patients were highly treatment resistant. Despite this, we observed a clinically relevant difference in remission rate between the filgotinib 200 mg group and the placebo group at week 10. In addition, a greater proportion of biologic-naive and biologic-experienced patients had clinical and endoscopic improvement after receiving filgotinib 200 mg for 10 weeks compared with those who received placebo. Efficacy was also reported in the maintenance study, in which the proportion of patients with clinical remission at week 58 was significantly higher in those who continued filgotinib 200 mg than those assigned to placebo. In subgroup analyses of clinical remission at week 58, efficacy of filgotinib 200 mg was observed for both biologic-naive and biologic-experienced patients.

All of the prespecified secondary endpoints of MCS remission, endoscopic remission, and histologic remission were met at week 10 in biologic-naive patients and at week 58 in patients given filgotinib 200 mg. These results are encouraging given the stringent definitions of endoscopic remission (Mayo endoscopic subscore of 0) and histological remission (absence of neutrophils in the lamina propria or the epithelium) used. In addition, a significantly greater proportion of patients given filgotinib 200 mg than placebo had 6-month corticosteroid-free remission at week 58, despite the stringent definition of corticosteroid-free remission used. The results for filgotinib 100 mg versus 200 mg suggest a clear dose-response relationship, with the 100 mg dose not showing significant differences versus placebo in the induction studies; this suggestion is supported by both MCS response and endoscopic improvement data. These data could warrant investigation of doses higher than 200 mg; however, higher doses could negate filgotinib's preferential inhibition of the JAK1 subtype or compromise the safety profile. Although the secondary endpoint of endoscopic remission was not reported in induction study B, as previously noted, this was a stringent definition of success in a patient population that was difficult to treat. By contrast, analysis of the outcome of histologic remission identified a benefit of the 200 mg dose in these patients, suggesting that histopathology might be a more sensitive measure of treatment response.

Filgotinib was well tolerated at both doses and over all three studies. Rates of serious adverse events and discontinuations due to adverse events were similar between the filgotinib and placebo groups. Consistent with findings in patients with rheumatoid arthritis given filgotinib,[16–18] herpes zoster infections and serious infections were observed at low and similar rates in all treatment groups. This observation was despite the fact that concomitant therapy of corticosteroids and immunosuppressants was permitted, by contrast with a phase 3 trial of tofacitinib,[10] in which immunosuppressants were discontinued at induction screening. One venous thromboembolic event (pulmonary embolism) was reported in the filgotinib group, but the elevated risk of thromboembolism in patients with ulcerative colitis has been well documented,[27] and two venous thromboses occurred in the placebo group in the maintenance study after induction placebo. Malignancies and non-melanoma skin cancers each occurred in three patients treated with filgotinib.

Safety concerns outside those reported in this trial are being investigated. Findings in animal studies of filgotinib included impaired spermatogenesis and histopathological effects on male reproductive organs (testes and epididymis).[28] Two clinical studies investigating the potential translation of these observations to men are underway (NCT03926195, NCT03201445).

Key strengths of our study were the large sample size, and the simple dosing regimen that allowed patients to continue receiving the same oral dose of drug daily for both induction and maintenance, with no need for dose modification. The study also had some limitations, specifically, the short duration of the assessments inherent to randomised controlled trials. A separate, long-term extension study (SELECTIONLTE; NCT02914535) is underway. Further studies would be required to determine the effectiveness and safety of filgotinib in real-world clinical practice. The absence of dose intensification or extended therapy beyond week 10 for induction non-responders also requires evaluation in further trials.

Treatment with filgotinib 200 mg for up to 58 weeks was efficacious for induction and maintenance of clinical remission in both biologic-naive and biologic-experienced patients with moderately to severely active ulcerative colitis. Filgotinib was well tolerated.

Contributors

CT, CY, JM, and SZ contributed to study design. BGF, SD, EVL, SV, SS, TR, RFo, RM, SN, RK, RFi, IH, US, FS, ILPB, HJK, MW, WJS, GR, TH, and LP-B contributed to data collection. C-HH, CY, JM, SZ, and XL contributed to data analysis. RB and all other authors contributed to data interpretation and development of the manuscript and approved the final version. XL and SZ verified the underlying data and all authors agree to be accountable for all aspects of the work. 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

BGF reports grants and personal fees from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb (BMS), Janssen Biotech/Centocor, Johnson & Johnson (J&J)/Janssen, Pfizer, Receptos, and Takeda; personal fees from Ablynx, Actogenix, AdMIRx, Akebia Therapeutics, Allergan, Atlantic Pharma, Avaxia Biologics, Avir Pharma, Baxter Healthcare Corporation, Biogen Idec, BioMx Israel, Boehringer-Ingelheim, Boston Pharmaceuticals, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring, Galapagos, Genentech/Roche, GiCare Pharma, Gilead, Given Imaging, Gossamer Pharma, GSK, Inception IBD, Ironwood, Japan Tobacco Company, Kyowa Kakko Kirin, Lexicon, Lilly, Lycera Biotech, Merck, Mesoblast Pharma, Millennium, Nestles, NextBiotix, Novartis, Novo Nordisk, ParImmune, Progenity, Prometheus Therapeutics & Diagnostics, Protagonist, Qu Biologics, Salix, Shire, Sienna Biologics, Sigmoid Pharma, Synergy Pharma, Teva Pharma, TiGenix, Tillotts, UCB, Vertex, VHsquared, Vivelix Pharma, Wyeth, Zealand, and Zyngenia, outside the submitted work. 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Data sharing

Anonymised individual patient data will be shared upon request for research purposes dependent upon the nature of the request, the merit of the proposed research, the availability of the data, and its intended use. The full data sharing policy for Gilead Sciences can be found at https://www.gilead.com/about/ethics-and-code-of-conduct/policies.

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