



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

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Summary

Background Filgotinib (GLPG0634, GS-6034) is a once-daily, orally administered, Janus kinase 1 (JAK1)-selective inhibitor. The FITZROY study examined the efficacy and safety of filgotinib for the treatment of moderate-to-severe Crohn's disease.

Methods We did a randomised, double-blind, placebo-controlled phase 2 study, which recruited patients from 52 centres in nine European countries. We enrolled eligible patients aged 18–75 years with a documented history of ileal, colonic, or ileocolonic Crohn's disease for 3 months or more before screening, as assessed by colonoscopy and supported by histology, and a Crohn's Disease Activity Index (CDAI) score during screening between 220 and 450 inclusive. Patients were randomly assigned (3:1) to receive filgotinib 200 mg once a day or placebo for 10 weeks. Patients were stratified according to previous anti-tumour necrosis factor alpha exposure, C-reactive protein concentration at screening (≤ 10 mg/L or > 10 mg/L), and oral corticosteroid use at baseline, using an interactive web-based response system. The primary endpoint was clinical remission, defined as CDAI less than 150 at week 10. After week 10, patients were assigned based on responder status to filgotinib 100 mg once a day, filgotinib 200 mg once a day, or placebo for an observational period lasting a further 10 weeks. The filgotinib and placebo treatment groups were compared using ANCOVA models and logistic regression models containing baseline values and randomisation stratification factors as fixed effects. Analyses were done on the intention-to-treat non-responder imputation set. The trial was registered at ClinicalTrials.gov, number NCT02048618.

Findings Between Feb 3, 2014, and July 10, 2015, we enrolled 174 patients with active Crohn's disease confirmed by centrally read endoscopy (130 in the filgotinib 200 mg group and 44 in the placebo group). In the intention-to-treat population, 60 (47%) of 128 patients treated with filgotinib 200 mg achieved clinical remission at week 10 versus ten (23%) of 44 patients treated with placebo (difference 24 percentage points [95% CI 9–39], $p=0.0077$). In a pooled analysis of all periods of filgotinib and placebo exposure over 20 weeks, serious treatment-emergent adverse effects were reported in 14 (9%) of 152 patients treated with filgotinib and three (4%) of 67 patients treated with placebo.

Interpretation Filgotinib induced clinical remission in significantly more patients with active Crohn's disease compared with placebo, and had an acceptable safety profile.

Funding Galapagos.

Introduction

Crohn's disease is a chronic inflammatory bowel disease characterised by progressive transmural damage leading to complications. Chronic inflammation of the gastrointestinal tract, most commonly the proximal colon and distal small intestine, leads to symptoms including abdominal pain, diarrhoea, weight loss, and chronic fatigue, as well as progressive damage to the bowel.^{1,2} The course of Crohn's disease can be modified by treatment. Whereas the primary goal of therapy for Crohn's disease is to achieve clinical remission, the importance of patient-reported outcomes and endoscopic response are increasingly recognised and are now accepted as valid coprimary endpoints by regulatory agencies.³ Management of the disease has benefited from

the development of monoclonal antibodies targeting tumour necrosis factor alpha (TNF α), including infliximab, adalimumab, or certolizumab pegol. These are commonly used in combination with thiopurines or methotrexate. However, not all patients respond to anti-TNF agents and many of those who do will eventually become secondary non-responders. Only 10% of patients with Crohn's disease achieve prolonged clinical remission and 50% require surgery within 10 years of diagnosis.⁴ There is therefore a need for novel disease-modifying treatments with an alternative mechanism of action that are safe and well tolerated.

Janus kinases (JAKs) are intracellular cytoplasmic tyrosine kinases that transduce cytokine-mediated activation of membrane receptors, via phosphorylation of

Lancet 2017; 389: 266–75

Published Online

December 14, 2016

[http://dx.doi.org/10.1016/S0140-6736\(16\)32537-5](http://dx.doi.org/10.1016/S0140-6736(16)32537-5)

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Research in context

Evidence before this study

We searched PubMed using the terms “Crohn’s disease” and “treatment” and “(moderate to severe)” for articles published between Jan 1, 2000, and Aug 6, 2016, restricted to the English language. We found 353 articles, of which 77 were clinical trials in adults. These studies show that anti-tumour necrosis factor agents have been the mainstay of Crohn’s disease treatment in recent decades, but that many patients either fail to respond or become secondary non-responders. The scale of this clinical problem has also been confirmed by a systematic review published by the European Crohn’s and Colitis Organisation (ECCO). Given that only 10% of patients with Crohn’s disease are thought to achieve prolonged clinical remission, there is an urgent need for novel disease-modifying treatments with an alternative mechanism of action. Inhibition of members of the Janus kinase (JAK) family has shown efficacy in phase 3 studies in ulcerative colitis, an inflammatory bowel disease related to Crohn’s disease. We did the first randomised, placebo-controlled, phase 2 study of the efficacy and safety of a novel JAK1-selective inhibitor, filgotinib (GLPG0634, GS-6034), in patients with moderate-to-severe Crohn’s disease.

Added value of this study

Whereas previous studies in Crohn’s disease have recruited patients on the basis of clinical symptoms or endoscopies

read by local physicians, our study (FITZROY) is the first double-blind, placebo-controlled study to use centrally read endoscopies to ensure the selective recruitment of patients with active disease including mucosal ulceration. In the intention-to-treat population, a significantly greater proportion of patients achieved clinical remission (defined as a Crohn’s Disease Activity Index [CDAI] <150) with filgotinib 200 mg once a day than with placebo. Filgotinib was superior to placebo in CDAI-100 response and in mean change from baseline in quality of life, as revealed by the Inflammatory Bowel Disease Questionnaire score and subscores. Beneficial effects were additionally seen on D’Haens histopathology scores, the Simplified Endoscopy Score for Crohn’s Disease scale, and biomarkers of inflammatory activity.

Implications of all the available evidence

The FITZROY study provides the first evidence for the efficacy and safety of the JAK1 inhibitor filgotinib for the treatment of moderate-to-severe Crohn’s disease with mucosal ulceration. Filgotinib could represent the first new oral treatment for Crohn’s disease in many years, and phase 3 trials with the compound are underway.

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signal transducers and activators of transcription (STATs).⁵ There are four known JAK subtypes (JAK1, JAK2, JAK3, and TYK2) and blocking cytokine signalling via inhibition of the JAK–STAT pathway is a promising therapeutic option for inflammatory disease.⁶ Tofacitinib, a pan-JAK inhibitor that blocks JAK1 and JAK3, and to a lesser extent JAK2, is approved for the treatment of moderate-to-severe rheumatoid arthritis.⁷ It has also shown preliminary efficacy in ulcerative colitis, another type of inflammatory bowel disease.⁸ However, in randomised phase 2a⁹ and 2b¹⁰ studies in Crohn’s disease, tofacitinib did not differ significantly from placebo with respect to clinical remission. Therefore, it is unclear whether JAK inhibition is a viable therapeutic option for Crohn’s disease.

Filgotinib (GLPG0634, GS-6034) is a once-daily, orally administered inhibitor of JAK1, with about a 30 times selectivity for JAK1 over JAK2 in human whole blood,¹¹ and 50 times selectivity for JAK1 over JAK3. Filgotinib has an elimination half-life of 6 h; it gives rise to an active metabolite, with a terminal elimination half-life of 21–27 h.¹² Both the parent molecule and the active metabolite contribute to the clinical activity of filgotinib, and maximum pharmacodynamic effects are achieved at 200 mg filgotinib daily.¹² Filgotinib showed good efficacy in patients with active rheumatoid arthritis in two phase 2b studies, with beneficial effects on signs, symptoms, and patient-reported outcomes.^{13,14}

The FITZROY study examined the efficacy and safety of daily filgotinib for the treatment of active moderate-to-severe Crohn’s disease, in patients with mucosal ulceration identified by centrally read endoscopies at enrolment. The impact of filgotinib on biomarkers of inflammatory activity was also examined.

Methods

Study design and participants

We did a randomised, double-blind, placebo-controlled phase 2 study, which recruited patients from 52 centres in nine European countries (Belgium, Czech Republic, France, Germany, Hungary, Poland, Romania, Russian Federation, and the UK).

Eligible patients were aged 18–75 years with a documented history of ileal, colonic, or ileocolonic Crohn’s disease for 3 months or more before screening, as assessed by colonoscopy and supported by histology, and a Crohn’s Disease Activity Index (CDAI) score during screening between 220 and 450 inclusive. Evidence of active inflammation and ulceration was required at screening, in the form of a centrally read score of at least 1 in one or more ileocolonic segments in the Presence of Ulcers component of the Simplified Endoscopy Score for Crohn’s disease (SES-CD), as well as a total score of at least 7. Patients were either anti-TNF-naïve or anti-TNF-experienced (exposed to infliximab, adalimumab, or certolizumab pegol at a dose registered for the treatment

See Online for appendix

	Placebo (n=44)	Filgotinib 200 mg (n=130)
Age (years)		
Mean (SD)	35.1 (11.8)	37.4 (11.6)
Median (IQR)	33.0 (27.0–41.0)	36.0 (29.0–44.0)
Sex		
Male	18 (41%)	59 (45%)
Female	26 (59%)	71 (55%)
BMI (kg/m ²)		
Mean (SD)	23.9 (4.5)	23.8 (4.3)
Median (IQR)	23.1 (20.7–26.0)	23.4 (21.1–25.7)
BMI ≥30 kg/m ²	5 (11%)	13 (10%)
Current smoker	12 (27%)	39 (30%)
Duration of Crohn's Disease (years)		
Mean (SD)	6.8 (5.7)	8.8 (8.5)
Median (IQR)	5.4 (3.0–10.2)	6.2 (3.1–11.8)
Location		
Ileal	7 (16%)	24 (18%)
Colonic	6 (14%)	29 (22%)
Ileocolonic	31 (70%)	77 (59%)
History of surgical bowel resection		
Yes (>6 months before screening)	13 (30%)	34 (26%)
No	31 (70%)	96 (74%)
Previous anti-TNF exposure*	28 (64%)	73 (56%)
C-reactive protein (mg/L)		
Mean (SD)	19.8 (26.7)	14.2 (17.8)
Median (IQR)	8.1 (3.6–24.7)	8.2 (3.1–16.9)
C-reactive protein >10 mg/L	18 (41%)	54 (42%)
Faecal calprotectin (mg/kg)		
Median (IQR)	264.0 (134.5–900.5)	270.5 (172.0–540.0)
Faecal calprotectin >250 mg/kg	22 (50%)	78 (60%)
CDAI		
Mean (SD)	298.6 (56.8)	291.3 (53.8)
Median (IQR)	291.0 (255.5–348.0)	284.0 (251.0–322.0)
CDAI ≥300	21 (48%)	52 (40%)
SES-CD		
Mean (SD)	15.8 (7.2)	14.2 (6.8)
Median (IQR)	14.5 (10.0–21.5)	12.0 (10.0–19.0)
Oral corticosteroids (mg/day)		
Mean (SD) daily dose	21.3 (8.6)	20.7 (8.6)
Median (IQR) daily dose	20.0 (15.0–30.0)†	20.0 (15.0–30.0)‡
BMI=body-mass index. CDAI=Crohn's Disease Activity Index. SES-CD=Simplified Endoscopy Score for Crohn's Disease. *The anti-TNF-naïve group included four patients who were anti-TNF responders but who discontinued treatment for financial reasons. †n=22. ‡n=63.		
Table 1: Baseline patient demographics and disease characteristics of the safety population		

of Crohn's disease but discontinued at least 8 weeks before baseline). The anti-TNF-experienced group included patients deemed by their treating physician to

be primary or secondary non-responders, or anti-TNF intolerant.

Concurrent treatment with oral steroids (≤30 mg prednisolone equivalent per day or budesonide ≤9 mg per day) or probiotics was allowed if dosages had been stable for at least 2 weeks before the first dose of study drug. Concurrent treatment with Crohn's disease-related antibiotics, or with mesalazine or olsalazine, was permitted if dosages had been stable for at least 4 weeks before the first dose of study drug. Previous exposure to sulfasalazine was allowed, but must have been discontinued at least 4 weeks before screening in male patients, whereas immunomodulators (eg, thiopurines and methotrexate) must have been discontinued at least 25 days before the first dose of the study drug. The results of laboratory tests at screening were required to be within specified ranges (appendix). Patients with a diagnosis of indeterminate colitis or ulcerative colitis were not eligible, nor were those with a stoma, gastric, or ileanal pouch, (procto)colectomy, symptomatic stenosis or obstructive strictures, (suspected) abscess, a history of bowel perforation, or a known active infection. Full inclusion and exclusion criteria, and criteria for the removal of patients from therapy or assessments, are available in the appendix.

The study protocol was reviewed and approved by the relevant independent ethics committees for each centre and was devised in accordance with the Declaration of Helsinki,¹⁵ Good Clinical Practice guidelines,¹⁶ and all applicable regulatory requirements. The full trial protocol is available in the appendix. All patients provided written informed consent.

Randomisation and masking

The study consisted of two parts, each of 10 weeks' duration (appendix, p 97). In part 1, patients were randomly assigned (3:1) to receive filgotinib 200 mg once a day or placebo. A prespecified randomisation scheme prepared by an independent statistician was used to randomly allocate patients to treatment groups. Patients were stratified according to previous anti-TNF exposure, C-reactive protein concentration at screening (≤10 mg/L or >10 mg/L), and oral corticosteroid use at baseline, using an interactive web-based response system (S-Clinica, Brussels, Belgium). For each patient at each visit, the clinic contacted the interactive web-based response system to obtain a treatment number corresponding to the appropriate study drug.

After the first 10 weeks of treatment, patients were assigned based on CDAI clinical responder status as assessed by the investigator to receive either filgotinib 200 mg once a day, filgotinib 100 mg once a day, or placebo in part 2 for an additional 10 weeks. Treatment groups were stratified according to response in part 1, previous anti-TNF exposure, and oral corticosteroid use at baseline. Patients who were randomly assigned to placebo during part 1 continued with placebo in part 2 if they had shown a

clinical response (CDAI reduction of ≥ 100 points from baseline), and were switched to filgotinib 100 mg once a day if they had not shown a clinical response. Patients who received filgotinib 200 mg during part 1 and who achieved a clinical response were re-randomised (2:2:1) to receive either filgotinib 200 mg once a day, filgotinib 100 mg once a day, or placebo. Responders in part 1 underwent a forced steroid reduction after week 10. Patients who received filgotinib 200 mg once a day during part 1 and who did not achieve a clinical response were re-randomised (3:1) to receive either filgotinib 200 mg once a day or placebo.

Patients, investigators, study coordinators, the sponsor, and the entire study team were masked to treatment assignment. Filgotinib and placebo were presented as orally administered brown film-coated tablets that were identical in appearance and contained the same excipients.

Procedures

Patients were assessed during screening, at baseline, and at predefined intervals throughout the study (see protocol in appendix). Assessments included recording of serious adverse events and treatment-emergent serious adverse events; a full physical examination; monitoring of laboratory data including C-reactive protein, vital signs and ECG parameters; collection of stool samples for faecal calprotectin evaluation; and CDAI scoring. A colonoscopy was done and biopsies taken for histopathological analysis during screening and at week 10. For eligibility reads, a single central reader was assigned. Only reads which were discrepant between the endoscopic assessment of the colonoscopy site (local reader) and central reader (eligible vs not eligible) were allocated to an adjudicator, who did a separate scoring, masked to the original reads. The result of the adjudicator's read was used as the final determination of eligibility. For the efficacy reads, assessment was done by two independent central readers in a masked fashion. In the case of discrepant results, a third, independent read by an adjudicator was done and was used as the final determination of efficacy read. Patients completed diary cards to record adverse events, concomitant medications, dosing information and, for 7–8 days before each visit, number of stools, general wellbeing, and abdominal pain; the Inflammatory Bowel Disease Questionnaire (IBDQ) was completed at baseline, week 10, and week 20.

Outcomes

The primary endpoint was clinical remission, defined as CDAI less than 150 at week 10. Secondary endpoints included clinical remission at weeks other than week 10, and clinical response: change from baseline in overall CDAI score and in CDAI component subscores. Other secondary endpoints were endoscopic response (a reduction of SES-CD score by $\geq 50\%$ vs baseline); endoscopic remission (defined as SES-CD ≤ 4 and ulcerated surface subscore ≤ 1 in all five segments), mucosal healing (SES-CD=0), and deep remission (defined as CDAI < 150 ,

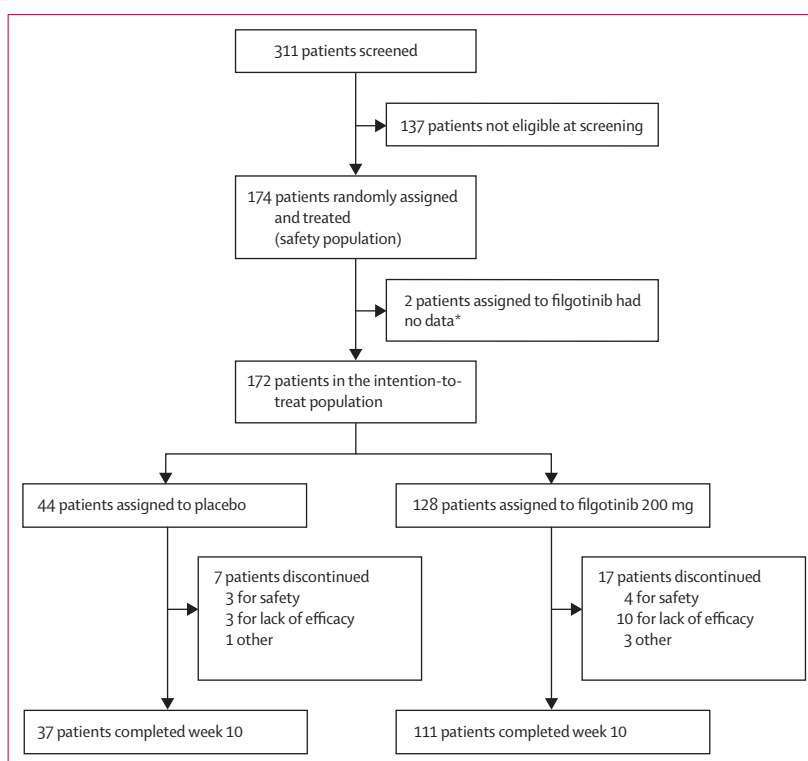


Figure 1: Trial profile for weeks 0–10 of the study

*No post-baseline data for at least one efficacy parameter.

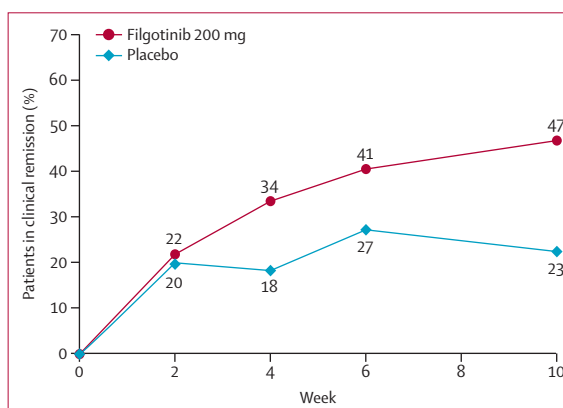


Figure 2: Clinical remission (defined as Crohn's Disease Activity Index <150) over time in response to filgotinib and placebo

SES-CD ≤ 4 and ulcerated surface subscore ≤ 1 in all five segments), as well as changes from baseline in histopathology scores and subscores (appendix) and IBDQ scores and subscores. Additional exploratory outcomes included changes in biomarkers of inflammatory activity (C-reactive protein and faecal calprotectin), and a patient-reported outcome measure (PRO2, a composite score based on daily stool frequency and self-reported abdominal pain, with remission defined as "7 × (mean daily number of liquid or very soft stools) + 7 × (mean daily self-reported abdominal pain)" ≤ 28).^{17,18}

	Overall population			Anti-TNF naive		Anti-TNF experienced	
	Placebo (n=44)	Filgotinib (n=128)	Difference (95% CI); p value	Placebo (n=16)	Filgotinib (n=57)	Placebo (n=28)	Filgotinib (n=71)
Clinical remission (CDAI <150)	10 (23%)	60 (47%)	24% (9 to 39); 0.0077	2 (13%)	34 (60%)	8 (29%)	26 (37%)
Clinical response (100-point reduction in CDAI)	18 (41%)	76 (59%)	19% (2 to 35); 0.0453	7 (44%)	38 (67%)	11 (39%)	38 (54%)
Endoscopic response based on central reading*							
50% response†	6 (14%)	32 (25%)	11% (-1 to 24); 0.16	3 (19%)	16 (28%)	3 (11%)	16 (23%)
Endoscopic remission‡	3 (7%)	18 (14%)	7% (-2 to 17); 0.31	1 (6%)	10 (18%)	2 (7%)	8 (11%)
Mucosal healing§	1 (2%)	5 (4%)	2% (-4 to 7); 0.82	0	3 (5%)	1 (4%)	2 (3%)
Deep remission¶	1 (2%)	10 (8%)	6% (-1 to 12); 0.31	0	6 (11%)	1 (4%)	4 (6%)
Mean (SE) change from baseline in total D'Haens score	-0.6 (1.9)	-3.5 (1.0)	-3.8 (-7.4 to -0.3) ; 0.0359	-0.3 (3.5)	-3.9 (1.4)	-0.7 (2.3)	-3.2 (1.4)
Mean (SE) change from baseline in activity D'Haens subscore	-0.5 (1.4)	-2.8 (0.7)	-3.0 (-5.6 to -0.4) ; 0.0252	-0.8 (2.5)	-3.1 (1.1)	-0.4 (1.7)	-2.5 (1.0)
Mean (SE) change from baseline in IBDQ score (quality of life)	17.6 (5.1)	33.8 (3.0)	16.0 (5.0 to 26.9) ; 0.0046	19.7 (5.7)	40.8 (4.3)	16.3 (7.4)	28.2 (4.0)

Data are n (%), unless otherwise stated. CDAI=Crohn's Disease Activity Index. IBDQ=Inflammatory Bowel Disease Questionnaire. SES-CD=Simplified Endoscopy Score for Crohn's Disease. *Using only segments that are evaluable both during screening and week 10 (matching segments approach). †SES-CD % improvement of 50 or more. ‡SES-CD ≤4, ulcerated surface subscore of 1 or less in all five segments. §SES-CD is zero. ¶|CDAI less than 150 points, SES-CD 4 or less, ulcerated surface subscore 1 or lower in all five segments. ||Least squares mean difference.

Table 2: Summary of the effects of filgotinib and placebo on clinical remission, clinical response, endoscopic response, and quality of life in the overall population and by previous anti-TNF exposure at week 10

Statistical analysis

The sample size was calculated based on expected clinical remission rates at week 10. The study had 80% power to detect a 22–24% treatment difference of filgotinib over the expected placebo response rate of 20–30% when 135 patients were randomly assigned to filgotinib and 45 patients were randomly assigned to placebo and assuming a 5% two-sided type I error. The study was not powered to detect differences between subgroups stratified by previous TNF exposure. Part 2 of the study was exploratory only and was not powered. The filgotinib and placebo treatment groups were compared using analysis of covariance (ANCOVA) models and logistic regression models containing baseline values and randomisation stratification factors as fixed effects. In part 1, the intention-to-treat population included all patients who received at least one dose of filgotinib or placebo, and who had at least one post-baseline assessment of CDAI in the study period. In part 2, the intention-to-treat population included all patients who received at least one dose of filgotinib or placebo, and who had at least one post-week 10 assessment of CDAI in the second part of the study period. Analyses were done on the intention-to-treat non-responder imputation set; intention-to-treat last observation carried forward (LOCF), intention-to-treat observed case, and per-protocol LOCF sensitivity analyses were also done. The safety population included all patients who received at least one dose of filgotinib or placebo. Pharmacodynamic data (C-reactive protein and faecal calprotectin) were summarised using descriptive statistics, and treatment groups were compared in the same manner as for the efficacy endpoints. Statistical analysis was done using SAS version 9.4. The trial was registered at ClinicalTrials.gov, number NCT02048618.

Role of the funding source

Employees of the sponsor were involved in the conception and design of the study and in the collection, analysis, and interpretation of the data. All authors, including authors employed by the sponsor, had full access to the data from the study and participated in developing the manuscript. The decision to submit for publication was that of the authors alone, and all authors were involved in this decision.

Results

311 patients were screened between Feb 3, 2014, and July 10, 2015. Of these, 174 were enrolled and randomly assigned to receive filgotinib 200 mg once a day (n=130) or placebo (n=44) in the first part of the study. Most patients in both groups completed this part (filgotinib, n=111 [85%]; placebo, n=37 [84%]). Baseline patient demographics and disease characteristics were similar between the two groups (table 1). The intention-to-treat population comprised 128 patients who received filgotinib, and 44 who received placebo (figure 1).

In the intention-to-treat non-responder imputation analysis set, 60 (47%) of 128 patients in the filgotinib group achieved clinical remission (CDAI <150) at week 10 compared with ten (23%) of 44 patients in the placebo group (difference 24 percentage points [95% CI 9–39], p=0.0077). The proportion of patients achieving clinical remission with filgotinib versus placebo increased steadily over the 10-week treatment period (figure 2). Among anti-TNF-naïve patients, 34 (60%) of 57 patients in the filgotinib group achieved clinical remission versus two (13%) of 16 patients in the placebo group. Among anti-TNF-experienced patients, 26 (37%) of 71 patients achieved clinical remission with filgotinib versus eight (29%) of 28 patients in the placebo group (table 2). Results from the intention-to-treat LOCF,

intention-to-treat observed case, and per-protocol LOCF sensitivity analyses support those from the primary non-responder imputation analysis (data not shown).

A significantly greater proportion of patients in the filgotinib group achieved a CDAI-100 response compared with the placebo group at week 10 (filgotinib, 76 [59%] of 128; placebo, 18 [41%] of 44; difference 19 percentage points [95% CI 2–35], $p=0.0453$). Among those who were anti-TNF naive, 38 (67%) of 57 patients in the filgotinib group achieved a CDAI-100 response versus seven (44%) of 16 patients in the placebo group. In those with previous anti-TNF treatment, a CDAI-100 response was recorded in 38 (54%) of 71 patients in the filgotinib group and 11 (39%) of 28 patients in the placebo group (table 2).

There was a larger mean change from baseline in total IBDQ score in the filgotinib group compared with the placebo group (filgotinib, +33.8 [SE 3.0] [baseline=123.0 {2.8}]; placebo, +17.6 [5.1] [baseline=120.8 {3.6}]; least squares mean difference 16.0 [95% CI 5.0–26.9], $p=0.0046$; table 2). Greater improvements were recorded in all IBDQ subscales in the filgotinib group compared with the placebo group: bowel symptoms: least squares mean difference 4.9 (95% CI 1.6–8.2), $p=0.0040$; systemic symptoms: 2.9 (0.9–4.8), $p=0.0044$; emotional status: 5.6 (1.4–9.8), $p=0.0094$; social functioning: 2.8 (0.4–5.1), $p=0.0202$ (figure 3).

Based on central reading, a greater proportion of patients treated with filgotinib achieved an SES-CD 50% endoscopic response, endoscopic remission, and deep remission at week 10. The differences versus the placebo group did not reach statistical significance ($p>0.05$; table 2). The percentage of patients with mucosal healing was low and similar in both groups (table 2). The results based on local reads were consistent with those from the central reads. Similar patterns were seen in endoscopic responses stratified by previous anti-TNF exposure (table 2). Histopathological analyses revealed a significantly larger reduction in the total D'Haens score (table 2), as well as the activity D'Haens subscore,^{19–21} in the filgotinib group versus the placebo group (table 2).

At week 10, a greater proportion of patients treated with filgotinib achieved PRO2 remission (filgotinib, 64 [50%] of 128 patients; placebo, 13 [30%] of 44 patients; difference 21 percentage points [95% CI 4–37], $p=0.0277$). For patients with elevated baseline C-reactive protein (≥ 8 mg/L), C-reactive protein was normalised in more patients receiving filgotinib than those receiving placebo (18 [27%] of 66 vs three [14%] of 22). Among patients with abnormally high baseline pharmacodynamic parameters (C-reactive protein >8 mg/L or faecal calprotectin >250 mg/kg, or both), a pharmacodynamic response including normalisation of these values (defined as CDAI <150 and C-reactive protein decrease $>50\%$ or faecal calprotectin decrease $>50\%$ from baseline) occurred in 25 (27%) of 93 patients in the filgotinib group, but only one (4%) of 27 in the placebo group (difference

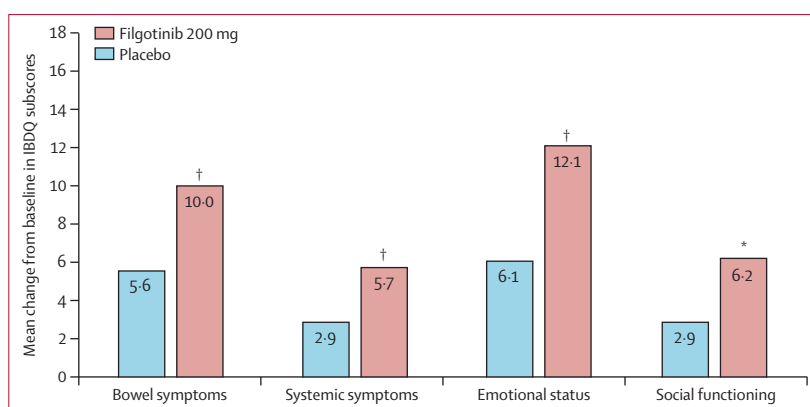


Figure 3: Improvements in quality of life with filgotinib and placebo at week 10, as revealed by change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) subscores

Placebo versus filgotinib 200 mg (mean, SE): bowel symptoms, 5.6 (1.5) vs 10.0 (0.9); systemic symptoms, 2.9 (0.9) vs 5.7 (2.1); emotional status, 6.1 (1.1) vs 12.1 (1.1); social functioning, 2.9 (1.1) vs 6.2 (0.7). * $p<0.05$. † $p<0.01$.

23 percentage points [95% CI 12–35]; $p=0.0289$). Additional C-reactive protein and faecal calprotectin data are presented in the appendix.

The safety analysis was done on data from parts 1 and 2 of the study combined (weeks 0–20; table 3, appendix). The pooled placebo group comprised all periods of placebo exposure across both parts of the study, whereas the pooled filgotinib group comprised all periods of filgotinib exposure (at either 100 mg once a day or 200 mg once a day). In the pooled analysis, the proportion of patients experiencing at least one treatment-emergent adverse event was similar with filgotinib (114 [75%] of 152 patients) and placebo (45 [67%] of 67 patients). Serious treatment-emergent adverse events were experienced by 14 (9%) of 152 patients in the filgotinib group and three (4%) of 67 patients in the placebo group. 27 (18%) of 152 patients in the filgotinib group and six (9%) of 67 patients in the placebo group had treatment-emergent adverse events leading to discontinuation. Serious infections were reported in four (3%) of 152 patients in the pooled filgotinib group, and in none of the pooled placebo group. The results of the safety analysis stratified by system organ class are shown in the appendix.

Mean haemoglobin concentrations showed small fluctuations over time within normal reference ranges in all treatment groups, and there were no clinically significant changes in haematocrit, neutrophils, lymphocytes, platelets, or liver function tests (appendix). Exposure to filgotinib 200 mg once a day for up to 20 weeks resulted in an 11% increase in mean HDL (mean change from baseline at week 20, 0.10 mmol/L [SE 0.06]) and a 12% increase in mean LDL at week 20 (mean change from baseline, 0.22 mmol/L [0.08]). By contrast, a 4% increase in mean HDL (mean change from baseline at week 20, 0.05 mmol/L [SE 0.05]) was seen in those with equivalent placebo exposure, along with a 13% increase in mean LDL (mean change from baseline, 0.30 mmol/L [0.10]). These changes correspond

	Placebo up to 20 weeks (n=22)	Placebo to filgotinib 100 mg (n=22)		Filgotinib 200 mg to placebo (n=23)		Filgotinib 200 mg to 100 mg up to 20 weeks (n=30)	Filgotinib 200 mg up to 20 weeks (n=77)
		Placebo (weeks 0–10; n=22)	Filgotinib 100 mg (weeks 10–20; n=22)	Filgotinib 200 mg (weeks 0–10; n=23)	Placebo (weeks 10–20; n=23)		
Treatment-emergent adverse event	18 (82%)	13 (59%)	11 (50%)	17 (74%)	14 (61%)	24 (80%)	62 (81%)
Serious treatment-emergent adverse event	3 (14%)	0	1 (5%)	0	0	1 (3%)	12 (16%)
Serious treatment-emergent infections	0	0	0	0	0	0	4 (5%)
Severe treatment-emergent adverse event	5 (23%)	0	1 (5%)	2 (9%)	1 (4%)	1 (3%)	14 (18%)
Treatment-emergent adverse event leading to temporary stop	0	0	0	0	0	3 (10%)	1 (1%)
Treatment-emergent adverse event leading to permanent stop*	6 (27%)	0	1 (5%)	0	0	4 (13%)	22 (29%)
Adverse events of special interest							
All infections	6 (27%)	5 (23%)	6 (27%)	7 (30%)	6 (26%)	9 (30%)	26 (34%)
All serious infections	0	0	0	0	0	0	4 (5%)
Urinary tract infections	2 (9%)	1 (5%)	1 (5%)	1 (4%)	2 (9%)	1 (3%)	3 (4%)
Nasopharyngitis	2 (9%)	1 (5%)	2 (9%)	1 (4%)	3 (13%)	2 (7%)	1 (1%)
Pneumonia	0	0	0	0	0	0	1 (1%)
Herpes zoster	0	0	0	0	0	1 (3%)	0
Oral candidiasis	0	0	0	0	0	1 (3%)	3 (4%)

Patients who discontinued during the first part of the study are included in the placebo and filgotinib 200 mg groups. *Two patients experiencing an adverse event that started before first study drug intake, but that stopped during treatment, are not included.

Table 3: Safety endpoints and treatment-emergent adverse events of special interest, by treatment assignment over weeks 0–10 (study part 1) and weeks 10–20 (study part 2)

to a 3% increase in the LDL to HDL ratio in patients treated with filgotinib at week 20 versus a 10% increase in the placebo group.

Part 2 of the study explored the maintenance of response beyond week 10 at different doses (see appendix for patient disposition during part 1 and part 2 of the study). Part 2 was observational in design and was not powered. At week 20, between 50% (15 of 30 patients) and 71% (10 of 14 patients) of initial filgotinib 200 mg responders showed clinical remission depending on whether they had been randomly assigned to filgotinib 200 mg, filgotinib 100 mg, or placebo in part 2, and between 67% (20 of 30 patients) and 79% (11 of 14 patients) showed a CDAI-100 response, again depending on dose level in part 2 (appendix). Among patients who did not respond to placebo in part 1, 13 (59%) of 22 patients showed a CDAI-100 response at week 20 after being switched to filgotinib 100 mg, and seven (32%) of 22 showed clinical remission.

Discussion

The phase 2 FITZROY study provides the first evidence for the efficacy and safety of a JAK1-selective inhibitor in patients with active Crohn's disease confirmed by centrally read endoscopy at enrolment. The primary endpoint of clinical remission at week 10 was achieved by significantly more patients with filgotinib 200 mg once a day than with

placebo. Filgotinib was superior to placebo in CDAI-100 response and in mean change from baseline in quality of life, as revealed by the IBDQ score and subscores. A greater proportion of filgotinib-treated patients achieved an SES-CD 50% response, endoscopic remission, and deep remission. Differences versus placebo did not reach statistical significance after 10 weeks; however, the study was powered to detect differences in clinical rather than endoscopic response. Also, the transmural character of the disease, in contrast to ulcerative colitis, means that longer treatment is required to show meaningful endoscopic improvement and the optimal definition for SES-CD endoscopic response is still under debate. Beneficial effects were additionally seen on D'Haens histopathology scores and biomarkers of inflammatory activity. With the limited number of patients and short follow-up (10 weeks of treatment only), significant differences in D'Haens score were not expected, especially in the case of the chronicity subscore. However, it is the consistency of the data (clinical, endoscopic, C-reactive protein, and histology), which all point in the same direction, that gives an overall robust signal of efficacy. Filgotinib was well tolerated and displayed an acceptable safety profile.

The international STRIDE initiative³ recently concluded that the principal goal of therapy in Crohn's disease should be to restore quality of life through a combination of clinical and endoscopic remission. Anti-TNF agents

have improved the management of Crohn's disease;²² however, not all patients respond to these drugs, and secondary loss of response is reported in up to 50% of patients per year in placebo-controlled trials.²³ The JAK1 inhibitor filgotinib might have the potential to become an addition to the Crohn's disease treatment arsenal given its efficacy in both anti-TNF-naïve and anti-TNF-experienced patients. Small molecule inhibitors offer the additional advantages over monoclonal antibodies of a lack of immunogenicity, lower interpatient pharmacokinetic variability, and suitability for oral administration.²⁴

By contrast with rheumatoid arthritis where most anti-TNF agents appear to have some efficacy, the efficacy of different anti-TNF agents can vary markedly between patients with Crohn's disease.²² This finding suggests that additional mechanisms besides the neutralisation of soluble TNF might contribute to the disease process in Crohn's disease. Blockade of cytokine signalling via inhibition of the JAK-STAT pathway has shown promise as a therapeutic strategy. In an initial phase 2 trial, the JAK1-JAK3 inhibitor tofacitinib reduced C-reactive protein and faecal calprotectin from baseline, suggesting that the drug has biological activity, but CDAI-100 response and clinical remission did not differ significantly from placebo.⁹ A high placebo response rate suggested, however, that the study population might have included patients whose symptoms were not due to active Crohn's disease.²⁴ Enrolment was based primarily on CDAI scores, which might correlate only weakly with endoscopic disease.²⁵ In a subsequent phase 2b study in which colonoscopy was used to confirm intestinal ulceration at enrolment, a significantly greater proportion of patients achieved a CDAI-100 response with tofacitinib compared with placebo, but rates of clinical remission did not differ.¹⁰ The same study reported a significantly larger reduction in C-reactive protein with tofacitinib versus placebo, but no difference in faecal calprotectin.

FITZROY is the first double-blind, placebo-controlled study in Crohn's disease to use centrally read endoscopies as enrolment criteria rather than relying on clinical signs and symptoms or endoscopy readings by local physicians only. Central readings reduce interobserver variability and help to ensure standardised, unbiased scoring, as well as the selective enrolment of patients with active disease.²⁶ For example, in a study in ulcerative colitis, the retrospective use of central reading revealed that many patients who had been enrolled on the basis of local readings did not meet the study inclusion criteria for disease severity; excluding these patients increased the difference in outcomes between the placebo and active treatment groups.²⁷ The high rate of screening failure in FITZROY (44%), which was mainly driven by failure to meet the SES-CD-based severity criterion, is testament to the importance of centrally read endoscopies before enrolment to ensure a population with active Crohn's disease. However, this approach poses its own challenges, including technical difficulties

related to the acquisition of data in a standardised format, ensuring that the same anatomical segments are scored in all patients, and dealing with missing segments. Further work is also required to improve patients' acceptance of colonoscopy, as well as the procedures involved in preparation of the bowel.

The relatively young age of onset of Crohn's disease and the often unpredictable nature of the disease course mean that Crohn's disease results in a substantial reduction in quality of life.^{28,29} Relapses often necessitate absence from work,³⁰ adding to the financial burden of the disease. However, early restoration of health-related quality of life is associated with sustained remission.³¹ Patients treated with filgotinib showed a significant improvement in mean IBDQ scores at week 10, and this improvement in quality of life was observed for all four components of the IBDQ, related to bowel functioning, systemic symptoms, and emotional and social functioning. However, these results should be interpreted with caution given the short (10 week) duration over which the data were analysed.

The reported rate of serious infections was higher with filgotinib compared with placebo. There is evidence that use of tofacitinib (a JAK1, JAK2, and JAK3 inhibitor) might be associated with a dose-dependent increase in the risk of serious and opportunistic infections in rheumatoid arthritis.³² An analysis of pooled data from phase 2, phase 3, and long-term extension studies in rheumatoid arthritis concluded that the rate of serious infections with tofacitinib usage was 3.1 events per 100 patient-years.³³ The OCTAVE³⁴ series of trials of tofacitinib in ulcerative colitis showed serious infections in up to 5% of patients. These data suggest that increased risk of serious infections, including herpes zoster, might be a class effect of JAK inhibitors, as also seen in other disease populations.^{35,36} Further exposure to filgotinib will be required to better characterise the incidence of infections in Crohn's disease.

One limitation of the FITZROY study is that part 2, which examined initial maintenance of response beyond week 10, was not powered for statistical analysis and continued only for a period of 10 additional weeks. Also, the 10-week duration of part 1 limited the interpretation of endoscopic changes and mucosal healing, which are typically delayed relative to clinical remission.²²

In conclusion, the results of the 20-week FITZROY study provide the first evidence for the potential clinical efficacy and safety of the JAK1 inhibitor filgotinib for the treatment of active Crohn's disease. A significantly greater proportion of patients achieved clinical remission (defined as CDAI <150) with filgotinib 200 mg once a day than with placebo. Almost half of those treated with filgotinib achieved clinical remission after 10 weeks. Filgotinib was superior to placebo in CDAI-100 response and in mean change from baseline in quality of life, as revealed by the IBDQ score and subscores. Beneficial effects were additionally seen on D'Haens histopathology scores, SES-CD endoscopic responses, and biomarkers

of inflammatory activity. Filgotinib could represent a new oral treatment for Crohn's disease, pending the results of ongoing phase 3 trials.

Contributors

SV, SS, CT, AvdA, and PH were involved in the conception and design of the study. All authors contributed to the acquisition or analysis of data. SV, SS, RP, TK, XH, XR, MK, AG, MW-J, AB, RS, CT, AvdA, and PH were involved in the interpretation of data. All authors read and approved the final manuscript.

Declaration of interests

SV has received research funding from Abbvie, Galapagos, MSD, and Takeda; speaker fees from Abbvie, Falk Pharma, Ferring, Hospira, MSD, Takeda, and Tillotts; and consultancy fees from Abbvie, Celgene, Ferring, Galapagos, Genentech/Roche, Hospira, Janssen, MSD, Mundipharma, Pfizer, Second Genome, Shire, and Takeda. SS has received research funding from Galapagos; consultancy fees from Abbvie, Galapagos, and Pfizer; and speaker fees from Abbvie. RP has received research funding from Galapagos. TK has received research funding from Galapagos; speaker fees from Abbvie, Almirall, Arena, Falk Pharma, Ferring, MSD, Mundipharma, and Takeda; consultancy fees from Arena, MSD, Mundipharma, Stelic, and Takeda. XH has received research funding from Galapagos; consultancy fees from Abbvie, Fresenius Kabi, Galapagos, MSD, Nutricia, Takeda, and Vifor, and has served on an advisory board for Janssen. XR has received research funding from Galapagos; speaker fees from Abbvie, Janssen, MSD, and Takeda; consultancy fees from Abbvie, Janssen, MSD, and Takeda; and support to attend congresses from Abbvie, Janssen, MSD, and Takeda. MK has received research funding from Galapagos; speaker fees from Abbvie, Alvogen, Ferring, and Takeda; and support to attend congresses from Abbvie, Alvogen, and Ferring. AG has received research funding from Galapagos. MW-J has received research funding from Galapagos. AB has received research funding from Galapagos. RS has received research funding from Galapagos. KS has received fees for medical monitoring and data cleaning from Galapagos. CT, AvdA, and PH are employees of Galapagos and receive warrants (ie, rights to subscribe to new shares at a predetermined price) from the company.

Acknowledgments

We wish to thank the study investigators and patients who contributed to this study. We also thank Chohee Yun and Bittoo Kanwar from Gilead Sciences Inc for feedback on the manuscript. Editorial support in the form of developing manuscript drafts in consultation with the authors, assembling tables and figures, collating author comments, copyediting, fact checking, referencing, and graphical services was provided by Louisa Lyon (Aspire Scientific Ltd, Bollington, UK); this support was co-funded by Galapagos and Gilead Sciences Inc.

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