Efficacy and safety of filgotinib as induction and maintenance therapy for Crohn's disease (DIVERSITY): a phase 3, double-blind, randomised, placebo-controlled trial

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Summary

Background There is a need for efficacious therapies for patients with Crohn's disease that are better tolerated and more durable than available treatments. We aimed to evaluate the efficacy and safety of filgotinib, an oral Janus kinase 1 preferential inhibitor, for treating Crohn's disease.

Methods This phase 3, double-blind, randomised, placebo-controlled trial was conducted in 371 centres in 39 countries. Eligible patients were aged 18–75 years with moderately to severely active Crohn's disease for at least 3 months before enrolment. Patients were enrolled into one of two induction studies on the basis of their experience with biological agents (induction study A included biologic-naive and later biologic-experienced patients and induction study B included biologic-experienced patients). In both induction studies, patients were randomly assigned (1:1:1), using an interactive web response system, to receive oral filgotinib 200 mg, filgotinib 100 mg, or placebo once daily for 11 weeks. Patients who received filgotinib and had two-item patient-reported outcome (PRO2) clinical remission or an endoscopic response at week 10 were re-randomised (2:1) to receive their induction dose or placebo orally, once daily to the end of week 58 in the maintenance study. Co-primary endpoints were PRO2 clinical remission and an endoscopic response at week 10 (induction studies) and week 58 (maintenance study). PRO2 clinical remission was defined as an abdominal pain subscore of not more than 1 and a liquid or very soft stool frequency subscore of not more than 3 (from eDiary data) and endoscopic response was defined as a reduction of at least 50% in Simple Endoscopic Score for Crohn's disease from induction baseline (from central reading of endoscopy). For the induction studies, efficacy was assessed in all randomly assigned patients who received at least one dose of study drug. For the maintenance study, efficacy was assessed in all patients from either filgotinib treatment group in the induction studies who reached PRO2 clinical remission or an endoscopic response at week 10, and who were re-randomised and received at least one dose of study drug in the maintenance study. Patients who received placebo throughout the induction and maintenance studies 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 study drug. This trial is complete and is registered with ClinicalTrials.gov, NCT02914561.

Findings Between Oct 31, 2016, and Nov 11, 2022, 2634 patients were screened, of whom 1372 were enrolled (induction study A: n=707, induction study B: n=665, and maintenance study: n=481). There were 346 (49%) women and 358 (51%) men in induction study A, 356 (54%) women and 303 (46%) men in induction study B, and 242 women (51%) and 236 men (49%) in the maintenance study. Significantly more patients had PRO2 clinical remission at week 10 with filgotinib 200 mg than with placebo in induction study B (29·7% *vs* 17·9%, difference 11·9%; 95% CI 3·7 to 20·2, p=0·0039) but not induction study A (32·9% *vs* 25·7%, 6·9%; –1·4 to 15·2, p=0·0963); there was no significant difference for endoscopic response (induction study A: 23·9% *vs* 18·1%, difference 5·5%; 95% CI –2·0 to 12·9, p=0·1365; induction study B: 11·9% *vs* 11·4%, 0·1%; –6·5 to 6·6, p=0·9797). At week 58, both co-primary endpoints were reported in greater proportions of patients who received filgotinib 200 mg than in those who received placebo (PRO2 clinical remission: 43·8% *vs* 26·4%, difference 16·8%; 95% CI 2·0 to 31·6, p=0·0382; endoscopic response: 30·4% *vs* 9·4%, difference 20·6%; 95% CI 8·2 to 33·1, p=0·0038). Co-primary endpoints were not met for filgotinib 100 mg in any study. In the induction studies, the most frequently reported treatment-emergent adverse events (TEAEs; ≥5% of patients in any group) were abdominal pain; arthralgia; an exacerbation, flare, or worsening of Crohn's disease; headache; nasopharyngitis; nausea; and pyrexia. In the maintenance study, the most frequently reported TEAEs (≥5% of patients in any filgotinib or associated placebo group) were those reported in the induction studies (except for headache) and abdominal distension, upper abdominal pain, anaemia, and flatulence. Serious TEAEs were reported in 49 patients in induction study A (18 [8%]) of 222 patients in the filgotinib 200 mg group, 16 [7%] of 245 patients in the filgotinib 100 mg group, and 15 [6%] of 237 patients in the placebo group), 81 patients in induction study B (19 [9%] of 202 patients in the filgotinib 200 mg group, 36 [16%] of 228 patients in the filgotinib 100 mg group, and 26 [11%] of 229 patients in the placebo group), and 49 patients in the maintenance study (13 [11%] of 118 patients in the filgotinib 200 mg–filgotinib 200 mg group, five [9%] of 56 patients in the

filgotinib 200 mg–placebo group, 14 [13%] of 104 patients in the filgotinib 100 mg–filgotinib 100 mg group, three [5%] of 55 patients in the filgotinib 100 mg–placebo group, and 14 [10%] of 145 patients in the placebo–placebo group). No deaths were reported during the induction and maintenance studies.

Interpretation **Filgotinib 200 mg did not meet the co-primary endpoints of clinical remission and an endoscopic response at week 10, but did meet the co-primary endpoints at week 58. Filgotinib treatment was well tolerated, and no new safety signals were reported.**

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Introduction

Crohn's disease is a chronic, progressive, and relapsing form of inflammatory bowel disease, characterised by transmural inflammation of the gastrointestinal tract.[1] The widespread effect of Crohn's disease on physical, psychological, and social functioning can reduce health-related quality of life.[2]

The principal goal of therapy in Crohn's disease is to achieve disease control by inducing and maintaining clinical and endoscopic remission.[3] Long-term treatment goals are to improve endoscopic healing, reduce disability rates, and restore health-related quality of life.[4] Treatment options include conventional therapies (corticosteroids or immunomodulators) and biologic therapies (such as those targeting TNF, the p40 subunit of interleukin-12/23, the p19 subunit of interleukin-23, and integrin α4β7).[5–7]

Although the introduction of biological therapies has improved response rates in Crohn's disease, limitations of these therapies include primary non-response, secondary loss of response, and potential safety concerns.[1,8–11] Therefore, there is a need for efficacious therapies for patients with Crohn's disease that are better tolerated and more durable.[12] Treatment options with alternative mechanisms of action, such as JAK inhibitors, have been evaluated in clinical trials.[13,14] Upadacitinib is the only JAK inhibitor that is approved for treating Crohn's disease.[13,15]

Filgotinib is an oral, once-daily, JAK1 preferential inhibitor approved for the treatment of ulcerative colitis and rheumatoid arthritis in multiple regions.[16–20] The phase 2 FITZROY study demonstrated that filgotinib 200 mg was efficacious compared with placebo in inducing clinical remission at week 10 in patients with Crohn's disease, and that filgotinib had an acceptable safety profile.[1] We present results from the phase 3 DIVERSITY study, which evaluated filgotinib as induction and maintenance therapy in patients with moderately to severely active Crohn's disease.

Methods

Study design and participants

This phase 3, double-blind, randomised, placebo-controlled trial comprised two induction studies and one maintenance study in adults with moderately to severely active Crohn's disease enrolled from 371 study centres in 39 countries (appendix p 4). Patient safety and data integrity were assessed and considered minimally affected by the COVID-19 pandemic.

See **Online** for appendix

Research in context

Evidence before this study

Several therapies are available for the treatment of Crohn's disease; however, there remains an unmet need for efficacious treatments. We searched PubMed on July 9, 2024, using the terms "Crohn's disease" AND "moderate*" AND "severe*" AND "treatment" AND "Janus kinase inhibitor" for articles published in English from Jan 1, 2016, to July 9, 2024. We identified 57 articles describing the use of JAK inhibitors in the treatment of Crohn's disease. Filgotinib is a once-daily, oral, JAK1 preferential inhibitor that is approved for the treatment of ulcerative colitis and rheumatoid arthritis. The efficacy and safety of filgotinib in Crohn's disease has been evaluated in a phase 2, randomised, placebo-controlled trial.

Added value of this study

DIVERSITY is the first phase 3, double-blind, randomised, placebo-controlled trial to evaluate the efficacy and safety of filgotinib in patients with moderately to severely active Crohn's disease. Filgotinib was not efficacious as induction therapy compared with placebo, but it was efficacious at a dosage of 200 mg once daily in achieving clinical remission and an endoscopic response during the maintenance study. Filgotinib was well tolerated, with a safety profile in Crohn's disease that is generally consistent with that in ulcerative colitis and rheumatoid arthritis. These data add to the phase 2 results previously published and provide additional evidence of the safety profile of filgotinib in Crohn's disease from a phase 3 study.

Implications of all the available evidence

Results from DIVERSITY support the safety assessments of filgotinib reported in patients with ulcerative colitis and rheumatoid arthritis. The unexpectedly high clinical remission and endoscopic response rates with placebo in the induction studies could inform future trial designs (including patient eligibility criteria).

The final protocol and nine amendments were reviewed and approved by the independent ethics committee, the institutional review board, competent authorities, or any other ethics committee according to local regulations before initiation of the trial. Relevant sections of the protocol can be found in the appendix (pp 4–13).

The study was carried out in accordance with the International Council on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent before enrolment.

Eligible patients were aged 18–75 years with a diagnosis of moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220–450, a two-item patient-reported outcome [PRO2] abdominal pain subscore of ≥2 or daily stool frequency subscore of ≥4, and evidence of active disease as measured by the Simple Endoscopic Score for Crohn's disease [SES-CD] based on a central reading [a total SES-CD of ≥6 or, if Crohn's disease was limited to the ileum or right colon, a combined SES-CD of ≥4 in these two segments]). The laboratory tests done during screening for eligibility were evaluation of a hepatic panel, creatinine clearance, haemoglobin, neutrophil count, platelet count, white blood cell count, and absolute lymphocyte count (laboratory parameter criteria are described in appendix pp 4–8). Self-reported patient sex data were collected at screening.

Patients were enrolled into one of two induction studies (A and B) based on their experience with biologic agents (TNF antagonists, vedolizumab, or ustekinumab). Biologic-naive patients (those who had an inadequate clinical response, who had a loss of response or an intolerance to corticosteroids or immunomodulators, and who were naive to predefined biological agents) were enrolled in induction study A. Biologic-experienced patients (those who had an inadequate clinical response, a loss of response, or an intolerance to any predefined biologic agent) were enrolled in induction study B (use of ≥1 biologic agent). Following trial commencement, the protocol was amended to allow both biologic-naive and biologic-experienced patients to enter induction study A, facilitating enrolment completion in this study part. This resulted in a mixed study population in induction study A (biologic-naive and biologic-experienced). Patients who had received any TNF antagonist or vedolizumab in the 8 weeks before screening, or ustekinumab in the 12 weeks before screening were excluded from enrolling in either study.

Full details of inclusion and exclusion criteria (including non-permitted comorbidities) and permitted concomitant medications (including 5-aminosalicylic acid, corticosteroids, and immunomodulators) are provided in the appendix (pp 4–9). From week 14, the corticosteroid dose had to be reduced at a rate starting at 2·5 mg per week to 5 mg per week (or using an equivalent taper if corticosteroid used was not prednisone) until the patient was no longer receiving corticosteroids. Patients who were receiving budesonide had their daily dose reduced by 3 mg every 3 weeks until they were no longer receiving corticosteroids.

Randomisation and blinding

Patients were randomly assigned (1:1:1) to receive oral filgotinib 200 mg, filgotinib 100 mg, or matched placebo once daily for 11 weeks in both induction studies A and B.

Efficacy was assessed at week 10, and patients who had either PRO2 clinical remission or an endoscopic response were re-randomised (2:1) at week 11 to continue their induction filgotinib dose (filgotinib 200 mg–filgotinib 200 mg or filgotinib 100 mg–filgotinib 100 mg) or to receive placebo (filgotinib 200 mg–placebo or filgotinib 100 mg–placebo) up to the end of week 58 in the maintenance study. Placebo responders (defined as those who had either PRO2 clinical remission or an endoscopic response at week 10) continued to receive placebo in the maintenance study (placebo–placebo). Patients who had neither PRO2 clinical remission nor an endoscopic response at week 10 and patients who met protocol-specified disease worsening criteria (appendix p 8) in the maintenance study were offered open-label filgotinib in the separate long-term extension study (NCT02914600).

Men from South Korea and the USA in whom TNF antagonist and vedolizumab treatment did not fail (non-dual refractory) were randomly assigned (1:1) to receive filgotinib 100 mg or placebo, following concerns about the potential effect of filgotinib on semen parameters and sex hormones.[16,21,22] The findings from the MANTA trial subsequently resolved these concerns; the trial evaluated the effects of filgotinib on semen parameters and sex hormones over 13 weeks of treatment in men with inflammatory bowel disease (including in 124 men with ulcerative colitis).[22] After commencement of the DIVERSITY trial, the protocol was amended to allow men from South Korea to be randomly assigned to filgotinib 200 mg if both a TNF antagonist and vedolizumab had failed.

In induction studies A and B, patients were stratified by the number of previous biologic agent (induction study A: 0, 1, >1; induction study B: ≤1, >1), concomitant use of oral systemic corticosteroids (yes or no), and concomitant use of immunomodulators (yes or no). In the maintenance study, patients were stratified by previous exposure to a biologic agent (yes or no), concomitant use of oral systemic corticosteroids (yes or no), and concomitant use of immunomodulators (yes or no). Block randomisation was done within each stratum using a block size of six for both the induction and maintenance studies.

Randomisation was done by the investigator through an interactive web response system. Everyone directly involved in the study conduct (including investigators, study personnel, and patients) was fully blinded to treatment allocation until the last patient completed the follow-up visit 30 days after completing 58 weeks of

treatment. Any unblinding of patients was documented (including reasons for unblinding). The appearance, packaging, and handling of active treatment (filgotinib 200 mg and filgotinib 100 mg) and placebo were identical to maintain blinding.

Procedures

In the induction studies, patients received oral tablets of filgotinib 200 mg, filgotinib 100 mg, or matched placebo once daily for 11 weeks. In the maintenance study, filgotinib-treated patients received their induction filgotinib dose or placebo orally, once daily to the end of week 58. Placebo responders continued to receive placebo in the maintenance study. Dose reductions of active treatment were not permitted.

Patients recorded symptoms of stool frequency, abdominal pain, and general wellbeing daily in an eDiary. An ileocolonoscopy with biopsies was done at screening and at weeks 10 and 58, and was centrally read for scoring of SES-CD (appendix p 8). Laboratory assessments for chemistry and haematology parameters were done on day 1 and at weeks 2, 4, 6, 10, 14, 20, 26, 34, 42, 50, and 58. Blood samples for biomarker analyses were obtained on day 1 and at weeks 4, 10, 26, and 58 to determine high-sensitivity C-reactive protein and faecal calprotectin concentrations. Blood samples for pharmacokinetic assessments were obtained after treatment at week 4, at any time without regard to dosing at week 26, and before treatment at weeks 10 and 58 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 weeks 2 and 10.

Outcomes

Following consultation with the appropriate regulatory authorities in the EU and the USA, two separate analyses (EU-specific and non-EU-specific) were conducted with different co-primary endpoints (assessment of clinical remission by PRO2 or CDAI) and minor modifications to secondary endpoint analyses. Discussions were held in 2016 before study initiation with an additional consultation in 2019 with the MPA in Sweden.

The EU-specific co-primary endpoints were the proportions of patients with PRO2 clinical remission and an endoscopic response, assessed at weeks 10 and 58. PRO2 clinical remission was defined as having abdominal pain subscore of not more than 1 (on a scale of 0–3) and liquid or very soft stool (Bristol stool scale type 6 or 7) frequency subscore of not more than 3 (each PRO2 subscore was calculated as the mean of the corresponding eDiary data for 7 days). Endoscopic response was defined as a reduction of at least 50% in centrally read SES-CD from induction baseline. Key EU-specific secondary endpoints were CDAI clinical remission (defined as a CDAI score of <150 points), and PRO2 clinical remission and an endoscopic response (combined into a single endpoint on a patient level) at weeks 10 and 58. Sustained PRO2 clinical remission (defined as having PRO2 clinical remission at both weeks 10 and 58) and 6-month corticosteroid-free PRO2 clinical remission (defined as PRO2 clinical remission with no corticosteroid use for the indication of Crohn's disease for ≥6 months before week 58 in patients with corticosteroid use at maintenance baseline) were assessed as key secondary endpoints at week 58.

The non-EU-specific co-primary endpoints were the proportions of patients with CDAI clinical remission and an endoscopic response (both endpoints are defined above), assessed at weeks 10 and 58. Key non-EU-specific secondary endpoints included PRO2 clinical remission (defined as above) and CDAI clinical response (defined as a reduction in the CDAI score from induction baseline of ≥100 points or a CDAI score of <150) at weeks 10 and 58. Sustained clinical remission by PRO2 (defined as above) or CDAI (defined as having CDAI clinical remission at both weeks 10 and 58) and 6-month corticosteroid-free clinical remission by PRO2 (defined as above) or CDAI (defined as CDAI clinical remission with no corticosteroid use for the indication of Crohn's disease for ≥6 months before week 58 in patients with corticosteroid use at maintenance baseline) were assessed as key secondary endpoints at week 58.

Safety assessments included treatment-emergent adverse events (TEAEs), concomitant medications, clinical laboratory analyses, vital signs, electrocardiograms, and physical examinations. Considerations for study drug discontinuation are listed in the appendix (pp 12–13). Adverse events and clinical laboratory results were coded using the Medical Dictionary for Regulatory Activities version 25.0, and their severity was graded using the modified Common Terminology Criteria for Adverse Events version 4.03. An external, multidisciplinary data monitoring committee performed interim reviews of the safety data throughout the trial. All potential major adverse cardiovascular events (MACEs) and venous thromboembolic (VTE) events were reviewed and adjudicated periodically, and gastrointestinal perforation events were reviewed and adjudicated post hoc, in a blinded manner by an independent expert committee.

Pharmacokinetic assessments were conducted for filgotinib and its metabolite, GS-829845. Exploratory endpoints reported herein were endoscopic remission (defined as a total SES-CD score of ≤2) and complete endoscopic healing (defined as a total SES-CD ulcer size subscore of 0).

Statistical analysis

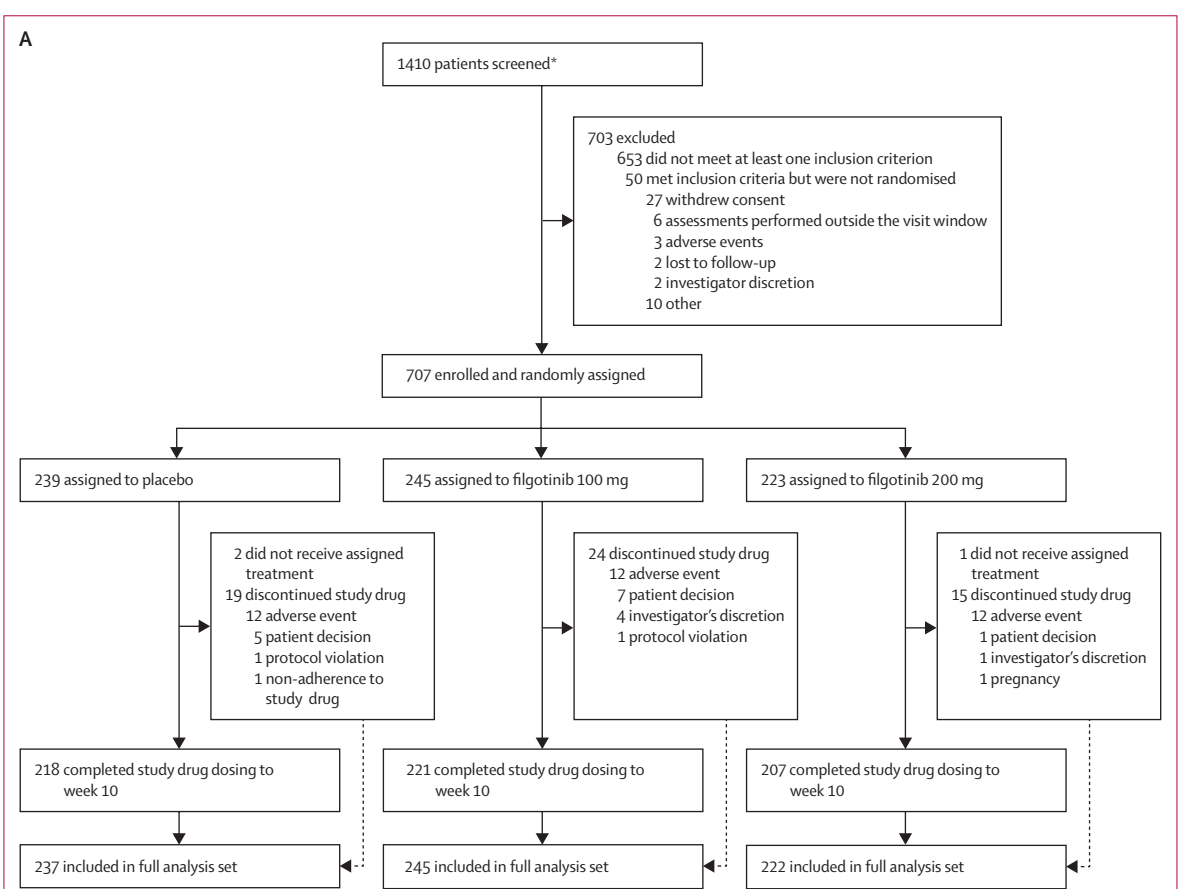
Sample sizes were chosen to allow for detection of clinically meaningful treatment effects within each study. A sample size of 220 patients in each treatment group

(660 patients in each induction study) was estimated to provide 93% overall power for comparing filgotinib 200 mg and placebo at a two-sided significance level of 0·05 to detect a difference of 15% in the PRO2 clinical remission rate (30% for filgotinib 200 mg *vs* 15% for placebo) and a difference of 15% in the endoscopic response rate (25% for filgotinib 200 mg *vs* 10% for placebo) at week 10. The overall power was calculated as the product of the two individual powers for each endpoint.

Assuming a response rate (defined as the proportion of patients with PRO2 clinical remission or an endoscopic response at week 10) of 40% in patients receiving filgotinib 200 mg or filgotinib 100 mg in the induction studies, approximately 176 patients from each filgotinib dose group from induction studies A and B combined were estimated to be eligible for re-randomisation in the maintenance study. A sample size of 120 patients in each filgotinib group and 60 patients in each placebo group in the maintenance study would provide 94% power for comparing filgotinib 200 mg with placebo at a two-sided significance level of 0·05 to detect a difference of 30% in the PRO2 clinical remission rate and in the endoscopic response rate at week 58 (50% for filgotinib 200 mg *vs* 20% for placebo). Details of sample size determination for the non-EU-specific analysis are provided in the appendix (p 9).

Efficacy endpoints were analysed using the full analysis sets. For the induction studies, the full analysis sets included all randomly assigned patients who received at least one dose of study drug within that study. For the maintenance study, the full analysis set included all patients randomly assigned to either filgotinib treatment group in the induction studies who had PRO2 clinical remission or an endoscopic response at week 10, and who were re-randomised and received at least one dose of study drug in the maintenance study. Patients who received placebo throughout the induction and maintenance studies were not included in the full analysis set for the maintenance study. Safety endpoints were analysed using data from all patients who received at least one dose of study drug within each study.

For each individual study, a graphical approach of sequentially rejective, Bonferroni-based, iterative multiple test procedures was used to control the overall study-wide, family-wise type I error rate at 5% for hypothesis testing of the co-primary and key secondary endpoints (appendix pp 9–12). For the co-primary and key secondary



(Figure 1 continues on next page)

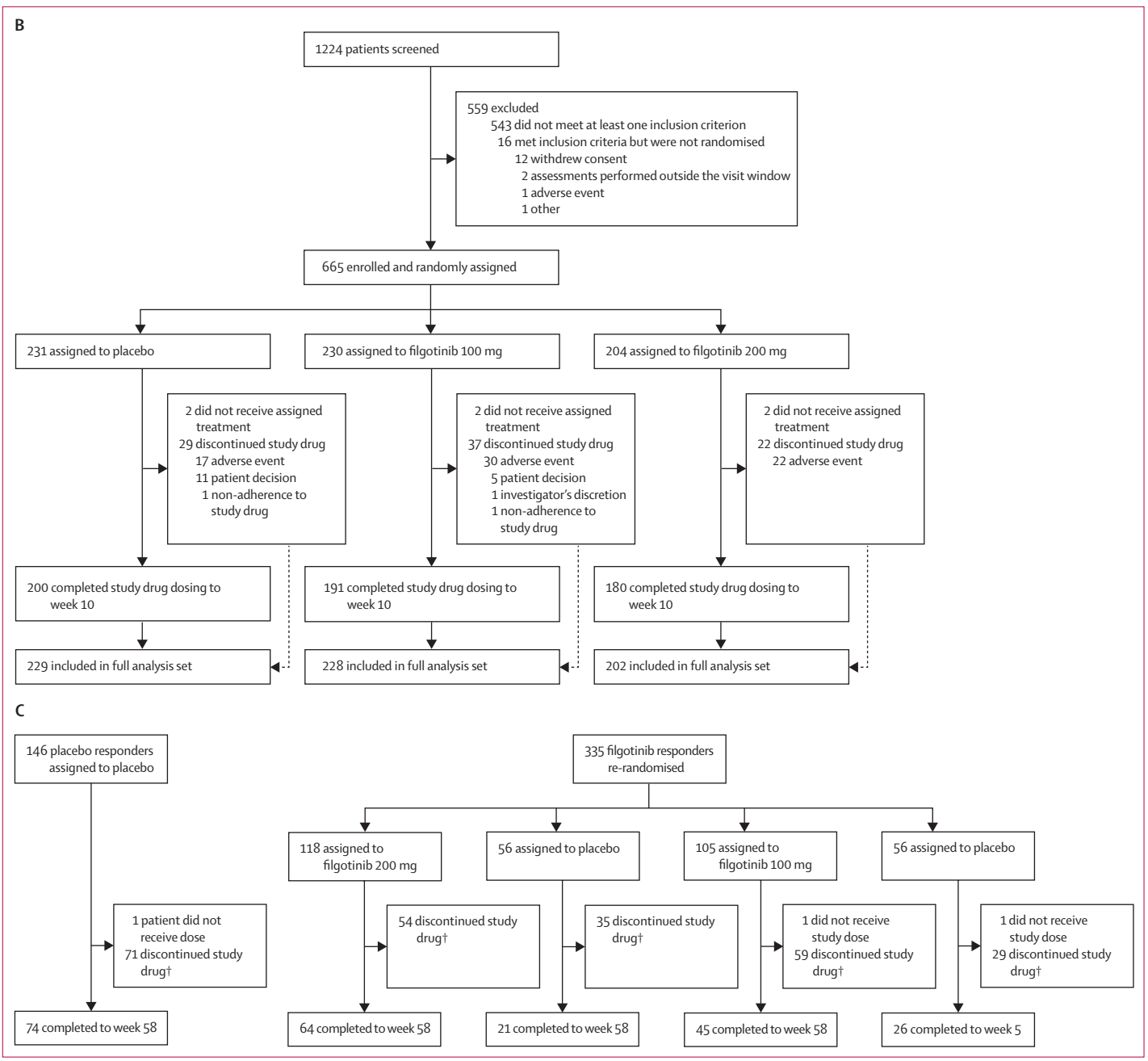


Figure 1: **Trial profile**

(A) Induction study A. (B) Induction study B. (C) Maintenance study. Responders were patients who reported PRO2 clinical remission or an endoscopic response at week 10. Non-responders were patients who did not report PRO2 clinical remission or an endoscopic response at week 10. Non-responders and patients in the maintenance study who met disease worsened criteria were offered open-label filgotinib in the long-term extension study. Patients who completed both the induction and maintenance studies could enter the long-term extension study (which also included patients from the DIVERGENCE1 [NCT03046056)] and DIVERGENCE2 [NCT03077412] studies). These patients continued to receive blinded study drug until the DIVERSITY database lock. PRO2=two-item patient-reported outcome. *Includes patients who were screened for induction study A and patients who were screened but for whom the induction study was not known. †Reasons for discontinuation of maintenance study drug shown in the appendix (pp 45–46).

efficacy binary endpoints the stratified proportion difference with 95% CIs was calculated for each filgotinib dose group versus placebo and p values were obtained from stratified Cochran–Mantel–Haenszel tests. Stratification factors are described in the appendix (p 12).

The primary analysis of co-primary efficacy endpoints was done according to the composite strategy using an estimand for each endpoint, whereby patients who met treatment failure criteria (received potentially effective medications other than study drug) or prematurely discontinued from the study without available

	Induction study A			Induction study B		
	Placebo (n=237)	Filgotinib 100 mg (n=245)	Filgotinib 200 mg (n=222)	Placebo (n=229)	Filgotinib 100 mg (n=228)	Filgotinib 200 mg (n=202)
Age, years	38 (14·0)	39 (14·1)	39 (13·8)	39 (12·5)	42 (13·5)	39 (14·2)
Median (IQR)	37 (26–49)	38 (26–49)	37 (27–48)	37 (29–48)	41 (30–53)	36 (27–49)
Sex*						
Female	130 (55%)	106 (43%)	110 (50%)	115 (50%)	127 (56%)	114 (56%)
Male	107 (45%)	139 (57%)	112 (50%)	114 (50%)	101 (44%)	88 (44%)
Race						
Asian	44 (19%)	52 (21%)	44 (20%)	31 (14%)	25 (11%)	24 (12%)
Black or African American	3 (1%)	6 (2%)	3 (1%)	6 (3%)	9 (4%)	6 (3%)
White	184 (78%)	179 (73%)	166 (75%)	176 (77%)	180 (79%)	156 (77%)
Other†	6 (3%)	8 (3%)	9 (4%)	16 (7%)	14 (6%)	16 (8%)
Geographical region, non-USA	193 (81%)	204 (83%)	200 (90%)	170 (74%)	145 (64%)	152 (75%)
BMI, kg/m²	24·4 (6·0)	24·0 (5·7)	23·9 (5·7)	24·3 (6·1)	24·8 (5·7)	25·1 (6·4)
Median (IQR)	23·5 (19·9–27·8)	23·5 (20·4–26·5)	23·1 (19·8–26·4)	23·1 (20·2–27·5)	24·2 (20·6–27·7)	23·5 (20·3–28·6)
Crohn's disease duration, years‡	9·3 (8·4)	9·9 (10·0)	9·2 (8·4)	13·0 (9·5)	13·3 (9·7)	11·5 (8·0)
Median (IQR)	7·5 (2·4–13·9)	6·9 (2·9–13·2)	6·3 (2·5–13·9)	10·9 (5·8–18·0)	10·3 (6·4–16·8)	9·8 (6·0–15·0)
Crohn's disease duration‡						
<1 year	24 (10%)	25 (10%)	20 (9%)	3 (1%)	3 (1%)	0
≥1 to <3 years	49 (21%)	40 (16%)	40 (18%)	23 (10%)	16 (7%)	13 (6%)
≥3 to <7 years	40 (17%)	58 (24%)	59 (27%)	44 (19%)	46 (20%)	53 (26%)
≥7 years	124 (52%)	122 (50%)	103 (46%)	159 (69%)	163 (71%)	136 (67%)
PRO2 score						
Daily liquid or very soft stool frequency subscore of ≥4	194 (82%)	218 (89%)	193 (87%)	202 (88%)	204 (89%)	179 (89%)
Abdominal pain subscore of ≥2	200 (84%)	202 (82%)	181 (82%)	172 (75%)	181 (79%)	159 (79%)
SES-CD (central read)	13 (7·2)	14 (7·9)	13 (7·1)	15 (7·8)	15 (8·2)	15 (7·9)
Median (IQR)	12 (7–18)	12 (8–18)	11 (7–18)	13 (8–20)	13 (8–21)	14 (8–20)
Location of Crohn's disease based on SES-CD (central read)						
Ileum only	33 (14%)	31 (13%)	31 (14%)	34 (15%)	39 (17%)	30 (15%)
Colon only	98 (41%)	104 (42%)	90 (41%)	106 (46%)	85 (37%)	67 (33%)
Ileum and colon	106 (45%)	110 (45%)	101 (45%)	89 (39%)	104 (46%)	105 (52%)
CDAI score at screening	320 (59·4)	322 (55·5)	323 (55·6)	322 (57·5)	321 (55·7)	306 (54·0)
Median (IQR)	320 (271–365)	317 (278–366)	326 (273–367)	320 (272–356)	321 (276–362)	299 (267–343)
Faecal calprotectin, µg/g	1912 (3719·6)	1870 (2944·5)	1891 (2725·7)	1882 (3016·2)	1833 (3117·9)	1864 (3208·1)
Median (IQR)	747 (264–1876)	895 (299–2160)	941 (310–2321)	900 (336–2134)	856 (242–2223)	939 (355–2073)
hs-CRP, mg/L	16·4 (25·3)	18·7 (27·3)	15·4 (23·4)	18·6 (23·4)	20·0 (29·1)	23·9 (33·7)
Median (IQR)	6·3 (2·8–19·2)	7·4 (2·7–22·3)	7·4 (2·6–17·9)	9·2 (3·3–25·3)	9·6 (3·9–24·3)	11·2 (4·8–31·0)
Treatment before induction baseline						
Number of biologic agents used§						
0	125 (53%)	134 (55%)	121 (55%)	2 (1%)¶	1 (<1%)¶	1 (<1%)¶
1	18 (8%)	11 (4%)	8 (4%)	55 (24%)	55 (24%)	41 (20%)
2	21 (9%)	17 (7%)	17 (8%)	63 (28%)	57 (25%)	41 (20%)
≥3	73 (31%)	83 (34%)	76 (34%)	109 (48%)	115 (50%)	119 (59%)
TNF antagonist	108 (46%)	109 (44%)	97 (44%)	219 (96%)	224 (98%)	197 (98%)
Previous failure of TNF antagonist	93 (39%)	91 (37%)	80 (36%)	186 (81%)	198 (87%)	175 (87%)
Vedolizumab	66 (28%)	71 (29%)	70 (32%)	97 (42%)	100 (44%)	106 (52%)
Previous failure of vedolizumab	58 (24%)	65 (27%)	62 (28%)	85 (37%)	87 (38%)	94 (47%)

(Table 1 continues on next page)

	Induction study A			Induction study B		
	Placebo (n=237)	Filgotinib 100 mg (n=245)	Filgotinib 200 mg (n=222)	Placebo (n=229)	Filgotinib 100 mg (n=228)	Filgotinib 200 mg (n=202)
(Continued from previous page)						
Both TNF antagonist and vedolizumab	63 (27%)	71 (29%)	66 (30%)	90 (39%)	97 (43%)	103 (51%)
Previous failure of both TNF antagonist and vedolizumab	49 (21%)	56 (23%)	53 (24%)	71 (31%)	73 (32%)	83 (41%)
Men from USA or South Korea	6 (3%)	7 (3%)	4 (2%)	13 (6%)	12 (5%)	16 (8%)
Concomitant use of systemic corticosteroid and immunomodulator						
Systemic corticosteroid only‖	53 (22%)	62 (25%)	56 (25%)	72 (31%)	66 (29%)	59 (29%)
Immunomodulator only**	52 (22%)	56 (23%)	54 (24%)	31 (14%)	35 (15%)	27 (13%)
Both systemic corticosteroid and immunomodulator‖**	23 (10%)	22 (9%)	18 (8%)	19 (8%)	15 (7%)	15 (7%)
Systemic corticosteroid						
Yes	76 (32%)	84 (34%)	74 (33%)	91 (40%)	81 (36%)	74 (37%)
Prednisone-equivalent dose, mg per day	19 (9·4)	18 (7·8)	21 (8·8)	17 (7·8)	20 (8·8)	17 (8·5)
Median (IQR)	20 (10–25)	20 (10–20)	20 (10–30)	20 (10–20)	20 (15–25)	20 (10–20)
No	161 (68%)	161 (66%)	148 (67%)	138 (60%)	147 (64%)	128 (63%)
Concomitant use of 5-aminosalicylic acid	96 (41%)	102 (42%)	101 (45%)	57 (25%)	47 (21%)	45 (22%)

Data are mean (SD) or n (%), unless otherwise specified. Percentages were calculated based on the number of patients in the safety analysis set. CDAI=Crohn's Disease Activity Index. hs-CRP=high-sensitivity C-reactive protein. PRO2=two-item patient-reported outcome. SES-CD=Simple Endoscopic Score for Crohn's Disease. *Sex was self-reported. †Includes American Indian or Alaska native, native Hawaiian or other Pacific Islander, other and not collected. ‡The duration of Crohn's disease refers to the duration up to induction baseline. §The number of previous biological agents used is based only on those approved for Crohn's disease. ¶Four patients (1%) randomly assigned into induction study B were biologic-naive owing to incorrect study assignment (one in the filgotinib 200 mg group, one in the filgotinib 100 mg group, and two in the placebo group). ‖For use of systemic corticosteroid, only records of oral, intravenous, and intramuscular routes were included. Systemic corticosteroids were prednisone prescribed at a stable dose of up to 30 mg per day or budesonide prescribed at a stable dose of up to 9 mg per day. **6-mercaptopurine, azathioprine, or methotrexate.

Table 1: **Baseline demographics and clinical characteristics in the full analysis set**

assessment results were considered as not having reached the endpoint. Furthermore, missing remission or response status data were imputed using the non-responder imputation approach. Separate comparisons were done between filgotinib dose groups and placebo in induction studies A and B, and between filgotinib dose groups and their respective placebo groups in the maintenance study. Baseline characteristics, and safety, biomarker, and pharmacokinetic data were summarised by descriptive statistics. Pharmacokinetic analyses were done using non-compartmental analyses of the plasma concentration–time profiles. For subgroup analyses by demographic data, the 95% CI for the non-stratified proportion difference was calculated using normal approximation with a continuity correction and p values were obtained from Fisher's exact test. For exploratory analyses, the 95% CI was calculated using normal approximation with continuity correction for each treatment group. In addition, group difference with 95% CI was provided using the stratum-adjusted Mantel–Haenszel approach. Statistical analyses were performed using SAS version 9.4. This study is registered with ClinicalTrials.gov (NCT02914561) and EudraCT (2016-001367-36).

Role of the funding source

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

Results

Between Oct 31, 2016, and Nov 11, 2022, 2634 patients were screened for eligibility for the induction studies (figure 1; appendix pp 4–9). Of the 1410 patients screened for induction study A, 707 biologic-naive or biologic-experienced patients were enrolled and randomly assigned to receive filgotinib 200 mg (n=223), filgotinib 100 mg (n=245), or placebo (n=239). Of the 1224 patients screened for induction study B, 665 biologic-experienced patients were enrolled and randomly assigned to receive filgotinib 200 mg (n=204), filgotinib 100 mg (n=230), or placebo (n=231). Among patients who received at least one dose of study drug, 629 (89%) of 704 completed

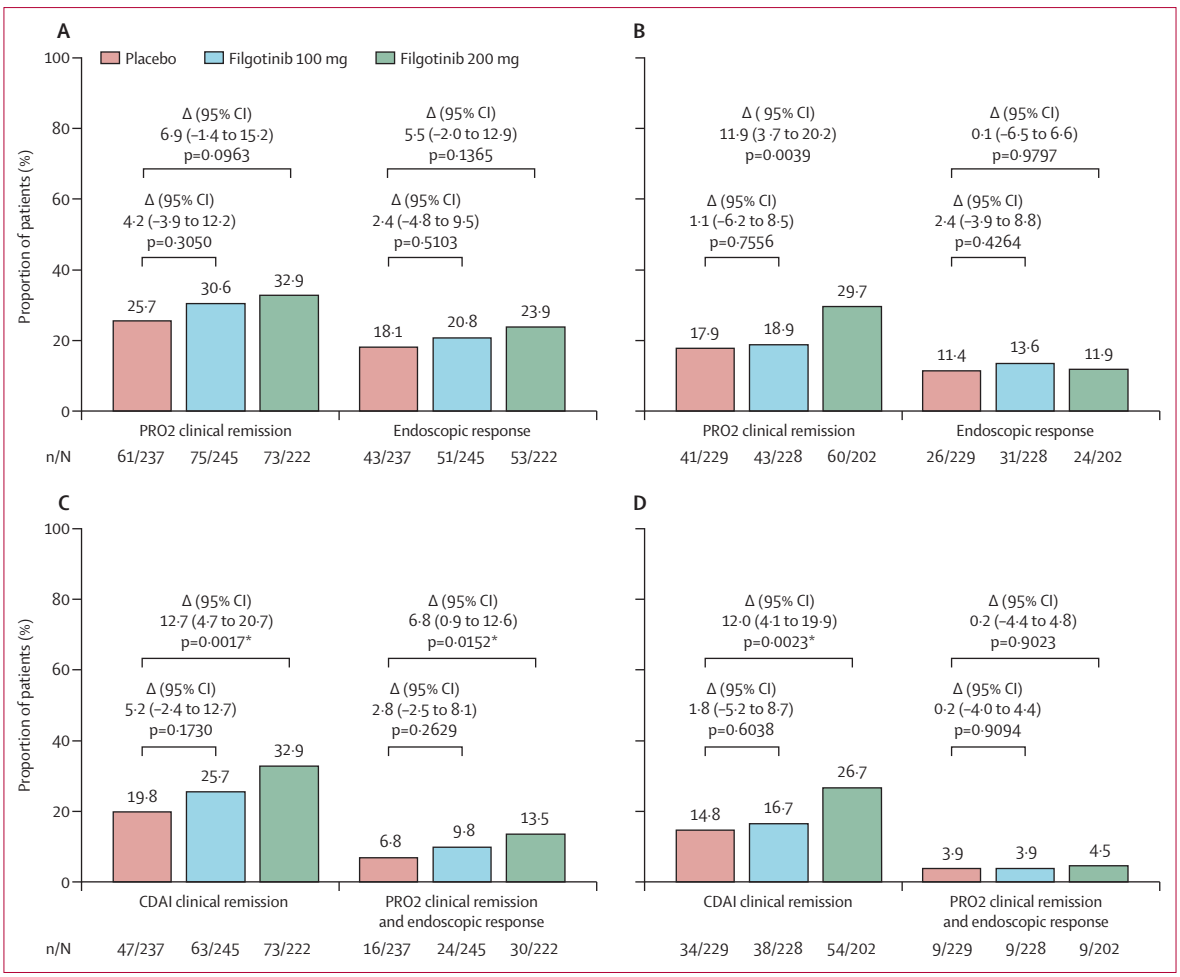


Figure 2: **Co-primary and key secondary endpoints at week 10 in the induction studies (EU-specific analysis)**
(A) Induction study A co-primary endpoints. (B) Induction study B co-primary endpoints. (C) Induction study A secondary endpoints. (D) Induction study B secondary endpoints. The full analysis set for the induction studies included all randomly assigned patients who received at least one dose of study drug in the corresponding study. p values <0·05 were considered significant. The stratified proportion difference (Δ) with 95% CI was calculated for each filgotinib group versus placebo. p values were obtained from the stratified Cochran–Mantel–Haenszel test. Δ=difference. CDAI=Crohn's Disease Activity Index. PRO2=two-item patient-reported outcome. *p values were considered nominally significant.

induction study A and 552 (84%) of 659 completed induction study B, to the end of week 11.

At week 11, of the 1181 patients who completed the induction studies, 335 filgotinib-treated patients were re-randomised to receive their induction filgotinib dose or placebo, and 146 placebo-treated patients were assigned to continue placebo for 47 weeks in the maintenance study (figure 1C, appendix pp 44–46). Of 478 patients who received at least one dose of study drug in the maintenance study, 230 (48%) completed the maintenance study to the end of week 58.

Baseline demographics and clinical characteristics were balanced across treatment groups in each induction study (table 1). There were 346 (49%) women and 358 (51%) men in induction study A and 356 (54%) women and 303 (46%) men in induction study B. The mean duration of Crohn's disease was longer in induction study B than in induction study A. In induction study A, 529 (75%) of 704 patients were White, 140 (20%) were Asian, and 12 (2%) were Black or African American. In induction study B, 512 (78%) of 659 patients were White, 80 (12%) were Asian, and 21 (3%) were Black or African American. In induction study A, 324 (46%) of 704 patients had previous exposure to at least one biologic agent compared with 655 (99%) of 659 patients in induction study B. Previous use of at least three biologic agents was reported in 232 (33%) and 343 (52%) of patients treated in induction studies A and B, respectively. Previous use of both a TNF antagonist and vedolizumab was reported in 103 (51%) of 202 patients treated with filgotinib 200 mg, 97 (43%) of 228 patients treated with filgotinib 100 mg, and 90 (39%) of 229 patients given placebo in induction study B. Baseline demographics and clinical characteristics were generally balanced across treatment groups in the maintenance study; the maintenance study included 242 (51%) women and 236 (49%) men

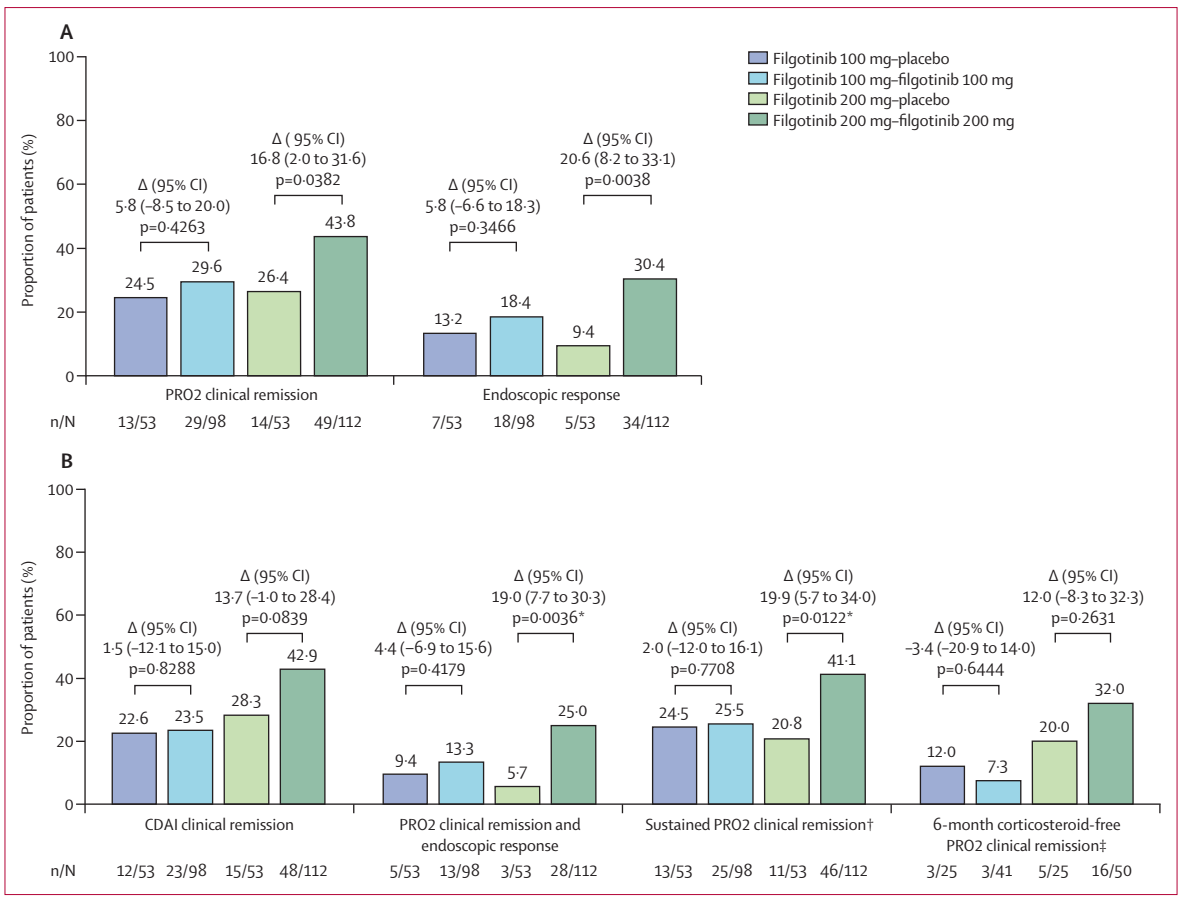


Figure 3: **Co-primary and key secondary endpoints at week 58 in the maintenance study (EU-specific analysis)**
(A) Co-primary endpoints. (B) Secondary endpoints. The full analysis set for the maintenance study included all re-randomised patients who met the protocol definition of PRO2 clinical remission or an endoscopic response at week 10 and received at least one dose of study drug during the maintenance study. p values <0·05 were considered significant. The stratified proportion difference (Δ) with 95% CI was calculated for each filgotinib group versus placebo. p values were obtained from the stratified Cochran–Mantel–Haenszel test. Δ=difference. CDAI=Crohn's Disease Activity Index. PRO2=two-item patient-reported outcome. *p values were considered nominally significant. †Sustained PRO2 clinical remission was defined as achieving PRO2 clinical remission at weeks 10 and 58. ‡The full analysis set for 6-month corticosteroid-free clinical remission was defined as re-randomised responders who received at least one dose of study drug and who were receiving corticosteroids at maintenance baseline. 6-month corticosteroid-free PRO2 clinical remission was defined as PRO2 clinical remission, with no corticosteroid use for the indication of Crohn's disease for at least 6 months before week 58 in the maintenance study among patients with corticosteroid use at maintenance baseline.

(appendix p 26–28). Corticosteroid tapering during the maintenance study is summarised in the appendix (p 29).

We describe first the results of the EU-specific analysis of efficacy endpoints. In induction study A, a larger proportion of patients treated with filgotinib 200 mg reported the co-primary endpoint of PRO2 clinical remission at week 10 than did placebo-treated patients, but the difference was not statistically significant (difference 6·9%, 95% CI –1·4 to 15·2; p=0·0963; figure 2A). Similarly, a larger proportion of patients treated with filgotinib 200 mg reported the co-primary endpoint of an endoscopic response than did placebo-treated patients; however, the difference was not statistically significant (5·5%, –2·0 to 12·9; p=0·1365; figure 2A). In induction study B, a statistically significantly greater proportion of patients had PRO2 clinical remission with filgotinib 200 mg than with placebo (difference 11·9%, 95% CI 3·7 to 20·2; p=0·0039; figure 2B). An endoscopic response was reported in similar proportions of patients across treatment groups, and there were no statistically significant differences (filgotinib 200 mg *vs* placebo 0·1%, –6·5 to 6·6; p=0·9797; figure 2B). For the key secondary induction endpoints, nominally significant differences were reported between filgotinib 200 mg and placebo for CDAI clinical remission in induction studies A and B, and for the combined endpoint of PRO2 clinical remission and an endoscopic response in induction study A (figure 2C, D).

In the maintenance study, a greater proportion of patients had PRO2 clinical remission with filgotinib 200 mg than with placebo at week 58 (filgotinib 200 mg–filgotinib 200 mg *vs* filgotinib 200 mg–placebo, figure 3A). Similarly, a greater proportion of patients treated with filgotinib 200 mg had an endoscopic

	Induction study A			Induction study B			Maintenance study				
	Placebo (n=237)	Filgotinib 100 mg (n=245)	Filgotinib 200 mg (n=222)	Placebo (n=229)	Filgotinib 100 mg (n=228)	Filgotinib 200 mg (n=202)	Placebo–placebo (n=145)	Filgotinib 100 mg–placebo (n=55)	Filgotinib 100 mg–filgotinib 100 mg (n=104)	Filgotinib 200 mg–placebo (n=56)	Filgotinib 200 mg–filgotinib 200 mg (n=118)
Total duration of study drug exposure, weeks	10·9 (2·2)	10·9 (2·3)	10·9 (2·9)	10·7 (2·0)	10·3 (2·5)	10·6 (2·0)	31·9 (17·6)	29·1 (18·4)	30·6 (16·8)	27·7 (18·7)	32·8 (17·8)
Median (IQR)	11·1 (11·0–11·4)	11·0 (11·0–11·4)	11·0 (11·0–11·3)	11·0 (10·9–11·3)	11·0 (10·7–11·3)	11·0 (10·9–11·3)	45·6 (15·1–47·1)	27·0 (10·0–46·9)	34·1 (15·1–47·0)	27·8 (8·3–47·0)	46·1 (13·7–47·1)
TEAE*											
All	137 (58%)	136 (56%)	114 (51%)	156 (68%)	154 (68%)	141 (70%)	96 (66%)	36 (65%)	75 (72%)	35 (63%)	80 (68%)
TEAE with grade ≥3	24 (10%)	23 (9%)	25 (11%)	43 (19%)	47 (21%)	30 (15%)	26 (18%)	4 (7%)	18 (17%)	7 (13%)	21 (18%)
TEAE related to study treatment with grade ≥3	2 (1%)	2 (1%)	6 (3%)	7 (3%)	8 (4%)	9 (4%)	5 (3%)	0	4 (4%)	1 (2%)	5 (4%)
Serious TEAE	15 (6%)	16 (7%)	18 (8%)	26 (11%)	36 (16%)	19 (9%)	14 (10%)	3 (5%)	14 (13%)	5 (9%)	13 (11%)
Serious TEAE related to study treatment	0	1 (<1%)	3 (1%)	3 (1%)	6 (3%)	2 (1%)	1 (1%)	0	2 (2%)	0	4 (3%)
TEAE leading to premature discontinuation of study drug	13 (5%)	15 (6%)	16 (7%)	19 (8%)	31 (14%)	24 (12%)	13 (9%)	2 (4%)	11 (11%)	2 (4%)	12 (10%)
Serious TEAE leading to death	0	0	0	0	0	0	0	0	0	0	0
Death†	0	0	0	0	0	0	0	0	0	0	0
TEAE of interest											
Infection‡	41 (17%)	38 (16%)	39 (18%)	59 (26%)	58 (25%)	47 (23%)	40 (28%)	14 (25%)	28 (27%)	15 (27%)	40 (34%)
Opportunistic infection	1 (<1%)	0	0	1 (<1%)	0	1 (<1%)	0	0	0	0	1 (1%)
Serious infection§	0	2 (1%)	8 (4%)	7 (3%)	8 (4%)	5 (2%)	3 (2%)	1 (2%)	2 (2%)	0	3 (3%)
Herpes zoster	0	1 (<1%)	0	1 (<1%)	0	0	1 (1%)	1 (2%)	1 (1%)	0	0
Malignancy¶	0	0	0	0	0	0	0	0	1 (1%)	0	0
NMSC	0	0	0	1 (<1%)	0	0	0	0	1 (1%)‖	1 (2%)**	0
MACE†††‡‡	0	0	0	0	1 (<1%)	0	0	0	0	0	0
VTE event††	0	0	0	1 (<1%)	0	0	0	0	0	0	1 (1%)
Gastrointestinal perforation§§	0	4 (2%)	2 (1%)	2 (1%)	2 (1%)	1 (<1%)	0	0	0	0	1 (1%)
Treatment-emergent laboratory abnormalities (grade 3 or 4)¶¶‖‖‖											
Haemoglobin <8 g/dL	1/235 (<1%)	5/241 (2%)	0/219	4/229 (2%)	6/228 (3%)	2/201 (1%)	1/143 (1%)	0/55	3/103 (3%)	1/55 (2%)	3/116 (3%)
Lymphocytes ≤750/μL	6/235 (3%)	7/241 (3%)	9/219 (4%)	5/229 (2%)	5/228 (2%)	7/201 (3%)	7/143 (5%)	0/55	4/103 (4%)	4/55 (7%)	5/116 (4%)
Neutrophils <1500/μL	0/235	0/241	1/219 (<1%)	0/229	1/228 (<1%)	0/201	0/143	0/55	1/103 (1%)	0/55	0/116
WBCs <3·0 × 10^9/L	0/235	0/241	1/219 (<1%)	0/229	1/228 (<1%)	0/201	0/143	0/55	2/103 (2%)	0/55	0/116

(Table 2 continues on next page)

response than did placebo-treated patients (filgotinib 200 mg–filgotinib 200 mg *vs* filgotinib 200 mg–placebo). For the key secondary maintenance endpoints, nominally significantly greater proportions of patients in the filgotinib 200 mg group had combined PRO2 clinical remission and an endoscopic response, and sustained PRO2 clinical remission than in the placebo group (figure 3B).

No statistically significant differences were reported in the co-primary or key secondary endpoints for filgotinib 100 mg compared with placebo at weeks 10 and 58.

The non-EU-specific analysis of efficacy endpoints is reported in the appendix (pp 47–50). For the co-primary induction endpoints, greater proportions of patients had CDAI clinical remission with filgotinib 200 mg than with placebo in both induction study A (32·9% *vs* 19·8%, difference 12·7%; 95% CI 4·7 to 20·7, p=0·0017) and induction study B (26·7% *vs* 14·8%, 12·0%; 4·1 to 19·9, p=0·0023; appendix p 47–48). No statistically significant difference in the endoscopic response rate was reported in either induction study for filgotinib 200 mg compared with placebo. For the co-primary maintenance endpoints, no statistically significant difference was observed in the CDAI clinical remission rate for filgotinib 200 mg compared with placebo. A greater proportion of patients had an endoscopic response with filgotinib 200 mg than with placebo at week 58 (filgotinib 200 mg–filgotinib 200 mg *vs* filgotinib 200 mg–placebo 30·4% *vs* 9·4%, difference 20·6%; 95% CI 8·2 to 33·1, p=0·0038, appendix pp 47–48). No statistically significant differences were reported in the co-primary endpoints for filgotinib 100 mg compared with placebo at week 10 or 58.

The proportions of patients who did not reach the co-primary and key secondary endpoints in the induction and maintenance studies are reported in the appendix (pp 30–33).

Subgroup analyses of EU-specific and non-EU-specific efficacy co-primary endpoints by previous exposure to biological agents are reported in the appendix (pp 49–50). In the combined induction studies A and B, nominally significant differences were reported between filgotinib 200 mg and placebo for CDAI clinical remission in biologic-naive patients (difference 14·3%, 95% CI 1·7 to 26·8; p=0·0240). In biologic-experienced patients, nominally significantly greater proportions of patients in the filgotinib 200 mg group had PRO2 clinical remission (difference 9·8%, 3·1 to 16·5; p=0·0029) and CDAI clinical remission (difference 11·6%, 5·2 to 17·9; p=0·0002) than in the placebo group. In the maintenance study, a nominally significantly greater proportion of biologic-naive patients treated with filgotinib 200 mg had an endoscopic response than did placebo-treated patients (filgotinib 200 mg–filgotinib 200 mg *vs* filgotinib 200 mg–placebo difference 32·7%, 95% CI 12·9 to 52·6; p=0·0070). In biologic-experienced patients, nominally significant differences were reported between filgotinib

	Induction study A			Induction study B			Maintenance study					
	Placebo (n=237)	Filgotinib 100 mg (n=245)	Filgotinib 200 mg (n=222)	Placebo (n=229)	Filgotinib 100 mg (n=228)	Filgotinib 200 mg (n=202)	Placebo–placebo (n=145)	Filgotinib 100 mg–placebo (n=55)	Filgotinib 100 mg–filgotinib 100 mg (n=104)	Filgotinib 200 mg–placebo (n=56)	Filgotinib 200 mg–filgotinib 200 mg (n=118)
(Continued from previous page)											
ALT >2×ULN	0/236	0/241	2/220 (1%)	0/229	0/228	2/202 (1%)	0/140	1/54 (2%)	1/102 (1%)	0/52	0/116
AST >2×ULN	0/236	2/241 (1%)	0/219	NA	NA	NA	0/140	0/54	1/102 (1%)	0/52	0/116
Hypophosphataemia	7/236 (3%)	13/241 (5%)	7/221 (3%)	12/229 (5%)	7/228 (3%)	10/202 (5%)	0/140	1/55 (2%)	4/102 (4%)	0/52	10/116 (9%)

Data are mean (SD), n (%), or n/N (%), unless otherwise specified. For the induction studies, TEAEs were defined as any adverse events that began on or after the date of the first induction dose up to 1 day before the first maintenance dose date or 30 days after the last induction dose date, whichever came earlier, or that led to premature discontinuation of induction study drug. For the maintenance study, TEAEs were defined as any adverse events that began on or after the date of the first maintenance dose up to 30 days after the last maintenance dose date, or that led to premature discontinuation of maintenance study drug. Adverse events and clinical laboratory results were coded using the Medical Dictionary for Regulatory Activities version 25.0. ALT=alanine aminotransferase. AST=aspartate aminotransferase. MACE=major adverse cardiovascular event. NA=not available. NMSC=non-melanoma skin cancer. TEAE=treatment-emergent adverse event. ULN=upper limit of normal. VTE=venous thromboembolism. WBC=white blood cell. *Severity grades were defined by the Common Terminology Criteria for Adverse Events version 4.03. †Death was defined as any death that occurred during the induction or maintenance studies. ‡The most frequently reported infections (≥3 patients in any group) in the induction studies were anal abscess, bronchitis, conjunctivitis, gastroenteritis, nasopharyngitis, oral herpes, pharyngitis, SARS-CoV-2 infection, sinusitis, tooth infection, upper respiratory tract infection, urinary tract infection, and vulvovaginal candidiasis; in the maintenance study, they were bronchitis, gastroenteritis, influenza, nasopharyngitis, SARS-CoV-2 infection, sinusitis, tooth abscess, upper respiratory tract infection, and urinary tract infection. §The most frequently reported serious infections (at least two patients in any group) were SARS-CoV-2 infection in induction study A; abdominal abscess, anal abscess, gastroenteritis, and pneumonia in induction study B; and anal abscess in the maintenance study. ¶Excludes NMSC. ||Basal cell carcinoma (grade 3). **Squamous cell carcinoma of the skin at three different timepoints and locations (grade 1 or 2). ††All potential MACEs and VTE events were adjudicated by an external expert committee. ‡‡Includes cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. §§None of the gastrointestinal perforations were considered related to study treatment according to post hoc adjudication by an external expert committee, but instead were considered related to underlying disease progression or colonoscopy. ¶¶For the induction studies, 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 first maintenance dose date or 30 days after the last induction dose date, whichever was earlier. For the maintenance study, 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. The abnormality with the most severe grade for each test was counted. ||||Percentages were calculated based on the number of patients in the safety analysis set with at least one post-baseline value for each test.

Table 2: **Summary of safety outcomes in the induction and maintenance studies**

200 mg and placebo for PRO2 clinical remission (filgotinib 200 mg–filgotinib 200 mg *vs* filgotinib 200 mg–placebo difference 25·0%, 95% CI 5·2 to 44·8; p=0·0197) and CDAI clinical remission (filgotinib 200 mg–filgotinib 200 mg *vs* filgotinib 200 mg–placebo difference 23·4%, 4·7 to 42·2; p=0·0172). Treatment differences between the filgotinib 100 mg and placebo groups were not nominally significant for any of the endpoints in biologic-naive or biologic-experienced patients in the induction and maintenance studies.

In the subgroup analyses by sex, the proportions of patients with the co-primary and key secondary endpoints with filgotinib 200 mg (*vs* placebo) were generally in line with the overall population in each induction study (A or B) or in the maintenance study (appendix pp 34–35).

Exploratory endpoint analyses (endoscopic remission, complete endoscopic healing) are reported in the appendix (p 36).

In the induction studies, mean duration of exposure to study drug was approximately 10·9 and 10·5 weeks in induction studies A and B, respectively (table 2). Similar proportions of patients had TEAEs across treatment groups within each induction study (table 2). Smaller proportions of patients had TEAEs in induction study A than in induction study B. Most TEAEs were mild or moderate in severity. The most frequently reported TEAEs (≥5% of patients in any group) in the induction studies were abdominal pain; arthralgia; an exacerbation, flare, or worsening of Crohn's disease; headache; nasopharyngitis; nausea; and pyrexia (appendix pp 37–38). Incidences of TEAEs leading to treatment discontinuation are shown in table 2.

Serious TEAEs were reported in similar proportions of patients across treatment groups in induction study A. In induction study B, serious TEAEs occurred in 19 (9%) of 202 patients in the filgotinib 200 mg group, 36 (16%) of 228 patients in the filgotinib 100 mg group, and 26 (11%) of 229 patients in the placebo group. The most frequently reported serious TEAE (≥2% of patients in any group) in the induction studies was an exacerbation, flare, or worsening of Crohn's disease (appendix p 39).

TEAEs of interest in the induction studies are summarised in table 2. In induction study A, serious infections were reported in eight (4%) patients in the filgotinib 200 mg group and in two (1%) patients in the filgotinib 100 mg group; no serious infections were reported in the placebo group. In induction study B, the incidence of serious infections was generally similar between treatment groups. The most frequently reported infections and serious infections are described in table 2. Herpes zoster was reported in one (<1%) patient in each of the induction studies (appendix p 40). No malignancies (excluding non-melanoma skin cancer) were reported in the induction studies. Non-melanoma skin cancer was reported in one (<1%) patient in the placebo group in induction study B (basal cell carcinoma; grade 1). A VTE event occurred in one (<1%) placebo-treated patient in induction study B (jugular vein thrombosis; grade 2). A MACE was reported in one (<1%) patient in the filgotinib 100 mg group in induction study B (acute respiratory failure, adjudicated as myocardial infarction). Details of MACEs and VTE events that occurred during the study are provided in the appendix (p 41).

Gastrointestinal perforations were reported in six patients in induction study A (two [1%] of 222 patients in the filgotinib 200 mg group and four [2%] of 245 patients in the filgotinib 100 mg group) and five patients in induction study B (one [<1%] of 202 patients in the filgotinib 200 mg group, two [1%] of 228 patients in the filgotinib 100 mg group, and two [1%] of 229 patients in the placebo group). After post hoc adjudication by an external expert committee, none of the gastrointestinal perforations were considered related to study treatment, but instead were considered related to underlying disease progression or secondary to the colonoscopies (appendix pp 42–43).

In the maintenance study, the mean duration of exposure to study drug was approximately 30·4 weeks (table 2). TEAEs were reported in 62·5–72·1% of patients (table 2). Most TEAEs were mild or moderate in severity. The most frequently reported TEAEs (≥5% of patients in any filgotinib or associated placebo group) were abdominal distension; abdominal or upper abdominal pain; anaemia; arthralgia; an exacerbation, flare, or worsening of Crohn's disease; flatulence; nasopharyngitis; nausea; and pyrexia (appendix pp 37–38). The incidence of TEAEs leading to treatment discontinuation is shown in table 2.

Serious TEAEs in the maintenance study occurred in a greater proportion of patients in the filgotinib 200 mg and filgotinib 100 mg groups than in their respective placebo groups (13 [11%] of 118 patients in the filgotinib 200 mg–filgotinib 200 mg group *vs* five [9%] of 56 patients in the filgotinib 200 mg–placebo group and 14 [13%] of 104 patients in the filgotinib 100 mg–filgotinib 100 mg group *vs* three [5%] of 55 patients in the filgotinib 100 mg–placebo group). The most frequently reported serious TEAE (≥2% of patients in any filgotinib or associated placebo group) was an exacerbation, flare, or worsening of Crohn's disease (appendix p 39).

TEAEs of interest in the maintenance study are summarised in table 2. Herpes zoster was reported in one patient each in the filgotinib 100 mg–filgotinib 100 mg (1%; grade 2), filgotinib 100 mg–placebo (2%; grade 1), and placebo–placebo (1%; grade 2) groups in the maintenance study. One (1%) patient in the filgotinib 100 mg–filgotinib 100 mg group had malignancy (metastases to lung [primary origin unknown]; grade 3). NMSC was reported in one (1%) patient in the filgotinib 100 mg–filgotinib 100 mg group and in one (2%) patient in the filgotinib 200 mg–placebo group. Deep vein thrombosis occurred in one (1%) patient in the filgotinib 200 mg–filgotinib 200 mg group in the maintenance study, with risk factors

of immobility, history of Crohn's disease, and pneumonia. No MACEs were reported in the maintenance study. A gastrointestinal perforation was reported in one (1%) patient in the filgotinib 200 mg–filgotinib 200 mg group in the maintenance study Details of the VTE and gastrointestinal perforation events are provided in the appendix (pp 41–43).

No deaths were reported during the induction and maintenance studies.

The pharmacokinetics of filgotinib and GS829845 are reported in the appendix (p 44).

Laboratory abnormalities and biomarker data are described in table 2 and the appendix (p 25).

Discussion

In this phase 3 study in patients with moderately to severely active Crohn's disease, filgotinib 200 mg did not meet the co-primary induction endpoints, but it did meet the co-primary maintenance endpoints (in the EU-specific analyses). Filgotinib was generally well tolerated, and no new safety signals were reported.

Two separate analyses (EU-specific, non-EU-specific) were conducted with differing co-primary endpoints (clinical remission assessed by PRO2 or CDAI) and minor modifications to the secondary endpoint analyses. Based on the EU-specific analyses, the proportion of patients with PRO2 clinical remission was significantly higher with filgotinib 200 mg than with placebo in induction study B. Nonetheless, filgotinib 200 mg was not efficacious as induction therapy compared with placebo, as assessed across both co-primary outcomes, but it was efficacious in achieving PRO2 clinical remission and an endoscopic response at week 58 in patients who had either endpoint at week 10 with induction filgotinib 200 mg. Neither of the co-primary induction or maintenance endpoints were reached with filgotinib 100 mg.

By contrast with the EU-specific analyses, the non-EU-specific analyses indicated that filgotinib 200 mg was not efficacious as induction or maintenance therapy compared with placebo. In both induction studies, only the co-primary endpoint of CDAI clinical remission was met with filgotinib 200 mg versus placebo. In the maintenance study, significant improvements compared with placebo were observed with filgotinib 200 mg for only the co-primary endpoint of an endoscopic response. Therefore, filgotinib 200 mg did not meet both co-primary endpoints in any of the studies. Furthermore, no significant improvements were reported in the co-primary endpoints for filgotinib 100 mg compared with placebo in any of the studies.

Filgotinib was well tolerated in patients with Crohn's disease, and treatment discontinuation rates were generally low across treatment groups. The incidence of adverse events was similar between treatment groups, and low proportions of filgotinib-treated patients had malignancies, MACEs, and VTE events. Following adjudication by an external expert committee, none of the gastrointestinal perforations reported in the study were considered related to study treatment. Overall, the safety profile of filgotinib in Crohn's disease was generally consistent with its safety profile for the approved indications of ulcerative colitis and rheumatoid arthritis,[23,24] and no new safety signals were observed in DIVERSITY.

Although the co-primary induction endpoints of CDAI clinical remission and an endoscopic response were not met at week 10 in DIVERSITY, there were significant improvements in the CDAI clinical remission rate with filgotinib 200 mg compared with placebo. This observation generally aligns with results from the phase 2 FITZROY study in Crohn's disease. In FITZROY, the primary endpoint of CDAI clinical remission occurred in significantly more patients treated with filgotinib 200 mg than with placebo at week 10.[1] By contrast with DIVERSITY, the phase 2 DIVERGENCE1 trial in small-bowel Crohn's disease did not meet the primary endpoint of CDAI clinical remission after 24 weeks of filgotinib treatment.[25] For an endoscopic response at week 10, no significant differences were detected between filgotinib 200 mg and placebo in this endpoint in either DIVERSITY or FITZROY.[1] Despite taking into account the central reading paradigm in DIVERSITY, a high endoscopic response rate was observed with placebo that could account for the absence of a treatment effect observed for this endpoint with filgotinib 200 mg.

At week 58 of DIVERSITY, PRO2 clinical remission and an endoscopic response were seen in a significantly greater proportion of patients treated with filgotinib than patients treated with placebo among those who had already reached either of these co-primary endpoints with induction therapy. Similar findings were observed in a tofacitinib phase 2b trial, which found evidence of minor clinical efficacy for tofacitinib in inducing and maintaining remission in patients with Crohn's disease. However, no significant differences between tofacitinib and placebo were observed for the primary efficacy endpoints at week 8 or 26.[26] Conversely, the upadacitinib phase 3 Crohn's disease clinical programme demonstrated that upadacitinib was efficacious compared with placebo in both reaching and maintaining CDAI clinical remission and an endoscopic response, assessed at both weeks 12 and 52.[14] The discrepancy between our results and those from the upadacitinib phase 3 trial might be explained by the filgotinib dose evaluated during DIVERSITY. JAK inhibitors have generally been evaluated in Crohn's disease using doses from rheumatoid arthritis trials.[26,27] As such, DIVERSITY used the same filgotinib dose for induction and maintenance treatment. By contrast, the upadacitinib trial that demonstrated efficacy in Crohn's disease used a higher induction dose than the maintenance dose.[14] Furthermore, of the biologic-experienced patients in induction study B in DIVERSITY, 52% had previously used at least three biological agents and 34% had experienced failure

of both a TNF antagonist and vedolizumab; this might have resulted in a difficult-to-treat population. Nonetheless, caution is warranted when comparing different studies owing to variations in treatment durations and outcome definitions.

A high proportion of patients (≥32%) in DIVERSITY were receiving corticosteroids at induction and maintenance baselines. Although the prescribed corticosteroid dose was required to be stable, subgroup analyses suggest that the high clinical remission rate observed with placebo at week 10 might have been driven by corticosteroid use (data not shown). The concomitant dose of prednisone allowed in DIVERSITY (30 mg/day) was equivalent to that in the tofacitinib phase 2b trial (which did not meet its endpoints) and was higher than that in the risankizumab phase 3 trial (20 mg/day; trial endpoints met) in Crohn's disease.[10,26] Mandatory corticosteroid tapering began in the maintenance study (week 14) of DIVERSITY, whereas mandatory glucocorticoid tapering occurred in the induction study (week 4) of the upadacitinib phase 3 trial.[14] Tapering corticosteroids earlier than week 14 may have resulted in detectable treatment differences in efficacy outcomes between induction filgotinib and placebo in DIVERSITY.

A key strength of our study is the large number of patients enrolled. In addition, the study design enabled the enrolment of a representative study population, of biologic-naive and biologic-experienced patients, and the evaluation of two filgotinib doses.

A limitation might be that one of the criteria for re-randomisation in the maintenance study was PRO2 clinical remission or an endoscopic response. Using a subjective measure of clinical symptoms (such as PRO2) to determine re-randomisation could have resulted in higher than expected proportions of patients given placebo with the subjective outcome of PRO2 clinical remission in the induction studies. In addition, we note that a proportion of patients who had a CDAI clinical response but not PRO2 clinical remission or an endoscopic response at week 10 could have benefitted further from filgotinib maintenance therapy if they had been eligible to enter the maintenance study. Furthermore, the SES-CD-based severity criterion (which has also been used in other phase 3 Crohn's disease trials)[28] allowed SES-CD scores to be combined across two bowel segments (terminal ileum and ascending colon), potentially resulting in enrolment of a study population with wide disease variability.

In conclusion, although filgotinib 200 mg showed signs of clinical activity in patients with Crohn's disease in DIVERSITY compared with placebo, the trial did not meet both co-primary endpoints of PRO2 clinical remission and an endoscopic response in the induction studies (for the EU-specific analyses). Both co-primary endpoints were met in the maintenance studies with filgotinib 200 mg. For the non-EU-specific analyses, in which CDAI instead of PRO2 was used to assess clinical remission, the trial did not meet both co-primary endpoints in any study. Filgotinib treatment was well tolerated and showed a safety profile in Crohn's disease in line with the known safety profile of filgotinib in other indications.

Contributors

SV, SS, DTR, MW, and SD contributed to conceptualisation and design of the work and data interpretation, and participated in the study advisory board. GD'H, WR, RM, XR, IB, PG, TH, IH, and TR contributed to data interpretation. MCG and PK contributed to the design of the work and data interpretation. ES contributed to data acquisition and analysis and data interpretation. F-OLB contributed to conceptualisation and design of the work, data acquisition and analysis, and data interpretation. RB and TM contributed to conceptualisation and design of the work and data interpretation. SV and TM had full access to and verified all the data in the study. All authors had access to the underlying data, approved the final version of the manuscript, and accept responsibility to submit for publication.

Declaration of interests

SV reports consulting and/or speaker fees from AbbVie, Abivax, AbolerIS Pharma, AgomAb Therapeutics, Alimentiv, Arena Pharmaceuticals, AstraZeneca, Biora Therapeutics (formerly Progenity), Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Cytoki Pharma, Dr Falk Pharma, Eli Lilly, Ferring Pharmaceuticals, Galapagos, Genentech/Roche, Gilead Sciences, GSK, Hospira, IMIDomics, Janssen Pharmaceuticals, Johnson & Johnson, Materia Prima, Mestag Therapeutics, MiroBio, Morphic Therapeutic, MRM Health, MSD, Mundipharma, Pfizer, ProDigest, Prometheus Biosciences, Robarts Clinical Trials, Surrozen, Takeda, Theravance Biopharma, Tillotts Pharma, VectivBio, Ventyx Biosciences, and Zealand Pharma; grants from AbbVie, Galapagos, Johnson & Johnson, Pfizer, and Takeda; and participation on a data safety monitoring board for Sanofi. SV is Professor of Medicine at KU Leuven. SS reports consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Dr Falk Pharma, Eli Lilly, Ferring Pharmaceuticals, Fresenius Kabi, Galapagos/Gilead Sciences, Hikma Pharmaceuticals, I-Mab, Janssen Pharmaceuticals, Morphic Therapeutic, MSD, Mylan, Pfizer, Protagonist Therapeutics, Provention Bio, Sandoz/Hexal, Takeda, Theravance Biopharma, and Ventyx Biosciences. DTR reports consulting fees from AbbVie, AltruBio, Amgen, Avalo Therapeutics, Bristol Myers Squibb, Buhlmann Diagnostics Corp, Chronicles Health, ClostraBio, Connect Biopharma, Cytoki Pharma, Douglas Pharmaceuticals, EcoR1, Eli Lilly, Ferring Pharmaceuticals, Image Analysis Group, InDex Pharmaceuticals, Iterative Health, Janssen Pharmaceuticals, Odyssey Therapeutics, Pfizer, Prometheus Biosciences, Reistone Biopharma, Samsung NeuroLogica, Sangamo Therapeutics, Shanghai Pharma Biotherapeutics USA, Takeda, TISSIUM, and Trellus Health; and grants from Takeda. GD'H reports consulting fees from AbbVie, Alimentiv, AstraZeneca, Biora Therapeutics (formerly Progenity), Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly, Galapagos, GSK, Immunic Therapeutics, and Ventyx Biosciences; grants from AbbVie, Eli Lilly, Pfizer, and Takeda; participation on a data safety monitoring board or advisory board for AstraZeneca and Seres Health; and speaker fees from AbbVie, Biogen, Galapagos, Johnson & Johnson, Pfizer, Takeda, and Tillotts Pharma. WR reports consulting fees from AbbVie, Amgen, AOP Health (formerly AOP Orphan), Boehringer Ingelheim, Bristol Myers Squibb, Calyx, Celltrion, Eli Lilly, Galapagos, Gilead Sciences, InDex Pharmaceuticals, Janssen Pharmaceuticals, MEDahead, Microbiotica, Pfizer, and Takeda; participation on an advisory board for AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Galapagos, Janssen Pharmaceuticals, and Pfizer; research funding from AbbVie, Janssen Pharmaceuticals, Sandoz, Sanofi, and Takeda; and speaker fees from AbbVie, Celltrion, Ferring Pharmaceuticals, Galapagos, Janssen Pharmaceuticals, MEDICE, MSD, Pfizer, Roche, Sobi, and Takeda. MW reports consulting fees from AbbVie, EA Pharma, Eli Lilly Japan, Gilead Sciences, and Nippon Boehringer Ingelheim; grants from AbbVie, EA Pharma, Mitsubishi Tanabe Pharma Corporation, Nippon Kayaku, Takeda, and Zeria Pharmaceutical; and speaker fees from EA Pharma, Eli Lilly Japan, Gilead Sciences, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Miyarisan, Mochida Pharmaceutical, Takeda, and Zeria Pharmaceutical. XR reports personal fees from AbbVie, Amgen, Bristol Myers Squibb, Celltrion, Eli Lilly,

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Data sharing

Anonymised individual patient data will be shared upon request (beginning 6 months and ending 5 years following manuscript publication) for research purposes, dependent upon the nature of the request, the merit of the proposed research, the availability of the data, and their intended use. Scientifically sound proposals should be directed to evidencegenerationcommittee@alfasigma.com. The full data sharing policies for Galapagos and Gilead Sciences can be found at https://www.clinicaltrials-glpg.com/us/en/data-transparency.html and https://www.gileadclinicaltrials.com/en/transparency-policy#DataSharing, respectively.

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References

1 Vermeire S, Schreiber S, Petryka R, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. *Lancet* 2017; **389:** 266–75.

2 Mitropoulou MA, Fradelos EC, Lee KY, et al. Quality of life in patients with inflammatory bowel disease: importance of psychological symptoms. *Cureus* 2022; **14:** e28502.

3 Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012; **380:** 1590–605.

4 Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the international organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* 2021; **160:** 1570–83.

5 Cushing K, Higgins PDR. Management of Crohn disease: a review. *JAMA* 2021; **325:** 69–80.

6 Macaluso FS, Papi C, Orlando A, et al. Use of biologics for the management of Crohn's disease: IG-IBD clinical guidelines based on the GRADE methodology. *Dig Liver Dis* 2023; **55:** 442–53.

7 AbbVie Ltd. Summary of product characteristics. Skyrizi. 2024. https://www.ema.europa.eu/en/documents/product-information/skyrizi-epar-product-information_en.pdf (accessed Feb 19, 2024).

8 Kayal M, Ungaro RC, Bader G, Colombel JF, Sandborn WJ, Stalgis C. Net remission rates with biologic treatment in Crohn's disease: a reappraisal of the clinical trial data. *Clin Gastroenterol Hepatol* 2023; **21:** 1348–50.

9 Shivaji UN, Sharratt CL, Thomas T, et al. Review article: managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2019; **49:** 664–80.

10 D'Haens G, Panaccione R, Baert F, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. *Lancet* 2022; **399:** 2015–30.

11 Harris C, Cummings JRF. JAK1 inhibition and inflammatory bowel disease. *Rheumatology (Oxford)* 2021; **60** (suppl 2)**:** ii45–51.

12 Santiago P, Braga-Neto MB, Loftus EV. Novel therapies for patients with inflammatory bowel disease. *Gastroenterol Hepatol (N Y)* 2022; **18:** 453–65.

13 Honap S, Agorogianni A, Colwill MJ, et al. JAK inhibitors for inflammatory bowel disease: recent advances. *Frontline Gastroenterol* 2023; **15:** 59–69.

14 Loftus EV Jr, Panés J, Lacerda AP, et al. Upadacitinib induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2023; **388:** 1966–80.

15 AbbVie Ltd. Full prescribing information. Upadacitinib. 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211675s015lbl.pdf (accessed June 26, 2024).

16 Galapagos NV. Summary of product characteristics, Jyseleca. 2023. https://www.ema.europa.eu/en/documents/product-information/jyseleca-epar-product-information_en.pdf (accessed Feb 19, 2024).

17 Galapagos Biotech Limited. Summary of product characteristics, Jyseleca. 2023. https://www.medicines.org.uk/emc/files/pil.11810.pdf (accessed Feb 19, 2024).

18 Gilead Sciences K.K. Jyseleca (Filgotinib) approved in Japan for rheumatoid arthritis. 2020. https://www.gilead.com/news-and-press/press-room/press-releases/2020/9/jyseleca-filgotinib-approved-in-japan-for-rheumatoid-arthritis (accessed Feb 19, 2024).

19 Galapagos NV. Jyseleca approved in Japan for ulcerative colitis. 2022. https://www.glpg.com/press-release/3571/jyseleca-approved-in-japan-for-ulcerative-colitis (accessed Feb 19, 2024).

20 Taiwan Food and Drug Administration. Assessment report. 2022. https://www.fda.gov.tw/tc/includes/GetFile.ashx?mid=189&id=39893&t=s (accessed Feb 19, 2024).

21 Hellstrom WJG, Dolhain RJEM, Ritter TE, et al. MANTA and MANTA-RAy: rationale and design of trials evaluating effects of filgotinib on semen parameters in patients with inflammatory diseases. *Adv Ther* 2022; **39:** 3403–22.

22 Reinisch W, Hellstrom W, Dolhain RJEM, et al. Effects of filgotinib on semen parameters and sex hormones in male patients with inflammatory diseases: results from the phase 2, randomised, double-blind, placebo-controlled MANTA and MANTA-RAy studies. *Ann Rheum Dis* 2023; **82:** 1049–58.

23 Feagan BG, Danese S, Loftus EV Jr, et al. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. *Lancet* 2021; **397:** 2372–84.

24 Winthrop K, Aletaha D, Caporali RF, et al. An update on the integrated safety analysis of filgotinib in patients with moderately to severely active RA. *Arthritis Rheumatol* 2022; **74** (suppl 9)**:** 273 (abstr).

25 D'Haens GR, Lee S, Taylor SA, et al. Filgotinib for the treatment of small bowel Crohn's disease: the DIVERGENCE 1 trial. *Gastroenterology* 2023; **165:** 289–92.

26 Panés J, Sandborn WJ, Schreiber S, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. *Gut* 2017; **66:** 1049–59.

27 Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022; **386:** 316–26.

28 Feagan BG, Schreiber S, Afzali A, et al. Ozanimod as a novel oral small molecule therapy for the treatment of Crohn's disease: the YELLOWSTONE clinical trial program. *Contemp Clin Trials* 2022; **122:** 106958.