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Rapid and Sustained Symptom Relief in Patients With Ulcerative Colitis Treated With Filgotinib: Data From the Phase 2b/3 SELECTION Trial

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INTRODUCTION: **Patients with ulcerative colitis (UC) regard rapid onset of action among the most important aspects of their treatment. We used the partial Mayo Clinic Score (pMCS) and component patient-reported subscores to assess the rapidity and sustainability of response to filgotinib, a once-daily, oral Janus kinase 1 preferential inhibitor, in adults with moderately to severely active UC in the phase 2b/3 SELECTION trial. The association between early symptomatic improvements and health-related quality of life (HRQoL) outcomes was also assessed.**

METHODS: **In these *post hoc* analyses of the double-blinded, randomized, placebo-controlled 58-week SELECTION trial (NCT02914522), rectal bleeding and stool frequency diary data on days 1–15 and pMCS remission and response at multiple time points including weeks 10 and 58 were evaluated. HRQoL was assessed using the Inflammatory Bowel Disease Questionnaire at weeks 10 and 58.**

RESULTS: **Filgotinib 200 mg relative to placebo improved rectal bleeding and stool frequency within 7 days ($P < 0.05$). By week 2, greater proportions of filgotinib 200 mg-treated patients than placebo-treated patients achieved pMCS remission (biologic-naive, 15.1% vs 8.0%, $P = 0.0410$; biologic-experienced, 10.3% vs 4.2%, $P = 0.0274$). A similar treatment effect was observed at week 58 ($P < 0.0001$). Day 7 rectal bleeding and stool frequency subscores were associated with the Mayo Clinic Score response at weeks 10 and 58. Patients in pMCS remission at weeks 10 and 58 had greater improvements in the Inflammatory Bowel Disease Questionnaire score than those not in pMCS remission.**

DISCUSSION: **Filgotinib 200 mg daily resulted in rapid and sustained improvements in both UC symptoms and HRQoL.**

SUPPLEMENTARY MATERIAL accompanies this paper at https://links.lww.com/AJG/C661

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INTRODUCTION

Ulcerative colitis (UC) is a chronic and debilitating disease of the colon, characterized by mucosal inflammation and ulceration and symptoms of rectal bleeding and diarrhea (1). Short-term treatment goals for patients with UC include achieving clinical remission and reducing inflammation (2). Longer term goals include improving health-related quality of life (HRQoL), achieving corticosteroid-free remission and endoscopic healing, and preventing surgery and colorectal cancer (Plain Language Summary, Supplementary Digital Content 1, https://links.lww.com/AJG/C661) (1,2).

Rapid onset of action is regarded as one of the most important aspects of UC treatment (3,4) and has been demonstrated to occur with some therapies (5). Frequent assessment of UC

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outcomes can be used to evaluate response after treatment initiation and to monitor longer term response. Although endoscopy provides an objective assessment of disease activity and is critical for disease diagnosis, it is an invasive procedure. By contrast, patient-reported outcomes (PROs), including rectal bleeding and stool frequency evaluated using patient diary data, can be assessed frequently and between endoscopy visits (6). Importantly, normalization of rectal bleeding and stool frequency has been associated with endoscopic improvement (6–8). Early symptomatic predictors of later clinical response might, therefore, be valuable for clinicians in choosing an appropriate treatment or stopping an ineffective treatment earlier.

Filgotinib is a once-daily, oral Janus kinase 1 preferential inhibitor (9) being developed for the treatment of several inflammatory diseases. In the phase 2b/3 SELECTION trial, treatment with filgotinib 200 mg once daily was well tolerated and effective in inducing and maintaining clinical remission in patients with moderately to severely active UC (10). Filgotinib was recently approved in the European Union and the United Kingdom for the treatment of adults with moderately to severely active UC (11,12).

In these *post hoc* analyses, we assessed the rapidity and sustainability of response to filgotinib in the SELECTION trial by examining patient-reported UC symptoms and using the partial Mayo Clinic Score (pMCS). In addition, we evaluated the association between symptomatic improvements and HRQoL and clinical outcomes.

METHODS

Study design

SELECTION was a phase 2b/3 double-blinded, randomized, placebo-controlled trial comprising 2 induction studies and a Maintenance Study (NCT02914522). Supplementary Figure 1 (Supplementary Digital Content 1, https://links.lww.com/AJG/C661) shows the study design, details of which have been described by Feagan et al. (10). Eligible patients with moderately to severely active UC were enrolled into either Induction Study A (biologic-naive) or Induction Study B (biologic-experienced). Eligibility criteria for enrollment into each induction study are given in Supplementary Material 1 (Supplementary Digital Content 1, https://links.lww.com/AJG/C661) and have been described by Feagan et al. (10). Patients were randomized 2:2:1 to receive oral filgotinib 200 mg, filgotinib 100 mg, or placebo once daily for 11 weeks. Those who achieved either clinical remission or Mayo Clinic Score (MCS) response at week 10 (responders) were rerandomized 2:1 at week 11 to their induction filgotinib regimen or placebo in the Maintenance Study through week 58. Placebo responders continued placebo. Week 10 nonresponders were excluded from the Maintenance Study but could enter an ongoing long-term extension study, SELECTIONLTE (NCT02914535). Each study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent.

In these *post hoc* analyses of the SELECTION trial, rapidity of response to filgotinib was assessed by evaluating rectal bleeding and stool frequency subscores (the PRO components of MCS) on days 1–15. Remission and response were also assessed over time in the induction and maintenance studies using pMCS (combination of Mayo rectal bleeding, stool frequency, and physician's global assessment subscores). In addition, the association between UC symptoms and Inflammatory Bowel Disease Questionnaire (IBDQ) total score, and the predictive value of early response on achievement of MCS response, endoscopic improvements, clinical remission, and IBDQ remission at weeks 10 and 58 were evaluated.

Outcome measures and assessments

Definitions used for efficacy outcomes are provided in Supplementary Table 1 (Supplementary Digital Content 1, https://links.lww.com/AJG/C661) and have been described by Feagan et al. (10). The proportions of patients in pMCS remission (pMCS ≤ 2 and no individual rectal bleeding, stool frequency, or physician's global assessment subscore >1) and in pMCS response (a reduction in pMCS of ≥ 2 and $\geq 30\%$ from induction baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 or an absolute rectal bleeding subscore of 0 or 1) were assessed at baseline and at weeks 2, 4, 6, 10, 11, 14, 20, 26, 34, 42, 50, and 58. Patients recorded rectal bleeding and stool frequency symptoms daily in an electronic diary (with a 24-hour recall period). The proportions of patients with a rectal bleeding subscore of 0, stool frequency subscore ≤ 1, and a combined rectal bleeding subscore of 0 and stool frequency subscore ≤ 1 were evaluated on days 1–15 and at weeks 10 and 58. The proportions of patients achieving rectal bleeding and stool frequency subscore cutoffs at week 10 by the use of corticosteroids at induction baseline (yes/no) were also determined. The IBDQ total score was used to assess disease-specific HRQoL at induction baseline, week 10, maintenance baseline, and week 58. IBDQ comprises 32 items within 4 domains (bowel symptoms, systemic symptoms, emotional function, and social function) (13). The total score for the sum of the 32 items ranges from 0 to 224, with higher scores indicating better HRQoL (13). The minimal clinically important difference (MCID) was defined as a 16-point increase from induction baseline in the IBDQ total score (14). IBDQ remission was defined as IBDQ total score ≥ 170 (15).

Statistical analyses

These *post hoc* analyses were conducted using the SELECTION induction and maintenance full analysis sets (10). All missing data were handled using a nonresponder imputation approach, except change from induction and maintenance baseline in IBDQ total score data, which were as observed. Because these were *post hoc* analyses, all *P* values were nominal. Full details of statistical analyses are given in Supplementary Material 2 (Supplementary Digital Content 1, https://links.lww.com/AJG/C661).

RESULTS

Patient disposition and baseline characteristics

Overall, 659 biologic-naive and 689 biologic-experienced patients in Induction Studies A and B, respectively, and 320 biologic-naive and 238 biologic-experienced patients in the Maintenance Study were included in these analyses. Patient baseline demographic and disease characteristics were similar across treatment groups in each induction study (10).

Changes in rectal bleeding and stool frequency subscores between days 1 and 15

The proportions of patients who achieved predefined rectal bleeding and stool frequency subscores were evaluated daily between days 1 and 15. A treatment effect of filgotinib 200 mg vs placebo on the achievement of a rectal bleeding subscore of

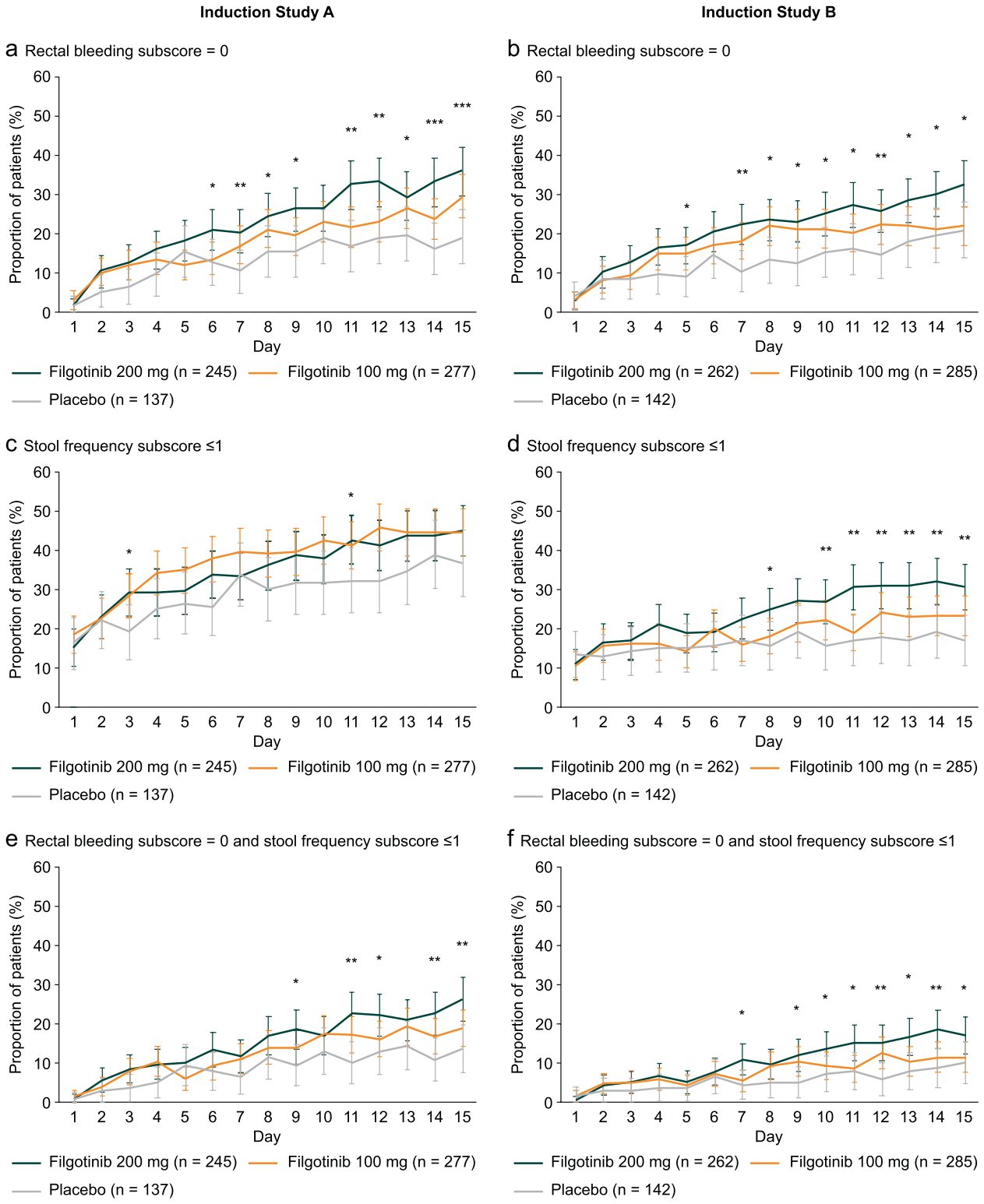

Figure 1. Proportions of patients in Induction Studies A (biologic-naive) and B (biologic-experienced) who achieved (**a**, **b**) a rectal bleeding subscore of 0, (**c**, **d**) a stool frequency subscore ≤1, and (**e**, **f**) a combined rectal bleeding subscore of 0 and stool frequency subscore ≤1 during days 1–15 of treatment. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$ filgotinib 200 mg vs placebo.

0 was observed by day 6 in biologic-naive patients (20.8% vs 12.4%, $P = 0.0373$) and day 5 in biologic-experienced patients (17.2% vs 9.2%, $P = 0.0209$) (Figure 1a, b). A similar treatment effect on the achievement of a stool frequency subscore of ≤1 was detected by day 3 in biologic-naive patients (29.0% vs 19.0%, $P = 0.0311$) and day 8 in biologic-experienced patients (24.8% vs

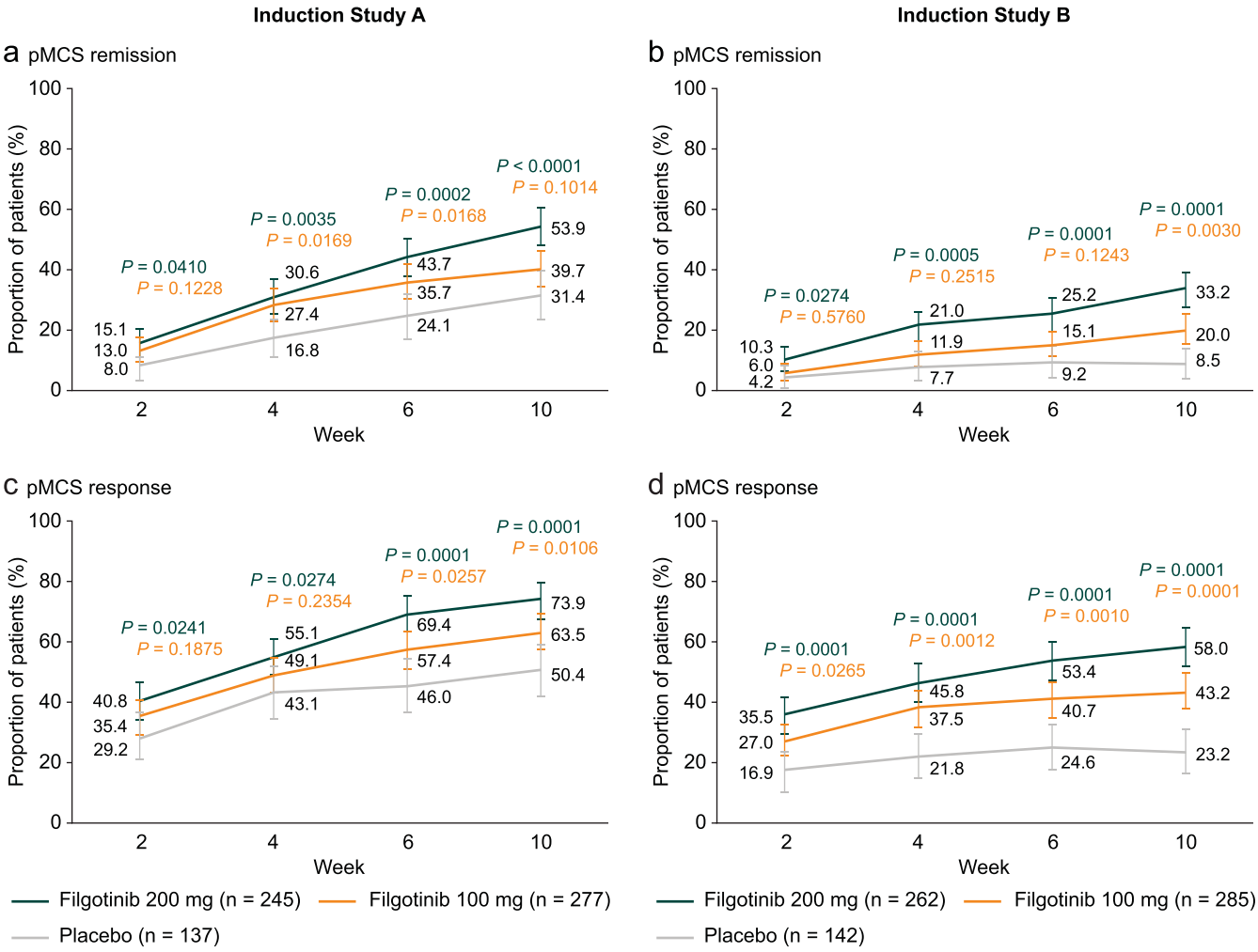

Figure 2. Proportions of patients in Induction Studies A (biologic-naive) and B (biologic-experienced) who achieved (**a**, **b**) pMCS remission and (**c**, **d**) pMCS response over time. Error bars represent 95% confidence intervals. Baseline values for pMCS response are not available because pMCS response was calculated based on changes in pMCS from baseline. pMCS remission was defined as pMCS ≤2 and no individual rectal bleeding, stool frequency, or physician's global assessment subscore >1. pMCS response was defined as a reduction in pMCS of ≥2 and ≥30% from induction baseline with a decrease in rectal bleeding score of ≥1 or an absolute rectal bleeding subscore of 0 or 1. pMCS, partial Mayo Clinic Score.

15.5%, $P = 0.0173$) (Figure 1c, d). A treatment effect of filgotinib 200 mg vs placebo on the achievement of a combined rectal bleeding subscore of 0 and stool frequency subscore ≤1 was observed by day 9 in biologic-naive patients (18.8% vs 9.5%, $P = 0.0144$) and day 7 in biologic-experienced patients (10.7% vs 4.2%, $P = 0.0155$) (Figure 1e, f). Among biologic-experienced patients, the treatment effect of filgotinib 200 mg vs placebo on the achievement of predefined rectal bleeding and stool frequency subscores was similar in those who had experienced failure of 1 or 2 treatment mechanisms of action (a tumor necrosis factor antagonist and the α4β7 integrin antagonist, vedolizumab) (Supplementary Figure 2, Supplementary Digital Content 1, https://links.lww.com/AJG/C661).

pMCS remission and response over time during induction

A difference in the pMCS remission rate between the filgotinib 200 mg and placebo groups was achieved as early as week 2 in both patient populations (biologic-naive, 15.1% vs 8.0%, $P = 0.0410$; biologic-experienced, 10.3% vs 4.2%, $P = 0.0274$; Figure 2a, b). In addition, over half of biologic-naive patients (53.9%) treated with filgotinib 200 mg were in pMCS remission at week 10 vs 31.4% of those treated with placebo. Similarly, approximately one-third of biologic-experienced patients (33.2%) who received filgotinib 200 mg were in pMCS remission at week 10 vs 8.5% of those who received placebo. A treatment effect of filgotinib 100 mg vs placebo on pMCS remission was observed at weeks 4 and 6 in biologic-naive patients and at week 10 in biologic-experienced patients (but not at other time points).

In addition, pMCS response was achieved by a greater proportion of filgotinib 200 mg-treated patients than placebo-treated patients by week 2 in both populations (biologic-naive, 40.8% vs 29.2%, $P = 0.0241$; biologic-experienced, 35.5% vs 16.9%, $P < 0.0001$; Figure 2c, d). A treatment effect of filgotinib 100 mg vs placebo on pMCS response was observed by week 6 in biologic-naive patients and week 2 in biologic-experienced patients.

pMCS remission and response over time during maintenance

Among patients treated with maintenance filgotinib 200 mg, the proportion of patients in pMCS remission remained relatively stable. At week 11, 72.9% of patients rerandomized to filgotinib

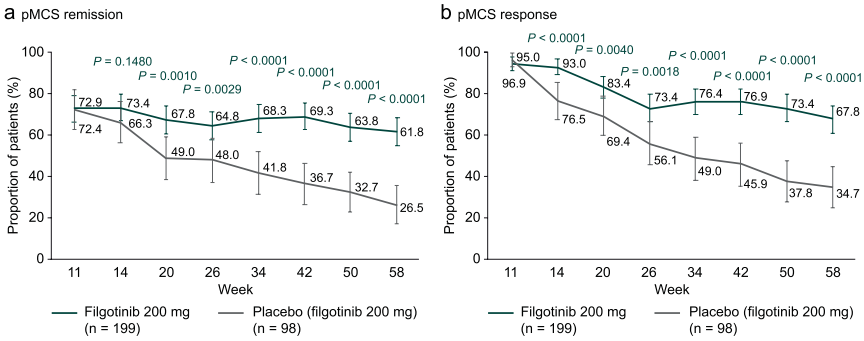

Figure 3. Proportions of patients treated with filgotinib 200 mg vs placebo in (**a**) pMCS remission and (**b**) pMCS response over time in the Maintenance Study. Error bars represent 95% confidence intervals. pMCS remission was defined as pMCS ≤2 and no individual rectal bleeding, stool frequency, or physician's global assessment subscore >1. pMCS response was defined as a reduction in pMCS of ≥2 and ≥30% from induction baseline with an accompanying decrease in rectal bleeding subscore of ≥1 or an absolute rectal bleeding subscore of 0 or 1. pMCS, partial Mayo Clinic Score.

200 mg and 72.4% of patients rerandomized to placebo were in pMCS remission. By week 58, 61.8% of patients who continued filgotinib 200 mg were in pMCS remission vs 26.5% who were rerandomized to placebo ($P < 0.0001$; Figure 3a). Similar trends in remission rates over time were observed in patients who responded to induction filgotinib 100 mg and who were maintained on filgotinib 100 mg relative to those who were rerandomized to placebo (Supplementary Figure 3a, Supplementary Digital Content 1, https://links.lww.com/AJG/C661).

At week 11, similar proportions of patients who were rerandomized to receive filgotinib 200 mg (95.0%) and placebo (96.9%) were in pMCS response; by week 58, the proportions of patients in pMCS response were 67.8% and 34.7% among those who continued filgotinib 200 mg and those rerandomized to placebo, respectively ($P < 0.0001$; Figure 3c). Trends were similar among patients treated with filgotinib 100 mg (Supplementary Figure 3b, Supplementary Digital Content 1, https://links.lww.com/AJG/C661).

Effect of corticosteroid use on rectal bleeding and stool frequency subscores at week 10

Approximately 30% of patients included in this *post hoc* analysis reported concomitant use of corticosteroids at baseline. To evaluate the potential impact of corticosteroids on filgotinib's speed of onset of action, we assessed rectal bleeding and stool frequency PROs among filgotinib-treated patients who were vs were not receiving corticosteroids at induction baseline. The 2 groups of patients had comparable rectal bleeding and stool frequency subscores at induction baseline, although patients who were receiving corticosteroids at baseline had more severe disease than those who were not receiving corticosteroids (data not shown). The proportions of patients treated with either filgotinib 200 mg or filgotinib 100 mg who achieved a rectal bleeding subscore of 0, a stool frequency subscore of ≤1, or a combined rectal bleeding subscore of 0 and stool frequency subscore ≤1 at week 10 were similar among those who were receiving corticosteroids at induction baseline and those who were not (Table 1).

Association between IBDQ and pMCS remission and rectal bleeding and stool frequency subscores

At week 10, a greater proportion of filgotinib 200 mg-treated patients than placebo-treated patients achieved MCID in the IBDQ total score (biologic-naive, 78.8% vs 60.6%, $P = 0.0002$; biologic-experienced, 68.7% vs 36.6%, $P < 0.0001$; Supplementary Figures 4a and b, Supplementary Digital Content 1, https://links.lww.com/AJG/C661). Similarly, at week 58, MCID in the IBDQ total score was achieved by a greater proportion of patients treated with filgotinib 200 mg than patients treated with placebo (68.3% vs 32.7%, $P < 0.0001$; Supplementary Figure 4c, Supplementary Digital Content 1, https://links.lww.com/AJG/C661). A treatment effect of filgotinib 100 mg vs placebo, albeit lower than for filgotinib 200 mg, was observed in all 3 studies ($P < 0.05$).

By week 10, both biologic-naive and biologic-experienced patients who achieved pMCS remission had a higher mean IBDQ total score and achieved a greater mean positive change in the IBDQ total score from baseline than patients who did not achieve pMCS remission (Supplementary Table 2a, Supplementary Digital Content 1, https://links.lww.com/AJG/C661). Patients in pMCS remission at week 58 reported improvements in the IBDQ score vs maintenance baseline, whereas a worsening IBDQ score was reported for patients not in pMCS remission (Supplementary Table 2b, Supplementary Digital Content 1, https://links.lww.com/AJG/C661). Similar trends in the IBDQ score were observed in patients who achieved a rectal

Table 1. Proportions of patients in Induction Studies A and B combined with a rectal bleeding subscore of 0, stool frequency subscore ≤1, and a combined rectal bleeding subscore of 0 and stool frequency subscore ≤1 at week 10 by corticosteroid use at induction baseline

	Not receiving corticosteroids at induction baseline			Receiving corticosteroids at induction baseline		
	Filgotinib, 200 mg (n = 277)	Filgotinib, 100 mg (n = 321)	Placebo (n = 158)	Filgotinib, 200 mg (n = 230)	Filgotinib, 100 mg (n = 241)	Placebo (n = 121)
Rectal bleeding subscore = 0, n (%)	175 (63.2)	160 (49.8)	67 (42.4)	138 (60.0)	123 (51.0)	41 (33.9)
Stool frequency subscore ≤1, n (%)	171 (61.7)	157 (48.9)	69 (43.7)	133 (57.8)	118 (49.0)	35 (28.9)
Rectal bleeding subscore = 0 and stool frequency subscore ≤1, n (%)	146 (52.7)	118 (36.8)	46 (29.1)	106 (46.1)	92 (38.2)	21 (17.4)

Table 2. Positive predictive value of day 7 rectal bleeding and stool frequency subscores on clinical and IBDQ outcomes in the induction and maintenance studies

	Rectal bleeding subscore = 0 on day 7		Stool frequency subscore ≤ 1 on day 7		Rectal bleeding subscore = 0 and stool frequency subscore ≤ 1 on day 7	
	n	PPV (%)	n	PPV (%)	n	PPV (%)
Induction Study A (N = 496)	97		190		60	
MCS response[a] at week 10						
Yes	73	75.3	128	67.4	48	80.0
No	24		62		12	
Endoscopic improvement[b] at week 10						
Yes	39	40.2	75	39.5	30	50.0
No	58		115		30	
Endoscopic remission[c] at week 10						
Yes	15	15.5	24	12.6	12	20.0
No	82		166		48	
Histological remission[d] at week 10						
Yes	38	39.2	69	36.3	27	45.0
No	59		121		33	
Clinical remission[e] at week 10						
Yes	36	37.1	57	30.0	28	46.7
No	61		133		32	
IBDQ remission[f] at week 10						
Yes	62	63.9	109	57.4	39	65.0
No	35		81		21	
Induction Study B (N = 521)	111		104		43	
MCS response[a] at week 10						
Yes	68	61.3	67	64.4	33	76.7
No	43		37		10	
Endoscopic improvement[b] at week 10						
Yes	21	18.9	25	24.0	11	25.6
No	90		79		32	
Endoscopic remission[c] at week 10						
Yes	2	1.8	5	4.8	1	2.3
No	109		99		42	
Histological remission[d] at week 10						
Yes	23	20.7	20	19.2	10	23.3
No	88		84		33	
Clinical remission[e] at week 10						
Yes	17	15.3	19	18.3	10	23.3
No	94		85		33	
IBDQ remission[f] at week 10						
Yes	55	49.5	52	50.0	26	60.5
No	56		52		17	

Table 2. (*continued*)

	Rectal bleeding subscore = 0 on day 7		Stool frequency subscore ≤ 1 on day 7		Rectal bleeding subscore = 0 and stool frequency subscore ≤ 1 on day 7	
	n	PPV (%)	n	PPV (%)	n	PPV (%)
Maintenance Study (N = 353)	93		124		56	
MCS response[a] at week 58						
Yes	59	63.4	83	66.9	41	73.2
No	34		41		15	
Endoscopic improvement[b] at week 58						
Yes	32	34.4	46	37.1	21	37.5
No	61		78		35	
Endoscopic remission[c] at week 10						
Yes	15	16.1	21	16.9	10	17.9
No	78		103		46	
Histological remission[d] at week 10						
Yes	27	29.0	45	36.3	18	32.1
No	66		79		38	
Clinical remission[e] at week 58						
Yes	30	32.3	43	34.7	21	37.5
No	63		81		35	
IBDQ remission[f] at week 58						
Yes	48	51.6	65	52.4	28	50.0
No	45		59		28	

Data are presented for patients who received filgotinib 200 mg or filgotinib 100 mg (full analysis set, patients with nonmissing rectal bleeding or stool frequency subscores at day 7). PPV, true positive/(true positive + false positive). PPVs were determined using only the filgotinib treatment arms and do not take into account the filgotinib dose. IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mayo Clinic Score; PPV, positive predictive value.

[a]A reduction of ≥3 points in MCS and ≥30% from induction baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1.

[b]Mayo endoscopic subscore of 0 or 1.

[c]Mayo endoscopic subscore of 0.

[d]Based on the Geboes scale. No or mild increase in chronic inflammatory infiltrate in lamina propria; no neutrophils in lamina propria or epithelium; and no erosion, ulceration, or granulation tissue (grade 0 of ≤0.3, grade 1 of ≤1.1, grade 2a of ≤2A.3, grade 2b of 2B.0, grade 3 of 3.0, grade 4 of 4.0, and grade 5 of 5.0).

[e]Mayo endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and a ≥1-point decrease in stool frequency from induction baseline to achieve a subscore of 0 or 1.

[f]IBDQ total score ≥170.

bleeding subscore of 0 or a stool frequency subscore of ≤1 by the end of the induction and maintenance studies and those who did not.

Concordance between IBDQ remission and each of pMCS remission status (74.6%), rectal bleeding subscore of 0 (71.9%), and stool frequency subscore ≤1 (72.8%) at week 10 was moderate (Supplementary Table 3a, Supplementary Digital Content 1, https://links.lww.com/AJG/C661). Substantial concordance between the same outcomes (83.7%, 85.3%, and 83.9%, respectively) was observed at week 58 (Supplementary Table 3b, Supplementary Digital Content 1, https://links.lww.com/AJG/C661).

Positive predictive value of rectal bleeding and stool frequency subscores on day 7

In all 3 studies, positive predictive values of symptomatic improvements (as measured by rectal bleeding and/or stool frequency subscores) at day 7 for achieving MCS response at weeks 10 and 58 were high among patients treated with filgotinib. Positive predictive values of a combined rectal bleeding subscore of 0 and stool frequency subscore ≤1 on day 7 (induction biologic-naive, 80.0%; induction biologic-experienced, 76.7%; maintenance, 73.2%) were higher than those for either subscore alone (Table 2). Positive predictive values of these PROs for IBDQ remission, endoscopic improvement, and clinical remission were lower than those for MCS response. Overall, positive predictive values were higher among biologic-naive patients than biologic-experienced patients.

DISCUSSION

In the phase 2b/3 SELECTION trial, filgotinib 200 mg resulted in improved UC symptoms within 7 days of treatment initiation in both biologic-naive and biologic-experienced patients. In addition, a greater proportion of patients treated with filgotinib

200 mg relative to placebo achieved pMCS remission and response by week 2 (the earliest postbaseline time point at which pMCS was assessed). These results indicate a rapid onset of symptom relief with filgotinib 200 mg. Early improvements in patient-reported rectal bleeding and stool frequency subscores of MCS were associated with a higher chance of achievement of an MCS response at weeks 10 and 58.

Rapid onset of action is rated as one of the most desirable features of UC treatment by patients, as revealed by real-world evidence and patient survey data (3,4). Although several other targeted therapies and biologics have demonstrated their ability to yield rapid responses (5,16–18), Janus kinase inhibitors may be particularly fast acting, as demonstrated by recent data on tofacitinib (5). Notably, in this study, rapid responses to filgotinib were evident in both biologic-naive and biologic-experienced patients, despite both groups having severe disease (55.8% and 77.8% of biologic-naive and biologic-experienced patients had a baseline Mayo endoscopic subscore of 3, respectively [10]). In addition, 43.1% of biologic-experienced patients had experienced failure of both a tumor necrosis factor antagonist and vedolizumab, indicating that this patient population was highly refractory to treatment (10).

In these analyses, we used PROs to frequently assess the efficacy of filgotinib. Although endoscopy, ultrasound (19), and fecal calprotectin levels (20) are typically used to confirm resolution of mucosal inflammation, resolution of UC symptoms, especially rectal bleeding, is associated with endoscopic response (6). We assessed rectal bleeding and stool frequency symptoms within the first 2 weeks of treatment initiation, during which greater proportions of patients treated with filgotinib than placebo achieved predefined rectal bleeding and stool frequency subscores. Although there is no universally accepted definition of a rapid response to treatment, 2 weeks is a time frame within which a patient with moderately to severely active disease might be re-examined and, therefore, is a relevant duration in clinical practice.

Importantly, symptomatic improvements (as measured by pMCS remission and response) were maintained in a relatively high proportion of patients treated with maintenance filgotinib 200 mg. Loss of response to therapy remains a common problem in the treatment of patients with UC (21,22), and incidences of secondary loss of response to advanced therapy of approximately 40% or higher within 1 year have been reported (23–25).

As expected, treatment differences compared with placebo were greatest for filgotinib 200 mg (the approved dose), although a similar (albeit less strong) trend between pMCS remission and response and early achievement of predefined rectal bleeding and stool frequency subscores was also observed for filgotinib 100 mg. Importantly, treatment with filgotinib led to symptomatic improvements at week 10, regardless of concomitant corticosteroid use at induction baseline, suggesting no additional benefit of coadministration of corticosteroids on measured PROs.

Improvements in both rectal bleeding and stool frequency on day 7 of treatment were strongly associated with MCS response, but only moderately associated with clinical remission and endoscopic improvement at weeks 10 and 58. Previous studies have demonstrated a moderate-to-strong association between resolution of rectal bleeding and endoscopic improvement (6–8). In the SELECTION trial, a high proportion of patients had a Mayo endoscopic score of 3 at baseline (10); it is possible that by day 7, the absence of rectal bleeding did not translate into endoscopic improvement in these patients and that week 10 PRO data may be more predictive of longer term endoscopic outcomes than earlier data. Only induction responders entered the Maintenance Study, thus reducing the reliability of these analyses at week 58. In addition, the stringent definition of clinical remission used in the SELECTION trial made this end point challenging to achieve. Nevertheless, the strong association between day 7 symptoms and longer term MCS response holds promise for the prediction of long-term treatment outcomes in the future. Predictive values were higher in biologic-naive patients than biologic-experienced patients, which may reflect the fact that the latter population is known to be difficult to treat (10).

Restoration of normal quality of life is an important and recognized treatment target for patients with UC (2). Achievement of pMCS remission at week 10 was associated with improved disease-specific HRQoL at the same time point, with over half of patients in pMCS remission achieving IBDQ remission and those patients in pMCS remission experiencing a greater improvement in the IBDQ total score from baseline than patients not in pMCS remission. In addition, longer term achievement of pMCS remission was associated with maintained improvements in the IBDQ total score, with patients who were not in pMCS remission at week 58 experiencing IBDQ worsening vs maintenance baseline. Furthermore, symptomatic improvements (measured using pMCS and diary data) were associated with better HRQoL as assessed by change in IBDQ scores from both induction and maintenance baseline and by concordance with IBDQ remission at weeks 10 and 58. Unsurprisingly, the substantial concordance between IBDQ remission and pMCS remission after maintenance vs the moderate concordance between the same outcomes after induction suggests that a longer time in remission further contributes to improved patient-reported HRQoL vs the beginning of treatment. This observation highlights the importance of sustainable efficacy as a key goal for the holistic treatment of UC.

Limitations of these analyses include the fact that the patient population was selected for entry into the Maintenance Study and that the use of PROs to assess the rapidity of response was limited (e.g., urgency was not evaluated). In the SELECTION trial, biomarkers (e.g., C-reactive protein, fecal calprotectin) were not measured within the first 2 weeks; however, future studies could evaluate the trajectory of symptoms and inflammatory biomarkers within individuals over time, to help determine whether a combination of PROs and biomarkers could better predict response and maintenance of that response. Time points other than day 7 could also be tested to establish whether improvements in PROs alone could predict UC short-term and long-term outcomes. Future studies could examine whether early and sustained achievement of disease control results in reduced corticosteroid use, fewer adverse events related to concomitant treatment or disease flares, and improved quality of life during a treatment course. This state of holistic remission should be considered a fundamental goal for the treatment of patients with UC.

In these SELECTION *post hoc* analyses, once-daily filgotinib 200 mg improved PROs within 7 days of treatment initiation in biologic-naive and biologic-experienced patients with moderately to severely active UC. Over half of the biologic-naive patients were in pMCS remission by the end of induction, and the beneficial treatment effect of filgotinib 200 mg on UC symptoms was maintained in a high proportion of patients who continued dosing through the end of the 58-week study. Filgotinib may, therefore, be a valuable treatment option for rapid and maintained relief of UC symptoms.

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CONFLICTS OF INTEREST

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Study Highlights

WHAT IS KNOWN

- ✓ Many patients with ulcerative colitis (UC) do not respond to existing treatments or lose response over time.
- ✓ In the phase 2b/3 SELECTION trial, filgotinib 200 mg once daily was well tolerated and effective in inducing and maintaining clinical remission in patients with moderately to severely active UC.

WHAT IS NEW HERE

- ✓ In the SELECTION trial, treatment with filgotinib 200 mg once daily resulted in rapid (within 7 days) and sustained (over 58 weeks) improvements in symptoms of UC.
- ✓ Symptomatic improvements were associated with both short-term and long-term improvements in health-related quality of life.

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

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