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Original Article

Corticosteroid-Sparing Effects of Filgotinib in Moderately to Severely Active Ulcerative Colitis: Data from the Phase 2b/3 SELECTION Study

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Abstract

Background and Aims: Corticosteroid-free remission is an important treatment goal for patients with ulcerative colitis [UC]. The corticosteroid-sparing effects of filgotinib, an oral, Janus kinase 1 preferential inhibitor, were assessed in SELECTION, a placebo-controlled, phase 2b/3 trial in moderately to severely active UC.

Methods: These post hoc analyses assessed 1-, 3-, 6-, and 8-month rates of corticosteroid-free clinical remission at Week 58 and change in median daily prednisone-equivalent dose over time. A matching-adjusted indirect comparison [MAIC] of maintenance studies assessed corticosteroid-free remission with filgotinib 200 mg, intravenous vedolizumab, subcutaneous vedolizumab, and oral tofacitinib.

Results: The Maintenance Study full analysis set included 199 patients receiving filgotinib 200 mg and 98 receiving placebo. Among patients receiving corticosteroids at Maintenance Study baseline, at Week 58, 30.4%, 29.3%, 27.2%, and 21.7% receiving filgotinib had been in corticosteroid-free remission for ≥1, ≥3, ≥6, or ≥8 months, respectively, versus 6.4% receiving placebo across thresholds [p <0.05]. Median daily prednisone-equivalent dose decreased from 17.5 mg/day to 10.0 mg/day with filgotinib treatment during the Maintenance Study. Based upon the MAIC, filgotinib was associated with greater likelihood of corticosteroid-free clinical remission versus intravenous vedolizumab (odds ratio [OR], 15.2; 95% confidence interval [CI], 1.6–139.9; p <0.05]) and similar odds to subcutaneous vedolizumab [OR, 3.8; CI, 0.2–63.8; p = 0.36] in biologic-naïve patients, and similar odds to tofacitinib overall [OR, 2.0; 0.4–9.1; p = 0.39].

Conclusions: Filgotinib 200 mg demonstrated corticosteroid-sparing effects and maintained corticosteroid-free clinical remission in patients with UC. MAIC results should be interpreted cautiously given the large CIs and differences in study design and patient populations. [ClinicalTrials.gov: NCT02914522].

Key Words: Filgotinib; ulcerative colitis; corticosteroids

1. Introduction

Moderately to severely active ulcerative colitis [UC] remains challenging to treat owing to multiple factors. These include: an unpredictable disease course, the lack of biomarkers predictive of treatment response, the frequent occurrence of primary or secondary treatment failure with biologic therapy, and the lack of robust non-invasive measures of treatment response.[1–3] Goals of therapy for UC have shifted over time from short-term symptomatic control alone to long-term prevention of disease and treatment-related complications.[4] Corticosteroids, a mainstay of UC treatment, are typically used to induce remission in patients who are not responding to first-line oral or topical mesalazine, to provide rapid relief to patients experiencing an exacerbation of symptoms despite maintenance therapy,[5] and to control UC until clinical remission is attained with disease-modifying agents (eg, tumour necrosis factor [TNF] antagonists).[6]

Clinical practice guidelines generally recommend that corticosteroids be used sparingly, owing to their potent, but non-specific, anti-inflammatory effects and association with systemic toxicities [eg, mood changes, insomnia, weight gain, acne, and increased risk of infection].[5,7–9] Long-term corticosteroid use is associated with additional adverse effects including osteoporosis, glaucoma, increased risk of diabetes and cardiovascular diseases, thromboembolism, poor wound healing, and other serious health effects.[5] Accordingly, achieving and maintaining corticosteroid-free remission is an important treatment goal for both patients and physicians.[10]

Although several effective treatments are now available for the induction and maintenance of clinical remission, there remains a need for treatments that provide rapid and sustained corticosteroid-free symptom relief, promote mucosal healing, and offer a satisfactory safety profile.

Filgotinib is an oral, Janus kinase 1 [JAK1] preferential inhibitor with a rapid onset of action, which has been approved for the treatment of UC in Europe, and of rheumatoid arthritis in Europe and Japan.[11,12] In the phase 2b/3 SELECTION trial, filgotinib 200 mg [FIL 200 mg] was identified as the effective therapeutic dose for induction and maintenance of clinical remission versus placebo, including in patients with treatment-refractory disease.[12] SELECTION was the first pivotal clinical trial in patients with UC to evaluate the stringent outcome of 6-month corticosteroid-free remission. Herein we present the results of exploratory analyses from SELECTION on the corticosteroid-sparing effects of filgotinib.

2. Materials and Methods

2.1. Study design

SELECTION was a phase 2b/3 double-blind, randomised, placebo-controlled trial comprising two induction studies and a maintenance study that evaluated the efficacy and safety of filgotinib versus placebo in patients with moderately to severely active UC [ClinicalTrials.gov: NCT02914522]. The trial design has been previously reported by Feagan *et al*.[12] Briefly, eligible adults were enrolled into one of two induction studies: Induction Study A [biologic-naïve patients] or Induction Study B [biologic-experienced patients]. Patients were randomised 2:2:1 to FIL 200 mg, FIL 100 mg, or placebo orally once daily for 11 weeks. Patients in clinical remission or with a Mayo Clinic Score [MCS] response at Week 10 were re-randomised 2:1 at Week 11 to continue their induction filgotinib regimen or to receive placebo in the Maintenance Study through to Week 58. Clinical remission was defined as a Mayo endoscopic subscore of 0 or 1, a rectal bleeding subscore of 0, and a ≥1-point decrease in stool frequency subscore from induction baseline to achieve a subscore of 0 or 1. MCS response was defined as a reduction of ≥3 points in MCS and of ≥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. The study protocol and five amendments were reviewed and approved by the independent ethics committee and/or institutional review board at each study site. The study was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent before inclusion in the study.

2.2. Corticosteroid usage

In SELECTION, patients who had received concomitant oral corticosteroids [prednisone ≤30 mg/day or budesonide ≤9 mg/day], were eligible provided the dose prescribed was stable for 2 weeks before and 14 weeks after randomisation. Corticosteroid use at maintenance baseline was defined as the use of corticosteroids indicated for UC. Prednisone-equivalent doses were derived from conversion factors sourced from well-established medical resouces and literature searches.

Starting at Week 14, during the Maintenance Study, corticosteroids were tapered according to a predefined schedule. The daily dose was to be reduced starting at a rate of 2.5 mg per week up to 5 mg per week [or equivalent if not prednisone] until the patient was no longer receiving corticosteroids. Budesonide was to be reduced by 3 mg every 3 weeks. Corticosteroids could be increased in dose or restarted at doses up to and including the baseline dose if symptoms returned, according to the investigator's judgement; this policy could be implemented multiple times, with corticosteroid tapering re-started as soon as symptoms subsided. However, treatment was considered to have failed for patients who received corticosteroids at a dose higher than their baseline dose, and these patients were considered to be non-responders for all clinical outcomes.

For both the Induction Studies and the Maintenance Study, treatment allocation was stratified according to concomitant use of oral, systemically absorbed corticosteroids on Day 1, to enable exploratory, post hoc analyses of corticosteroid usage.

2.3. Outcome measures and analyses

Endpoints from the SELECTION trial have been previously reported by Feagan *et al*., and included clinical remission [as defined above] as the primary endpoint, and 6-month corticosteroid-free remission [the proportion of patients receiving corticosteroids at maintenance baseline who did not use corticosteroids indicated for UC for at least 6 months before achieving clinical remission at Week 58] as a key secondary endpoint.[12]

In these post hoc analyses, the corticosteroid-sparing effect of filgotinib in the Maintenance Study was assessed further, using the following outcomes: the proportions of patients using corticosteroids indicated for UC at maintenance baseline with 1-, 3-, 6-, and 8-month corticosteroid-free clinical outcomes (clinical remission, MCS response, and partial MCS [pMCS] remission) at Week 58; and change from baseline in median daily prednisone-equivalent dose over time. Patients were considered corticosteroid-free if they had no systemic or localised corticosteroid use indicated for UC continuously for the specified time period [1, 3, 6, or 8 months] before Week 58. pMCS remission was defined as pMCS ≤2 and no individual rectal bleeding, stool frequency, or physician's global assessment subscore >1.

Additional analyses were performed to identify prognostic factors associated with corticosteroid-free status; correlation of 6-month corticosteroid-free clinical remission with safety outcomes (adverse events [AEs], serious adverse events [SAEs], and AEs of interest) during the Maintenance Study; and correlation of being corticosteroid-free for 6 months with health-related quality of life [HRQoL] as measured by Inflammatory Bowel Disease Questionnaire [IBDQ] remission [defined as IBDQ total score ≥170; score range 0–224, with higher scores indicating improvements[13]) at Week 58.

2.4. Matched-adjusted indirect comparison methods

In the absence of head-to-head trials, a matching-adjusted indirect comparison [MAIC] of similar trials [SELECTION, GEMINI 1, VISIBLE 1, and OCTAVE SUSTAIN][12,14–16] with similar corticosteroid-tapering requirements was used to compare the relative efficacy of: oral, once-daily FIL 200 mg; intravenous [IV] vedolizumab [300 mg every 8 weeks]; subcutaneous [SC] vedolizumab [108 mg every 2 weeks]; and oral [per os or PO] tofacitinib [5 mg twice daily] at Week 58 in patients receiving maintenance therapy for moderately to

severely active UC. Tofacitinib 10 mg was not included, given that the recommended maintenance dose for UC is 5 mg twice daily.[17] To adjust for differences in baseline characteristics between trials, for patients for whom individual-level patient data [IPD] were available [ie, patients from SELECTION], data were weighted based on a propensity score model such that after weighting, the average baseline characteristics of patients in SELECTION matched the baseline characteristics reported in the trials for which only aggregate data were published.

Using the MAIC, numerous efficacy outcomes at the end of the maintenance phase of each study [eg, Week 52 for vedolizumab IV] were compared across treatment arms, and among biologic-naïve and biologic-experienced subgroups separately. Forthcoming publications will present other results of the MAIC analysis; an outcome of relevance to be discussed herein is corticosteroid-free remission, the definition of which varied among trials. The original definition of the corticosteroid-free remission endpoint in SELECTION included a '6 months' criterion. For the MAIC, IPD were used to generate corticosteroid-free remission data without this criterion, to more closely match the definition of corticosteroid-free remission used in the GEMINI 1 [vedolizumab IV] and VISIBLE 1 [vedolizumab SC] trials: the proportion of patients using oral corticosteroids at baseline who discontinued corticosteroids and were in clinical remission at the end of the maintenance phase.[14,15] In OCTAVE SUSTAIN [tofacitinib PO], corticosteroid-free remission was defined as the proportion of patients in clinical remission [MCS ≤2, no subscore >1, and rectal bleeding subscore of 0] and who did not require any treatment with corticosteroids for at least 4 weeks before the end of maintenance, among patients who were receiving corticosteroids at maintenance baseline.[16] For the indirect comparison of filgotinib and tofacitinib, the definitions of corticosteroid-free remission were matched as closely as was feasible; there were no data to identify whether corticosteroids were discontinued at least 4 weeks before the Maintenance Study endpoint in SELECTION.

2.5. Statistical analysis

Post hoc analyses were conducted using the maintenance full analysis set of SELECTION, which comprised all patients randomised in the Induction Studies who achieved clinical remission or MCS response at Week 10, were re-randomised, and who took at least one dose of study drug in the Maintenance Study. A non-responder imputation approach was used to handle missing data.

Cochran–Mantel–Haenszel [CMH] tests were used to compare the treatment effect between FIL 200 mg or FIL 100 mg and placebo among patients from Induction Studies A and B combined. The CMH test was additionally stratified by participation in Induction Study A or B, concomitant use of oral, systemic corticosteroids at induction baseline, and concomitant use of immunosuppressives at maintenance baseline. Strata with low numbers of patients may have been aggregated for the CMH test. The stratified CMH χ^2 *p*-value was provided for each of the treatment comparisons. As these were post hoc analyses and statistical tests were not adjusted for multiple testing, the reported *p*-values are only nominal and should not be overinterpreted or used as claims for evidence or lack of statistical significance.

In patients receiving FIL 200 mg or FIL 100 mg in the Maintenance Study who were using corticosteroids at maintenance baseline, a univariate logistic regression was performed to identify prognostic factors of corticosteroid-free clinical remission at Week 58 among the following disease characteristics: histological remission at Week 10; endoscopic improvement at Week 10; previous biologic exposure [naïve vs experienced]; concomitant use of oral, systemic corticosteroids at maintenance baseline; concomitant use of immunosuppressives at maintenance baseline; C-reactive protein concentration at Week 10; faecal calprotectin concentration at Week 10; MCS at Week 10; duration of UC; and previous exposure to, and/or prior failure of, TNF antagonists and/or vedolizumab. A multivariate logistic regression was performed using all the eligible characteristics that were positively associated with corticosteroid-free clinical remission at Week 58 [$p < 0.05$] in the univariate analysis. Factors of previous exposure and/or prior failure of TNF antagonists and/or vedolizumab were not eligible for multivariate analysis but were highly correlated with previous biologic exposure.

The proportions of patients with AEs, SAEs, and AEs of interest during the Maintenance Study, and the proportion of patients achieving Week 58 IBDQ remission, were examined using descriptive statistics.

For the MAIC, data were matched based on the following demographic and clinical characteristics measured at induction baseline: sex, age, weight, smoking status, MCS, duration of UC, history of TNF antagonist failure [if applicable], and concomitant systemic corticosteroid use. The IPD of the SELECTION maintenance cohort were re-weighted to match the aggregated mean or proportion of these characteristics that were reported in comparator trials. Matching was conducted separately for the active treatment and placebo arms in the overall maintenance populations. Comparisons of corticosteroid-free remission were conducted separately for biologic-naïve and biologic-experienced patient groups if subgroup data were available [these data were not available for OCTAVE SUSTAIN]. Comparisons between FIL 200 mg and the comparator drugs in each trial were conducted using Wald tests, incorporating the weights obtained in the matching process. The MAIC analyses were conducted using R version 4.0.2 [R Foundation for Statistical Computing, Vienna, Austria]. All other analyses were conducted using SAS version 9.4 [SAS Institute Inc., Cary, NC, USA].

3. Results

These post hoc analyses focused on FIL 200 mg, as this was demonstrated to be the therapeutic effective dose and is the dose approved by the European Medicines Agency.[11,12] Analyses conducted on the 100-mg dose are provided in the Supplementary Material.

3.1. Baseline demographics and patient characteristics

Baseline characteristics of patients in SELECTION have been published previously.[12] Briefly, patients receiving FIL 200 mg [$n = 199$] or respective placebo [$n = 98$], or FIL 100 mg [$n = 172$] or respective placebo [$n = 89$], were included in the maintenance study full analysis set; all were classified as 'filgotinib induction responders'. The baseline characteristics of patients in the Maintenance Study were similar across treatment groups [Table 1 and Supplementary Table 1]. In total, 53.8% of patients who received FIL 200 mg entered the Maintenance Study from Induction Study A [biologic-naïve]

Table 1. Maintenance baseline [Week 11] demographics and characteristics of patients in the Maintenance Study [full analysis set].

Induction	**Filgotinib 200 mg**	
Maintenance	**Filgotinib 200 mg [*n* = 199]**	**Placebo [*n* = 98]**
Participation in Induction Study A [biologic-naïve at induction], *n* [%]	107 [53.8]	54 [55.1]
Age, years, mean ± SD	43 ± 13.9	42 ± 13.0
Women, *n* [%]	106 [53.3]	50 [51.0]
Race, *n* [%]		
Asian	56 [28.1]	29 [29.6]
Black or African American	4 [2.0]	0 [0.0]
White	135 [67.8]	67 [68.4]
Enrolled at a non-US site, *n* [%]	180 [90.5]	87 [88.8]
Duration of UC from diagnosis, years, mean ± SD	8.4 ± 7.41	8.8 ± 7.61
History of pancolitis	97 [48.7]	46 [46.9]
C-reactive protein [hsCRP], mg/L, mean ± SD	3.77 ± 10.201	2.47 ± 3.660
Faecal calprotectin, µg/g, mean ± SD	625 ± 950.9	926 ± 2633.9
Prior use of at least one anti-TNF agent and vedolizumab, *n* [%]	40 [20.1]	22 [22.4]
Prior use of at least two biologic agents, *n* [%]	55 [27.6]	27 [27.6]
Concomitant use of systemic corticosteroids, *n* [%]	78 [39.2]	40 [40.8]
Prednisone-equivalent dose, mg/day, median [IQR]	18.8 [10.0–20.0]	20.0 [10.0–30.0]

Percentages were calculated based on the number of patients in the full analysis set. For use of systemic corticosteroids, only records with oral, intravenous, and intramuscular routes of administration were included.
hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; SD, standard deviation; TNF, tumour necrosis factor; UC, ulcerative colitis.

and 46.2% entered from Induction Study B [biologic-experienced]. Approximately 40% of patients receiving FIL 200 mg had concomitant systemic corticosteroid use at maintenance baseline [Table 1]. In patients receiving corticosteroids indicated for UC at maintenance baseline, the median (interquartile range [IQR]) prednisone-equivalent dose was 17.5 [10.0–20.0] mg/day. Baseline characteristics of patients in the FIL 200 mg and respective placebo group receiving corticosteroids at maintenance baseline are presented in Table 2. Similar proportions of patients were from Induction Study A [46.7%] and Induction Study B [53.3%]. Baseline characteristics for the FIL 100 mg treatment group and the respective placebo group are presented in Supplementary Table 2.

3.2. Corticosteroid-free remission and response

As reported by Feagan *et al.*,[12] of the patients who entered the Maintenance Study, 74 [37.2%] patients who received FIL 200 mg and 11 [11.2%] who received placebo were in clinical remission at Week 58. Among patients in clinical remission, 69 [34.7%] FIL 200 mg-treated and 11 [11.2%] placebo-treated patients achieved at least 6-month corticosteroid-free remission at Week 58 (difference, 23.4%; 95% confidence interval [CI], 13.6–33.3; p <0.0001); meaning that 93.2% of filgotinib-treated patients in clinical remission at Week 58 had been corticosteroid-free for 6 months or longer.

Of patients receiving corticosteroids at maintenance baseline, 25 of 92 [27.2%] patients receiving FIL 200 mg during the Maintenance Study achieved at least 6-month corticosteroid-free clinical remission at Week 58, compared with three of 47 [6.4%] patients in the placebo group [difference, 20.8%; 95% CI, 7.7–33.9; p = 0.0055; Table 3].[12] Similar differences were observed for MCS response at Week 58: 45 [48.9%] patients receiving FIL 200 mg and 11 [23.4%] receiving placebo achieved 6-month corticosteroid-free MCS response [difference, 25.5; 95% CI, 8.1–43.0; p = 0.0050; Supplementary Table 3]. Sustained pMCS remission during the 6-month corticosteroid-free period was attained by 22 [23.9%] patients receiving FIL 200 mg and two [4.3%] patients receiving placebo [difference, 19.7%; 95% CI, 7.6–31.7; p = 0.0055; Supplementary Table 4]. Corticosteroid-free clinical remission, MCS response, and sustained pMCS remission were reported for a consistently and nominally significantly higher proportion of patients receiving FIL 200 mg compared with placebo at nearly all time points. The only exception was the 8-month corticosteroid-free MCS response, for which the difference between FIL 200 mg and placebo did not reach nominal significance [p = 0.0664]. The proportions of patients receiving FIL 100 mg with 1-month, 3-month, 6-month, and 8-month corticosteroid-free MCS response, and sustained pMCS remission, respectively, are reported in Supplementary Tables 3 and 4.

3.3. Corticosteroid-sparing effects of filgotinib

In the evaluation of the median daily prednisone-equivalent dose in patients receiving corticosteroids during the Maintenance Study, FIL 200 mg appeared to have a corticosteroid-sparing effect which was maintained over time [Figure 1]. For patients randomly assigned to continue filgotinib during the Maintenance Study, the median prednisone-equivalent dose was 17.5 mg/day [IQR, 10.0–20.0] at maintenance baseline and 10.0 mg/day [IQR, 5.0–12.5] at Week 58. Patients assigned to placebo during the Maintenance Study were receiving a median prednisone-equivalent dose of 20.0 mg/day [IQR, 10.0–30.0] at baseline and 15.0 mg/day [IQR, 10.0–20.0] at Week 58. This trend was not observed among patients receiving FIL 100 mg compared with respective placebo [Supplementary Figure 1].

Table 2. Maintenance baseline [Week 11] demographics and characteristics of patients in the Maintenance Study receiving corticosteroids indicated for UC at maintenance baseline [full analysis set].

Induction	**Filgotinib 200 mg**	
Maintenance	**Filgotinib 200 mg [*n* = 92]**	**Placebo [*n* = 47]**
Participation in Induction Study A [biologic-naïve at induction], *n* [%]	43 [46.7]	22 [46.8]
Age, years, mean ± SD	43 ± 14.4	43 ± 12.3
Women, *n* [%]	53 [57.6]	20 [42.6]
Race		
Asian	22 [23.9]	11 [23.4]
Black or African American	1 [1.1]	0
White	69 [75.0]	35 [74.5]
Enrolled at a non-US site, *n* [%]	81 [88.0]	43 [91.5]
Duration of UC from diagnosis, years, mean ± SD	7.7 ± 7.12	9.1 [8.43]
C-reactive protein [hsCRP], mg/L, mean ± SD	3.03 ± 3.971	2.70 ± 4.329
Faecal calprotectin, µg/g, mean ± SD	631 ± 920.3	1455 ± 3595.0
Total Mayo Clinic Score at maintenance baseline, mean ± SD	3.4 ± 2.00	3.3 ± 1.95
Partial Mayo Clinic Score at maintenance baseline, mean ± SD	1.7 ± 1.37	1.7 ± 1.27
Prior use of at least one anti-TNF agent and vedolizumab, *n* [%]	26 [28.3]	15 [31.9]
Prior use of at least two biologic agents, *n* [%]	32 [34.8]	18 [38.3]
Concomitant use of systemic corticosteroids indicated for UC, *n* [%]	77 [83.7]	39 [83.0]
Prednisone-equivalent dose, mg/day, median [IQR]	17.5 [10.0–20.0]	20.0 [10.0–30.0]

Percentages were calculated based on the number of patients in the full analysis set. For use of systemic corticosteroids, only records with oral, intravenous, and intramuscular routes of administration were included.
hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; SD, standard deviation; TNF, tumour necrosis factor; UC, ulcerative colitis.

Table 3. Proportions of patients in the Maintenance Study receiving corticosteroids at maintenance baseline who were in corticosteroid-free clinical remission at Week 58 [full analysis set].

Induction	**Filgotinib 200 mg**	
Maintenance	**Filgotinib 200 mg [*n* = 92]**	**Placebo [*n* = 47]**
≥1 month corticosteroid-free		
n [%]; 95% CI	28 [30.4]; 20.5–40.4	3 [6.4]; 0.0–14.4
Risk difference; 95% CI	24.1; 10.7–37.4	
p-value	0.0019	
≥3 months corticosteroid-free		
n [%]; 95% CI	27 [29.3]; 19.5–39.2	3 [6.4]; 0.0–14.4
Risk difference; 95% CI	23.0; 9.7–36.2	
p-value	0.0026	
≥6 months corticosteroid-free		
n [%]; 95% CI	25 [27.2]; 17.5–36.8	3 [6.4]; 0.0–14.4
Risk difference; 95% CI	20.8; 7.7–33.9	
p-value	0.0055	
≥8 months corticosteroid-free		
n [%]; 95% CI	20 [21.7]; 12.8–30.7	3 [6.4]; 0.0–14.4
Risk difference; 95% CI	15.4; 2.8–27.9	
p-value	0.0321	

CI, confidence interval.

3.4. Prognostic factors for corticosteroid-free clinical remission at Week 58

When considering all filgotinib-treated patients who were taking corticosteroids at maintenance baseline, the following factors were associated with corticosteroid-free clinical remission at Week 58 when assessed by univariate analysis: biologic-naïve (odds ratio [OR], 3.44; 95% CI, 1.54–7.68; $p = 0.0026$); no previous exposure to, and no prior failure of,

TNF antagonists and vedolizumab [all p <0.05]; and the presence of histological remission [OR, 2.67; 95% CI, 1.26–5.66; p = 0.0102] and endoscopic improvement [OR, 2.11; 95% CI, 1.00–4.45; p = 0.0490] at Week 10 [all binary variables]; lower MCS [OR, 0.64; 95% CI, 0.51–0.80; p <0.0001] at Week 10 [continuous variable] [see Supplementary Table 5 for details on how to interpret ORs for binary vs continuous variables]. However, in the subsequent multivariate analysis, only lower MCS at maintenance baseline remained significant [OR, 0.61; 95% CI, 0.43–0.85; p = 0.0034].

3.5. Relative efficacy of filgotinib versus comparators for corticosteroid-free remission

After matching in the MAIC analysis, FIL 200 mg was associated with greater odds of corticosteroid-free remission than vedolizumab IV at the end of the maintenance phase for patients who were biologic-naïve [OR, 15.2; 95% CI, 1.6–139.9; p <0.05; Table 4]; there was no significant difference observed between treatments for biologic-experienced patients [OR, 4.7; 95% CI, 0.2–93.2; p = 0.3100]. The odds of corticosteroid-free remission were similar between FIL 200 mg and vedolizumab SC for both biologic-naïve [OR, 3.8; 95% CI, 0.2–63.8; p = 0.3600] and biologic-experienced patients [OR, 3.2; 95% CI, 0.2–60.5; p = 0.4400].

After matching, the odds of corticosteroid-free remission were not significantly different for FIL 200 mg compared with tofacitinib 5 mg for the overall population [OR, 2.0; 95% CI, 0.4–9.1; p = 0.3900]. Data from OCTAVE SUSTAIN were not available for patient subgroups.

3.6. Impact of corticosteroid-sparing effects on safety

Among patients receiving corticosteroids at maintenance baseline and FIL 200 mg in the Maintenance Study, the safety analysis did not show a meaningful difference in proportions of AEs between subgroups of patients who were [n = 25] or were not [n = 67] in 6-month corticosteroid-free remission at Week 58 [Table 5]. The proportions of AEs were also similar for subgroups of patients receiving placebo during maintenance who were [n = 3] or who were not [n = 44] in 6-month corticosteroid-free remission, but sample sizes and

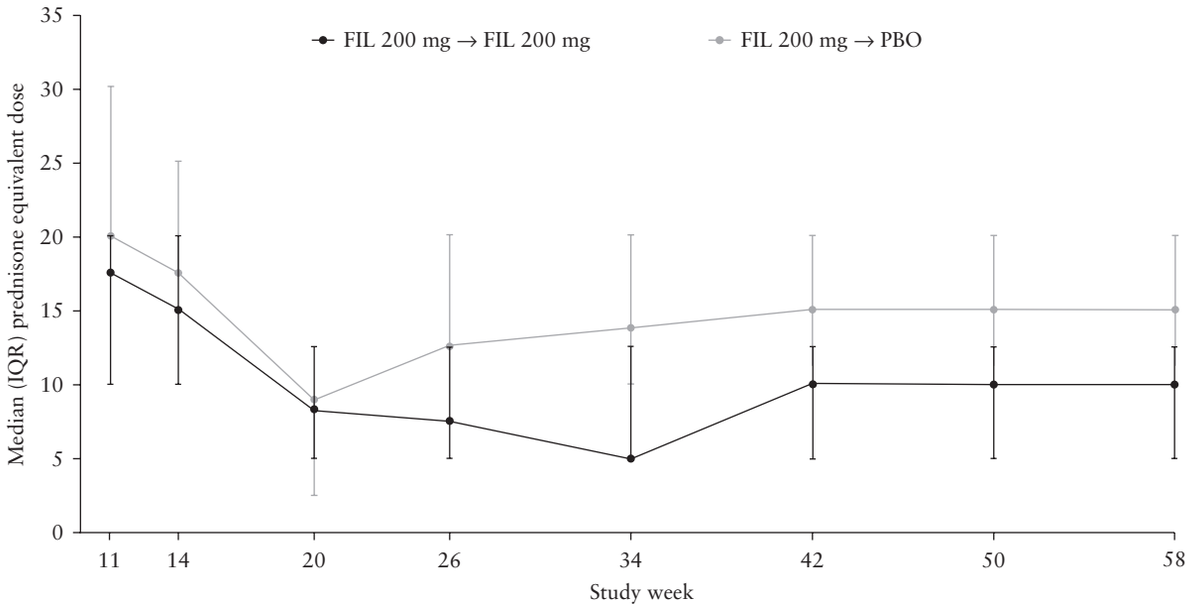

Figure 1. Median prednisone-equivalent dose in patients receiving corticosteroids during the Maintenance Study [full analysis set]. FIL, filgotinib; IQR, interquartile range; PBO, placebo.

Table 4. Matching-adjusted indirect comparison of corticosteroid-free remission with filgotinib 200 mg, vedolizumab IV and SC, or tofacitinib SC during the Maintenance Study

	Subpopulation	Odds ratio	95% CI	p-value[a]
FIL 200 mg vs vedolizumab IV	Biologic-naïve patients	15.2	[1.6–139.9]	<0.05
	Biologic-experienced patients	4.7	[0.2–93.2]	0.31
FIL 200 mg vs vedolizumab SC	Biologic-naïve patients	3.8	[0.2–63.8]	0.36
	Biologic-experienced patients	3.2	[0.2–60.5]	0.44
FIL 200 mg vs tofacitinib PO	N/A	2.0	[0.4–9.1]	0.39

Corticosteroid-free remission is defined as the proportion of patients using oral corticosteroids indicated for ulcerative colitis at induction baseline who discontinued corticosteroids and were in clinical remission at the end of maintenance phase.
CI, confidence interval; FIL, filgotinib; IV, intravenous; N/A, not available; PO, *per os*; SC, subcutaneous; N/A, not available..
[a]p-values were calculated using the Wald test.

the proportions were lower compared with the FIL 200 mg subgroups.

3.7. Impact of corticosteroid-sparing effects on HRQoL

Among patients in the maintenance full analysis set, there was a difference in proportions of patients in IBDQ remission between subgroups receiving FIL 200 mg in the Maintenance Study: a numerically greater proportion of patients who had been corticosteroid-free for 6 months at Week 58 [*n* = 52] were also in IBDQ remission at Week 58, compared with patients who had not been corticosteroid-free for 6 months [*n* = 147] [Table 6]. A similar trend was observed among subgroups of patients receiving placebo during the Maintenance Study.

4. Discussion

A key aim in the treatment of patients with moderately to severely active UC is to minimise cumulative exposure to corticosteroids, to reduce their adverse effects and associated costs. As such, corticosteroid-free remission is a highly relevant treatment objective for evaluation in clinical trials.[7–9] It is notable that SELECTION was the first clinical trial in UC to include the stringent outcome of 6-month corticosteroid-free clinical remission as a key secondary endpoint. Data were also collected on 1- and 3-month corticosteroid-free clinical remission, but these outcomes may be less clinically relevant because patients could still be receiving corticosteroids for longer than is advisable. Data supporting achievement of 6-month corticosteroid-free remission with FIL 200 mg, however, could have a substantial impact on clinical practice, given that societal guidelines recommend that corticosteroid courses be used less than twice per year.[8] We report that more than a quarter of patients receiving FIL 200 mg who used corticosteroids at maintenance baseline were able to achieve corticosteroid-free remission approximately 23 weeks post-maintenance baseline, and to maintain this status for at least 6 months. Notably, over 90% of patients in clinical remission at Week 58 treated with FIL 200 mg had been corticosteroid-free for the previous 6 months. Among patients receiving corticosteroids at maintenance baseline, improvements with FIL 200 mg were similarly demonstrated for other outcomes including 6-month corticosteroid-free MCS response. It is noteworthy that SELECTION included a refractory population with high inflammatory burden, as indicated by baseline characteristics [27.7% with prior use of two or more biologic

Table 5. Proportions of patients receiving corticosteroids at maintenance baseline who experienced an adverse event during the Maintenance Study by 6-month corticosteroid-free status at Week 58.

	All patients with corticosteroid use at maintenance baseline			
Induction	Filgotinib 200 mg		**Filgotinib 200 mg**	
Maintenance	**Filgotinib 200 mg**		**Placebo**	
	6-month corticosteroid-free remission [*n* = 25]	**Did not achieve 6-month corticosteroid-free remission [*n* = 67]**	**6-month corticosteroid-free remission [*n* = 3]**	**Did not achieve 6-month corticosteroid-free remission [*n* = 44]**
Any adverse event, *n* [%]	10 [40.0]	24 [35.8]	1 [33.3]	8 [18.2]
Serious adverse event, *n* [%]	1 [4.0]	2 [3.0]	-	-
Adverse event of interest, *n* [%]				
Infections and infestations	5 [20.0]	8 [11.9]	-	2 [4.5]

Table 6. Proportions of patients in the full analysis set in IBDQ remission at Week 58, by 6-month corticosteroid-free status at Week 58

Induction	**Filgotinib 200 mg**		**Filgotinib 200 mg**	
Maintenance	Filgotinib 200 mg		**Placebo**	
	Corticosteroid-free for 6 months [*n* = 52]	**Not corticosteroid-free for 6 months [*n* = 147]**	**Corticosteroid-free for 6 months [*n* = 13]**	**Not corticosteroid-free for 6 months [*n* = 85]**
Patients in IBDQ remission at Week 58, *n* [%]	42 [80.8]	73 [49.7]	6 [46.2]	19 [22.4]
Patients not in IBDQ remission at Week 58, *n* [%]	7 [13.5]	27 [18.4]	7 [53.8]	8 [9.4]
Patients with IBDQ score missing at Week 58, *n* [%]	3 [5.8]	47 [32.0]	-	58 [68.2]

IBDQ remission was defined as IBDQ score ≥170.
IBDQ, Inflammatory Bowel Disease Questionnaire.

agents, 37.6% with prior TNF antagonist failure, 19.8% with prior vedolizumab failure, and 48.5% with a history of pancolitis]. The present findings suggest FIL 200 mg could facilitate early corticosteroid tapering and reduce cumulative corticosteroid burden, even in treatment-resistant patients.

Predicting the clinical characteristics of patients most likely to achieve corticosteroid-free remission is important and increasingly relevant from a healthcare use standpoint. Multivariate analyses indicated that corticosteroid-free remission is largely achieved independently of medical history and the disease characteristics assessed. Nevertheless, lower MCS at maintenance baseline was positively correlated with corticosteroid-free remission at Week 58. This is perhaps unsurprising: lower MCS, indicating treatment response, is a condition for tapering corticosteroid doses. Therefore, it follows that the more robust the response/remission status, the greater the chance of successful steroid tapering and cessation.

Few head-to-head trials comparing the efficacy of advanced treatments for UC have been performed, and no randomised controlled trials to date have assessed corticosteroid-sparing effects as a key endpoint. The only study of comparative efficacy available, VARSITY, did not demonstrate a difference in corticosteroid-sparing effects of vedolizumab vs adalimumab.[18] No head-to-head trials have been conducted thus far involving filgotinib. Therefore, indirect treatment comparisons are desirable to support decision-making in the absence of higher-quality evidence. However, there are challenges in accounting for differences in patient populations and study designs. Unlike traditional network meta-analyses, a MAIC can adjust for heterogeneity in patient populations between trials and offers a reasonable comparison of efficacy in the absence of head-to-head trials. To adjust for imbalances between trials, a broad range of characteristics was matched between SELECTION and comparator trial populations. Our results suggest that the corticosteroid-sparing effect of filgotinib is similar to that of vedolizumab SC and tofacitinib PO overall, and potentially greater than that of vedolizumab IV among biologic-naïve patients. The difference in odds of corticosteroid-free remission between vedolizumab IV and vedolizumab SC could be explained by pharmacokinetics; vedolizumab SC every 2 weeks likely results in a higher trough concentration of drug than vedolizumab IV every 8 weeks.[15] However, in evaluation of the full analysis set of VISIBLE 1, the proportions of patients in corticosteroid-free clinical remission at Week 52 were comparable for vedolizumab IV and vedolizumab SC.[15] In the MAIC, no differences were observed between filgotinib and vedolizumab IV in biologic-experienced patients, possibly because these patients were more treatment-refractory at enrolment and hence less sensitive to differences between agents. It is possible that other unidentified factors may also account for the difference observed. Given the small patient numbers, and the large CIs, results of the MAIC should be interpreted with caution. Head-to-head trials involving larger cohorts or real-world settings are warranted.

To examine the wider impacts of the corticosteroid-sparing effect of filgotinib, we analysed safety and HRQoL data in patients using corticosteroids at maintenance baseline and in all patients, respectively. We hypothesised that AEs would be more common in the subgroup of patients who did not achieve 6-month corticosteroid-free clinical remission. However, our findings suggest that the frequency of AEs was not influenced by corticosteroid use. One reason for this may be the small sample sizes. Another could be that corticosteroid use was treated as a categorical variable [‘yes’ or ‘no’], which was not sensitive enough given the use of low prednisone-equivalent doses, which may result in a proportion of AEs comparable to that seen with corticosteroid absence for at least 6 months. Similarly, although some patients did not meet the 6-month criterion for this analysis, they may have been corticosteroid-free for up to 5 months, which could explain the minimal difference observed. Whereas achieving 6-month corticosteroid-free remission was not associated with fewer AEs, reducing or eliminating corticosteroid use may still provide long-term benefits to patients with UC.[5]

In the HRQoL analysis, it appeared that patients who had been corticosteroid-free for 6 months were more likely to have a normalised IBDQ score [≥170] than patients who had not. This could suggest that interruption or cessation of corticosteroid use might affect HRQoL independently of the occurrence of AEs. This may be related to overall improvements in factors that are not captured as AEs, such as energy levels or mental status.[19]

The main limitation of analyses is that they were not prespecified and hence were not powered to detect significant differences. Additionally, the randomised withdrawal design of SELECTION may have artificially inflated the proportion of placebo-treated patients who were in corticosteroid-free remission during maintenance; this subgroup may be experiencing ‘lasting’ effects of induction filgotinib. Furthermore, investigators were permitted to increase corticosteroid doses as many times as necessary, and patients who exceeded their baseline corticosteroid dose were excluded from efficacy analyses. There was no consequence for non-adherence to the strict tapering schedule, and there may have been patients who were maintained on corticosteroids to avoid the risk of symptom flares, which may have affected estimates. Nevertheless, our results are comparable to those from other exploratory analyses of disease-modifying drugs.[14–16] The use of stricter permissions and tapering rules may help to standardise treatment; however, we believe that the approaches taken by investigators more closely mimic patterns of corticosteroid rescue in clinical practice.

Finally, there are inherent limitations to indirect comparisons. Cross-sectional analyses of data collected at the end of maintenance provide no indication of the time needed to eliminate corticosteroid use. Furthermore, despite adjustment, trials may have been dissimilar in terms of the timing of tapering and protocols used, and the definition of corticosteroid-free remission. Specifically, in the MAIC analysis of FIL 200 mg versus vedolizumab IV, differences in efficacy endpoint definitions and patient populations between SELECTION and VISIBLE 1 added uncertainty to the model, and may account for the observed differences in corticosteroid-sparing effects of the two treatments and accompanying large CIs. Therefore, MAIC results reported herein should be interpreted with caution. In OCTAVE SUSTAIN, corticosteroid-free remission was defined as discontinuation of corticosteroids at least 4 weeks before the end of maintenance, whereas in SELECTION, it was discontinuation of corticosteroids at the end of maintenance. The inclusion of predefined, standardised, corticosteroid-free remission endpoints in future trials may be necessary to better interpret findings.

In summary, this study provides evidence to suggest that FIL 200 mg has rapid and sustained corticosteroid-sparing

effects, including in patients with UC refractory to prior treatments, compared with placebo. Corticosteroid tapering was generally completed within 20 weeks of initiation [based on the Weeks 14–32 tapering window], with little increment in dose observed in the later weeks, indicative of a robust and sustained effect. Overall, these findings indicate that filgotinib could reduce corticosteroid burden, aligning with clinical guidelines for patient care.

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Conflicts of Interest

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Author Contributions

All authors made a significant contribution to the work reported, whether in study concept, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Data Availability

Anonymised individual patient data will be shared upon request for research purposes dependent upon the nature of the request, the merit of the proposed research, the availability of the data, and their 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.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Feuerstein JD, Cheifetz AS. Ulcerative colitis: epidemiology, diagnosis, and management. *Mayo Clin Proc* 2014;**89**:1553–63.
2. Kobayashi T, Siegmund B, Le Berre C, *et al*. Ulcerative colitis. *Nat Rev Dis Primers* 2020;**6**:74.
3. Dhyani M, Joshi N, Bemelman WA, *et al*. Challenges in IBD research: novel technologies. *Inflamm Bowel Dis* 2019;**25**:S24–S30.
4. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012;**380**:1606–19.
5. Waljee AK, Wiitala WL, Govani S, *et al*. Corticosteroid use and complications in a US inflammatory bowel disease cohort. *PLoS One* 2016;**11**:e0158017.
6. Burri E, Maillard MH, Schoepfer AM, *et al*. Treatment algorithm for mild and moderate-to-severe ulcerative colitis: an update. *Digestion* 2020;**101**:2–15.
7. Harbord M, Eliakim R, Bettenworth D, *et al*. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis* 2017;**11**:769–84.
8. Lamb CA, Kennedy NA, Raine T, *et al*. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;**68**:s1–s106.
9. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol* 2019;**114**:384–413.
10. Peyrin-Biroulet L, Sandborn W, Sands BE, *et al*. Selecting Therapeutic Targets in Inflammatory Bowel Disease [STRIDE]: determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015;**110**:1324–38.
11. European Medicines Agency. *Jyseleca [filgotinib]*. 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/jyseleca. Accessed October 18, 2021.
12. Feagan BG, Danese S, Loftus EV, *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.
13. Yarlas A, Maher S, Bayliss M, *et al*. The inflammatory bowel disease questionnaire in randomized controlled trials of treatment for ulcerative colitis: systematic review and meta-analysis. *J Patient Cent Res Rev* 2020;**7**:189–205.
14. Feagan BG, Rutgeerts P, Sands BE, *et al*. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;**369**:699–710.
15. Sandborn WJ, Baert F, Danese S, *et al*. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. *Gastroenterology* 2020;**158**:562–72.e12.
16. Sandborn WJ, Su C, Sands BE, *et al*. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;**376**:1723–36.
17. European Medicines Agency. *Xeljanz [tofacitinib]*. 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/xeljanz. Accessed October 18, 2021.
18. Sands BE, Peyrin-Biroulet L, Loftus EV, *et al*. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med* 2019;**381**:1215–26.
19. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc* 2006;**81**:1361–7.