Integrated safety analysis of filgotinib for ulcerative colitis: Results from SELECTION and SELECTIONLTE

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Abstract: BACKGROUND: Filgotinib 200 mg (FIL200) is an approved treatment for adults with moderately to severely active ulcerative colitis (UC). AIM: To report integrated safety data from the phase 2b/3 SELECTION study (NCT02914522) and its ongoing long-term extension study SELECTIONLTE (NCT02914535). METHODS: Safety outcomes were analysed in adults with moderately to severely active UC who received FIL200, filgotinib 100 mg (FIL100) or placebo once daily throughout the 11-week SELECTION induction study, the 47-week SELECTION maintenance study (if applicable) and SELECTIONLTE (if applicable). Exposure-adjusted incidence rates (EAIRs) per 100 censored patient-years of exposure with 95% confidence intervals were reported for treatment-emergent adverse events (AEs). Certain AE data were presented in subgroups, including age and prior biologic exposure status. RESULTS: This interim analysis included 1348 patients representing 3326.2 patient-years of exposure. Baseline characteristics of patients entering SELECTION were similar across treatment groups. EAIRs for serious infection, thromboembolic events and major adverse cardiovascular events (MACE) were consistently low across treatment groups. Most patients with MACE had cardiovascular risk factors. The EAIR for herpes zoster was numerically higher for FIL200 than for placebo. Infection incidences were numerically higher in biologic-experienced than biologic-naive patients. Higher incidences of certain AEs in patients 65 years of age or older were as expected. Four deaths occurred, including three cardiovascular deaths, none of which was considered related to filgotinib. CONCLUSION: FIL200 and FIL100 were well tolerated with no unexpected safety signals in patients with moderately to severely active UC, regardless of previous biologic exposure or age.

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Summary

Background: Filgotinib 200 mg (FIL200) is an approved treatment for adults with moderately to severely active ulcerative colitis (UC).

Aim: To report integrated safety data from the phase 2b/3 SELECTION study (NCT02914522) and its ongoing long-term extension study SELECTIONLTE (NCT02914535).

Methods: Safety outcomes were analysed in adults with moderately to severely active UC who received FIL200, filgotinib 100 mg (FIL100) or placebo once daily throughout the 11-week SELECTION induction study, the 47-week SELECTION maintenance study (if applicable) and SELECTIONLTE (if applicable). Exposure-adjusted incidence rates (EAIRs) per 100 censored patient-years of exposure with 95% confidence intervals were reported for treatment-emergent adverse events (AEs). Certain AE data were presented in subgroups, including age and prior biologic exposure status.

Results: This interim analysis included 1348 patients representing 3326.2 patient-years of exposure. Baseline characteristics of patients entering SELECTION were similar across treatment groups. EAIRs for serious infection, thromboembolic events and major adverse cardiovascular events (MACE) were consistently low across treatment groups. Most patients with MACE had cardiovascular risk factors. The EAIR for herpes zoster was numerically higher for FIL200 than for placebo. Infection incidences were numerically higher in biologic-experienced than biologic-naive patients. Higher incidences of certain AEs in patients 65 years of age or older were as expected. Four deaths occurred, including three cardiovascular deaths, none of which was considered related to filgotinib.

Conclusion: FIL200 and FIL100 were well tolerated with no unexpected safety signals in patients with moderately to severely active UC, regardless of previous biologic exposure or age.

ClinicalTrials.gov Identifiers (NCT numbers): NCT02914522, NCT02914535.

1 | INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease for which there are no known curative interventions.[1] Therefore, the medical management of UC relies on prolonged, and often lifelong, treatment. Furthermore, the global incidence and prevalence of UC is increasing.[2] Thus, there is a clear need to understand the long-term safety and benefit–risk profiles of UC treatments.

The primary aim of UC treatment is to induce and maintain clinical and endoscopic remission in order to achieve disease control, with the long-term goal of improving outcomes by reducing the rates of disability, colectomy and colorectal cancer.[3–5] For moderately to severely active disease, immunosuppressants and biologics are recommended.[6–11] Primary failure and/or loss of response to biologics occur in approximately 50% of patients, highlighting the need for effective new drugs with good safety profiles.[12] To address this unmet need, novel treatments, including small-molecule therapies, are becoming available.

Janus kinase (JAK) inhibitors are a class of small-molecule drug that block one or more of the intracellular tyrosine kinases (JAK1–3 and tyrosine kinase 2) involved in signal transmission of interleukins, thereby suppressing cytokine signalling and reducing inflammation.[13,14] JAK inhibitors act by competitively binding to the adenosine triphosphate (ATP)-binding pocket of JAK to prevent its enzymatic activity, and have been proven to be effective in inducing clinical and endoscopic remission in UC.[14,15]

Filgotinib (FIL) is a second-generation, once-daily, oral JAK1 preferential inhibitor that is approved for the treatment of UC and rheumatoid arthritis (RA).[16,17] The efficacy and safety of FIL for the treatment of moderately to severely active UC were evaluated in the phase 2b/3 SELECTION study.[5] The SELECTION study demonstrated that FIL 200 mg (FIL200) once daily was well tolerated and effective in inducing and maintaining clinical remission compared with placebo in both biologic-naive and biologic-experienced patients with UC. In this interim analysis, we aimed to integrate and evaluate the safety results from the SELECTION study and its ongoing long-term extension study SELECTIONLTE.

2 | MATERIALS AND METHODS

2.1 | Study designs

The SELECTION study (ClinicalTrials.gov ID: NCT02914522) was a phase 2b/3, double-blind, randomised, placebo-controlled trial designed to evaluate the efficacy and safety of FIL for the induction and maintenance of remission in patients with moderately to severely active UC. A detailed description of the SELECTION study methods is provided elsewhere.[5] In brief, patients 18–75 years of age who had moderately to severely active UC were randomised (2:2:1) to receive FIL200, FIL 100 mg (FIL100) or placebo once daily orally for up to 11 weeks. Primary and secondary endpoints were assessed after 10 weeks of treatment. At week 11, FIL induction responders were re-randomised 2:1 to continue their FIL induction dose or receive placebo maintenance treatment for 47 weeks (up to week 58). Induction responders were patients who either were in clinical remission (defined as a Mayo endoscopic subscore of 0 or 1, rectal bleeding subscore of 0 and at least a 1-point decrease in stool frequency from induction baseline to achieve a subscore of 0 or 1) or who had a Mayo Clinic Score (MCS) response (defined as a reduction of at least three points in MCS and at least 30% from induction baseline, with an accompanying decrease in rectal bleeding subscore of at least one point or an absolute rectal bleeding subscore of 0 or 1).[5] Responders to placebo at week 11 continued to receive placebo. Both biologic-naive and biologic-experienced patients were included in the SELECTION study (induction study A and induction study B respectively).

SELECTIONLTE (ClinicalTrials.gov ID: NCT02914535) was a phase 3 trial designed to assess the long-term safety of FIL, which included individuals who either completed or met efficacy discontinuation criteria in the SELECTION study. Completion of the SELECTION study was defined as completion of both an 11-week induction study and a 47-week maintenance study. Efficacy discontinuation criteria in SELECTION comprised either non-response to treatment, assessed at week 10 of the induction study, or disease worsening during the maintenance study. Patients who completed the SELECTION study continued with the same blinded dosing in SELECTIONLTE, which was unblinded when the last patient completed SELECTION. Patients who met efficacy discontinuation criteria were offered open-label FIL200 once daily in SELECTIONLTE, with the exception of non-dual refractory male patients in the USA and the Republic of Korea who were offered open-label FIL100 once daily.

Both SELECTION and SELECTIONLTE were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent prior to entering the SELECTION programme.

2.2 | Patient involvement

Patients were not involved in the design or analysis of this study.

2.3 | Population and analysis cohorts

Cohort 1 included patients from the SELECTION induction studies A (biologic-naive patients) and B (biologic-experienced patients) who received placebo, FIL100 or FIL200 once daily for up to 11 weeks. Cohort 2 included responders to FIL induction therapy who were re-randomised to continue their FIL induction dose or to receive placebo in the maintenance study for 47 weeks, and responders to induction placebo who remained receiving placebo during the maintenance study. Cohort 3 comprised all patients who entered SELECTION (cohort 1) and may have participated in the maintenance study (cohort 2) and/or in SELECTIONLTE.

2.4 | Adverse event assessments and definitions

Safety assessments included monitoring of adverse events (AEs), serious AEs, severe AEs, discontinuations due to AEs, concomitant medications and vital signs, and conductance of clinical laboratory measurements, electrocardiograms (ECGs) and physical examinations. AEs were assessed throughout the studies. Treatment-emergent AEs (referred to herein as AEs) were defined as those temporally associated with treatment, regardless of whether they were considered related to the study drug. AEs occurring no later than 30 days after the last induction dose (FIL or placebo) were attributed to the induction studies; except if patients subsequently entered the maintenance or SELECTIONLTE study within 30 days, in which case only AEs that occurred before the first maintenance or SELECTIONLTE dose were attributed to the induction studies (cohort 1). AEs occurring no later than 30 days after the last maintenance dose (and before the first SELECTIONLTE dose, if the patient entered the SELECTIONLTE study) were attributed to the maintenance study (cohort 2). AEs occurring no later than 30 days after the last SELECTIONLTE dose were attributed to the SELECTIONLTE study.

Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (version 22.1). The severity of AEs was graded using the modified Common Terminology Criteria for Adverse Events (CTCAE; version 4.03). If a CTCAE criterion did not exist for an AE, the maximum intensity of the AE observed was described as either grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening) or grade 5 (fatal). Severe AEs were defined as those of grade 3 or higher. Serious AEs were defined as those leading to death, immediate risk of death, inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity, a congenital anomaly, or any other events that may have jeopardised the patient or required an intervention to prevent one of the outcomes listed above, as assessed by the investigator.

Cardiovascular (CV) risk factors were defined as an age above 50 years, a medical history of chronic kidney disease, CV disease, diabetes, dyslipidaemia, hypertension, ischaemic central nervous system (CNS), pulmonary embolism or deep vein thrombosis, a family history of CV disease before the age of 50 years and smoking status (current or former smoker).[18] Additional risk factors included a medical history of asthma, an age of at least 65 years or a body mass index of at least 30.0 kg/m^{2}.

2.5 | Analysis

This interim analysis evaluated safety endpoints in cohorts 1 and 2, and in cohort 3 up to 24 February 2022 (cut-off date). In SELECTIONLTE, the longest duration of follow-up reached by any patient was 259 weeks at the time of this interim analysis.

The current analysis considered AEs of interest to be infections (all, serious, herpes zoster [HZ]), venous thromboembolic events (pulmonary embolism, deep vein thrombosis), major adverse CV events (MACE; defined as myocardial infarction, stroke or CV death), malignancies (excluding nonmelanoma skin cancers [NMSCs]) and NMSCs. MACE and venous thromboembolic events were reviewed by an independent adjudication committee.

Exposure-adjusted incidence rates (EAIRs) per 100 censored patient-years of exposure (cPYE) were reported overall by treatment group in cohort 3. For patients with an event, the cPYE was calculated from the event start date minus the first dosing date (within the same treatment period) plus 1 day and adjusted for years. For AEs occurring in more than one treatment period, the patient contributed to the EAIR for that AE for each treatment period. For patients without an event, the cPYE was calculated from the last dosing date minus the first dosing date plus 1 day and adjusted for years. Total patient-years of exposure (PYE) to treatment were calculated for each treatment. AEs of special interest (AESIs) were also analysed in subgroups of patients according to age (<65 years and ≥65 years), sex, prior use of biologic therapy and prior failure of biologic therapy. Biologic-experienced patients were defined as those who had an inadequate clinical response, loss of response or intolerance to a tumour necrosis factor alpha (TNF-α) antagonist and/or vedolizumab. 'Failure' of biologic therapy was defined as discontinuation of biologic therapy due to treatment failure. 'No failure' of biologic therapy was defined as no prior use of biologics or discontinuation of biologic therapy due to reasons other than failure (including intolerance, such as an allergic response to biologics). Dual-refractory patients were those in whom treatment with both a TNF-α antagonist and vedolizumab failed. Within each treatment group (or subgroup), 95% confidence intervals (CIs) were calculated using the exact Poisson distribution method.

3 | RESULTS

3.1 | Patient flow, characteristics and treatment exposure

In cohort 1 (induction studies), 279 patients received placebo and 1069 patients received FIL (Figure S1). For cohort 1, the overall mean age was 43 years, mean UC duration was 8.4 years and mean MCS was 9.0. Baseline characteristics were generally similar across treatment groups (Table 1). Overall, 664 patients responded to induction treatment and participated in the maintenance study (cohort 2) (Figure S1). Baseline characteristics for cohort 2 are shown in Table S1. In total, 1170 patients were enrolled and treated in SELECTIONLTE, of whom 873 received FIL200, 160 received FIL100 and 137 received placebo (Figure S1). Treatment exposure for FIL200, FIL100 and placebo in cohort 3 was 387.8, 585.9 and 2352.5 patient-years respectively.

3.2 | Overall, serious and severe adverse events

The EAIRs of AEs of interest in cohorts 1 and 2 are reported in Table S2. In cohort 3, the EAIR per 100 cPYE for all AEs was similar

TABLE 1 Baseline characteristics for cohort 1 (induction studies).

	Induction study A: biologic-naive patients			Induction study B: biologic-experienced patients		
	PBO (n = 137)	FIL 100 mg (n = 277)	FIL 200 mg (n = 245)	PBO (n = 142)	FIL 100 mg (n = 285)	FIL 200 mg (n = 262)
Age, years, mean ± SD	41 ± 12.9	42 ± 13.3	42 ± 13.1	44 ± 14.9	43 ± 14.3	43 ± 14.2
Female sex, n (%)	50 (36.5)	120 (43.3)	122 (49.8)	56 (39.4)	99 (34.7)	114 (43.5)
Race, n (%)						
Asian	38 (27.7)	79 (28.5)	77 (31.4)	27 (19.0)	51 (17.9)	50 (19.1)
Black or African-American	1 (0.7)	3 (1.1)	2 (0.8)	3 (2.1)	6 (2.1)	4 (1.5)
White	95 (69.3)	192 (69.3)	165 (67.3)	98 (69.0)	212 (74.4)	190 (72.5)
Other	3 (2.2)	3 (1.1)	1 (0.4)	14 (9.9)	16 (5.6)	18 (6.9)
Enrolled at US site, n (%)	19 (13.9)	33 (11.9)	14 (5.7)	21 (14.8)	58 (20.4)	36 (13.7)
Duration of UC, years, mean ± SD	6.4 ± 7.4	6.7 ± 7.4	7.2 ± 6.9	10.2 ± 8.2	9.7 ± 7.2	9.8 ± 7.6
MCS, mean ± SD	8.7 ± 1.3	8.6 ± 1.4	8.6 ± 1.3	9.3 ± 1.4	9.3 ± 1.3	9.2 ± 1.4
Mayo endoscopy subscore of 3, n (%)	76 (55.5)	159 (57.4)	133 (54.3)	111 (78.2)	222 (77.9)	203 (77.5)
C-reactive protein, mg/L, mean ± SD	5.8 ± 7.6	7.8 ± 17.4	8.6 ± 16.3	14.0 ± 24.3	11.7 ± 18.0	12.2 ± 14.9
Faecal calprotectin, μg/g, mean ± SD	2231 ± 2917	2001 ± 3448	2059 ± 2639	2479 ± 3571	2236 ± 3095	2845 ± 4077
Treatment history prior to induction baseline						
Prior use of at least one TNF-α antagonist, n (%)	N/A	2 (0.7)[a]	N/A	130 (91.5)	266 (93.3)	242 (92.4)
Prior use of vedolizumab, n (%)	N/A	1 (0.4)[a]	N/A	85 (59.9)	145 (50.9)	164 (62.6)
Prior use of at least one TNF-α antagonist and vedolizumab, n (%)	N/A	1 (0.4)[a]	N/A	76 (53.5)	128 (44.9)	147 (56.1)
Prior failure of a TNF-α antagonist and vedolizumab, n (%)	N/A	N/A	N/A	64 (45.1)	113 (39.6)	120 (45.8)
Systemic CS and IM[b] use at induction baseline						
Use of systemic CS only, n (%)	34 (24.8)	67 (24.2)	54 (22.0)	51 (35.9)	103 (36.1)	94 (35.9)
Prednisone-equivalent dose, mg/day, median (Q1–Q3)	20.0 (15.0–30.0)	15.0 (10.0–25.0)	20.0 (10.0–25.0)	20.0 (10.0–20.0)	20.0 (10.0–20.0)	15.0 (10.0–20.0)
Use of IM only, n (%)	33 (24.1)	63 (22.7)	53 (21.6)	21 (14.8)	34 (11.9)	34 (13.0)
Use of systemic CS and IM, n (%)	8 (5.8)	19 (6.9)	20 (8.2)	11 (7.7)	28 (9.8)	28 (10.7)

Note: FIL and PBO were administered once daily throughout all studies.

Percentages were calculated based on the number of patients in the safety analysis set.

Abbreviations: CS, corticosteroid; FIL, filgotinib; IM, immunomodulator; MCS, Mayo Clinic Score; N/A, not applicable; PBO, placebo; Q1, first quartile; Q3, third quartile; SD, standard deviation; TNF-α, tumour necrosis factor alpha; UC, ulcerative colitis.

[a]Four patients who had previously received TNF-α antagonist and/or vedolizumab, entered induction study A owing to protocol deviation.

[b]6-Mercaptopurine, azathioprine and methotrexate.

for FIL100 (167.39) and placebo (166.65), and numerically lower for FIL200 (122.96) (Table 2). Serious AEs occurred at a low frequency across treatment groups (EAIR: 7.94 [FIL200], 9.62 [FIL100] and 9.00 [placebo] per 100 cPYE). The EAIR per 100 cPYE for severe AEs was similar for FIL100 (15.00) and placebo (18.84), and numerically lower for FIL200 (10.55). The EAIR per 100 cPYE of AEs leading to hospitalisation was similar for FIL100 (9.07) and placebo (9.00), and numerically lower for FIL200 (7.57). The EAIR per 100 cPYE for AEs leading to discontinuation of study drug was similar for FIL200 (9.05) and placebo (10.73), and numerically higher for FIL100 (12.35).

3.3 | Infections

The EAIR per 100 cPYE for overall infections in cohort 3 was generally similar for FIL200 (37.07), FIL100 (35.66) and placebo (39.83) (Table 3). Serious infections occurred at a similarly low rate across treatment groups (EAIR: 2.39 [FIL200], 2.41 [FIL100] and 2.07 [placebo] per 100 cPYE). The EAIR per 100 cPYE for HZ in cohort 3 was 1.44 in patients receiving FIL200, 0.69 in patients receiving FIL100 and 0.26 in patients receiving placebo. All 39 cases of HZ were limited to cutaneous involvement. Treatment was withdrawn in three cases of HZ that occurred during SELECTIONLTE (FIL100 blinded [$n=1$], open-label FIL200 [$n=2$]), including in the one serious case of HZ that was reported. The serious case of HZ occurred during SELECTIONLTE in a patient receiving FIL200. The patient was 60 years old, had participated in induction study B (biologic-experienced) and had no concomitant use of corticosteroids (CS). The patient, who had underlying coronary heart disease, was hospitalised following an arteriovenous fistula and a carotid artery stenosis and, during hospitalisation, developed HZ involving the right face, with no intraocular or CNS involvement. The patient was treated with intravenous acyclovir, and FIL treatment was discontinued per the study protocol for managing complicated cases of HZ.

In the analysis of different age subgroups, the EAIR of all infections was numerically higher in those 65 years of age or older than in younger patients across treatment groups. Among FIL200- and FIL100-treated patients, the EAIR per 100 cPYE for HZ was numerically higher in those 65 years of age or older (2.93 and 3.37) than in younger patients (1.32 and 0.54). Among FIL-treated patients, the EAIR for serious infections was numerically higher in those 65 years of age or older than in younger patients.

The EAIR of all infections in cohort 3 was consistently numerically higher among biologic-experienced patients and patients in whom biologic therapy had failed (TNF-α or vedolizumab failure or dual refractory) than in biologic-naive patients and patients in whom biologic therapy had not failed, particularly in the placebo group (Figure 1).

3.4 | Thromboembolic events

The EAIRs of venous thromboembolic events in cohort 3 were low overall (0.09 [FIL200], 0.17 [FIL100] and 0.26 [placebo] per 100 cPYE) and the 95% CIs overlapped between treatment groups (Table S3). Details (severity, timing) of thromboembolic events and characteristics (demographics, risk factors) of the patients who experienced them are reported in Table S3.

3.5 | Major adverse cardiovascular events

The EAIR was low for all MACE across all treatment groups in cohort 3 (0.31 [FIL200], 0.35 [FIL100] and 0.52 [placebo] per 100 cPYE) (Table 4). In the analysis of the EAIR of MACE by age subgroup, patients 65 years of age or older who received FIL200 (EAIR: 1.73 per 100 cPYE) or FIL100 (EAIR: 3.37 per 100 cPYE) had a numerically higher EAIR for MACE overall than did younger patient groups receiving the same treatment (EAIR: 0.19 [FIL200] and 0.18 [FIL100]

TABLE 2 EAIRs of treatment-emergent AEs in cohort 3.

	PBO ($n=469$) PYE = 387.8		FIL 100 mg ($n=583$) PYE = 585.9		FIL 200 mg ($n=971$) PYE = 2352.5	
	n^a (%)	EAIR (95% CI)^b	n^a (%)	EAIR (95% CI)^b	n^a (%)	EAIR (95% CI)^b
Overall AEs	306 (65.2)	166.65 (148.5–186.4)	388 (66.6)	167.39 (151.1–184.9)	817 (84.1)	122.96 (114.7–131.7)
Serious AEs	34 (7.2)	9.00 (6.2–12.6)	53 (9.1)	9.62 (7.2–12.6)	176 (18.1)	7.94 (6.8–9.2)
Severe AEs	68 (14.5)	18.84 (14.6–23.9)	80 (13.7)	15.00 (11.9–18.7)	224 (23.1)	10.55 (9.2–12.0)
AEs leading to hospitalisation^c	34 (7.2)	9.00 (6.2–12.6)	50 (8.6)	9.07 (6.7–12.0)	168 (17.3)	7.57 (6.5–8.8)
AEs leading to discontinuation of study drug	41 (8.7)	10.73 (7.7–14.6)	71 (12.2)	12.35 (9.6–15.6)	210 (21.6)	9.05 (7.9–10.4)

Note: FIL and PBO were administered once daily throughout all studies.

Abbreviations: AE, adverse event; CI, confidence interval; cPYE, censored patient-years of exposure; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; PBO, placebo; PYE, patient-years of exposure.

[a]n = number of patients with at least one event of that category within the specific treatment group.

[b]EAIR per 100 cPYE = (total number of patients with an event/total cPYE) × 100. 95% CIs calculated using the exact Poisson distribution method.

[c]Including all events that resulted in initial or prolonged hospitalisation.

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TABLE 3 EAIRs of treatment-emergent infections in cohort 3, analysed by age.

	PBO (n = 469) PYE = 387.8		FIL 100 mg (n = 583) PYE = 585.9		FIL 200 mg (n = 971) PYE = 2352.5	
	n[a] (%)	EAIR (95% CI)[b]	n[a] (%)	EAIR (95% CI)[b]	n[a] (%)	EAIR (95% CI)[b]
All infections	118 (25.2)	39.83 (33.0–47.7)	150 (25.7)	35.66 (30.2–41.8)	512 (52.7)	37.07 (33.9–40.4)
<65 years	107 (24.6)	37.79 (31.0–45.7)	141 (25.9)	35.03 (29.5–41.3)	470 (51.9)	36.57 (33.3, 40.0)
≥65 years	11 (32.4)	83.93 (41.9–150.2)	9 (23.1)	49.86 (22.8–94.6)	42 (64.6)	43.67 (31.5–59.0)
Serious infection	8 (1.7)	2.07 (0.9–4.1)	14 (2.4)	2.41 (1.3–4.0)	56 (5.8)	2.39 (1.8–3.1)
<65 years	8 (1.8)	2.18 (0.9–4.3)	12 (2.2)	2.18 (1.1–3.8)	51 (5.6)	2.35 (1.8–3.1)
≥65 years	0	0.00 (0.0–18.7)	2 (5.1)	6.63 (0.8–23.9)	5 (7.7)	2.81 (0.9–6.5)
Herpes zoster[c,d]	1 (0.2)	0.26 (0.0–1.4)	4 (0.7)	0.69 (0.2–1.8)	33 (3.4)	1.44 (1.0–2.0)
<65 years	1 (0.2)	0.27 (0.0–1.5)	3 (0.6)	0.54 (0.1–1.6)	28 (3.1)	1.32 (0.9–1.9)
≥65 years	0	0.00 (0.0–18.7)	1 (2.6)	3.37 (0.1–18.8)	5 (7.7)	2.93 (1.0–6.8)

Note: FIL and PBO were administered once daily throughout all studies.

For PBO, there were 435 patients <65 years of age with 368.0 PYE and 34 patients ≥65 years of age with 19.7 PYE in total. For FIL 100 mg, there were 544 patients <65 years of age with 555.5 PYE and 39 patients ≥65 years of age with 30.4 PYE in total. For FIL 200 mg, there were 906 patients <65 years of age with 2173.7 PYE and 65 patients ≥65 years of age with 178.8 PYE in total.

Abbreviations: CI, confidence interval; cPYE, censored patient-years of exposure; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; PBO, placebo; PYE, patient-years of exposure.

[a]n = number of patients with at least one event of that category within the specific treatment group and age subgroup.

[b]EAIR per 100 cPYE = (total number of patients with an event/total cPYE) × 100. 95% CIs calculated using the exact Poisson distribution method.

[c]Excludes one case of disseminated cutaneous herpes zoster, which was reported for FIL 200 mg.

[d]Herpes zoster cases reported during the study were cutaneous only; one was a serious adverse event (FIL 200 mg).
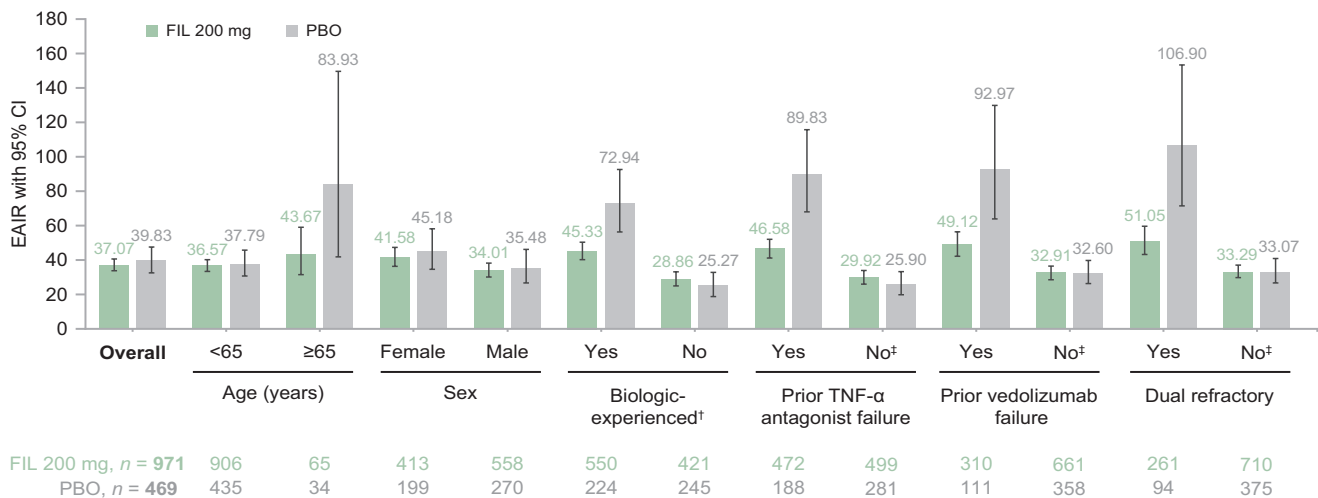

FIGURE 1 EAIRs (95% CI) for any treatment-emergent infection in cohort 3, analysed by patient subgroup. FIL and PBO were administered once daily throughout all studies. EAIR per 100 cPYE = (total number of patients with an event/total cPYE) × 100. 95% CIs calculated using the exact Poisson distribution method. [†]Patients were considered biologic-experienced (induction study B) if they demonstrated an inadequate clinical response, loss of response or intolerance to any TNF-α antagonist and/or vedolizumab. [‡]Patients were considered as not having failed biologic therapy if they were biologic-naive or were exposed to biologic therapy and stopped for reasons other than failure (including intolerance). CI, confidence interval; cPYE, censored patient-years of exposure; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; PBO, placebo; TNF-α, tumour necrosis factor alpha.

per 100 cPYE). Two cases of non-fatal stroke were reported in both FIL100 and placebo groups, and three cases were reported in the FIL200 group. At least one CV risk factor (age >50 years, asthma, body mass index ≥30.0 kg/m^2, chronic kidney disease, CV disease, diabetes, dyslipidaemia, hypertension, or current or former smoker) was identified in five out of seven patients who experienced a non-fatal stroke. A non-fatal myocardial infarction was experienced by one patient 65 years of age or older who received FIL200. At least one CV risk factor was identified in nine out of 11 patients who experienced any MACE (Table 5). The two patients who did not have a CV risk factor were receiving placebo when the MACE occurred.

TABLE 4 EAIRs for treatment-emergent MACE in cohort 3, analysed by age.

	PBO (n = 469) PYE = 387.8		FIL 100 mg (n = 583) PYE = 585.9		FIL 200 mg (n = 971) PYE = 2352.5	
	n[a] (%)	EAIR (95% CI)[b]	n[a] (%)	EAIR (95% CI)[b]	n[a] (%)	EAIR (95% CI)[b]
Overall MACE	2 (0.4)	0.52 (0.1–1.9)	2 (0.3)	0.35 (0.0–1.3)	7 (0.7)	0.31 (0.1–0.6)
<65 years	2 (0.5)	0.54 (0.1–2.0)	1 (0.2)	0.18 (0.0–1.0)	4 (0.4)	0.19 (0.1–0.5)
≥65 years	0	0.00 (0.0–18.7)	1 (2.6)	3.37 (0.1–18.8)	3 (4.6)	1.73 (0.4–5.1)
Non-fatal stroke	2 (0.4)	0.52 (0.1–1.9)	2 (0.3)	0.35 (0.0–1.3)	3 (0.3)	0.13 (0.0–0.4)
<65 years	2 (0.5)	0.54 (0.1–2.0)	1 (0.2)	0.18 (0.0–1.0)	3 (0.3)	0.14 (0.0–0.4)
≥65 years	0	0.00 (0.0–18.7)	1 (2.6)	3.37 (0.1–18.8)	0	0.0 (0.0–2.1)
Non-fatal myocardial infarction	0	0.00 (0.0–1.0)	0	0.00 (0.0–0.6)	1 (0.1)	0.04 (0.0–0.2)
<65 years	0	0.00 (0.0–1.0)	0	0.00 (0.0–0.7)	0	0.00 (0.0–0.2)
≥65 years	0	0.00 (0.0–18.7)	0	0.00 (0.0–12.4)	1 (1.5)	0.58 (0.0–3.2)
Myocardial infarction	0	0.00 (0.0–1.0)	0	0.00 (0.0–0.6)	2 (0.2)	0.09 (0.0–0.3)
<65 years	0	0.00 (0.0–1.0)	0	0.00 (0.0–0.7)	1 (0.1)	0.05 (0.0–0.3)
≥65 years	0	0.00 (0.0–18.7)	0	0.00 (0.0–12.4)	1 (1.5)	0.58 (0.0–3.2)
Cardiovascular death	0	0.00 (0.0–1.1)	0	0.00 (0.0–0.6)	3[c] (0.3)	0.13 (0.0–0.4)
<65 years	0	0.00 (0.0–1.0)	0	0.00 (0.0–0.7)	1 (0.1)	0.05 (0.0–0.3)
≥65 years	0	0.00 (0.0–18.7)	0	0.0 (0.0–12.4)	2 (3.1)	1.15 (0.1–4.2)

Note: FIL and PBO were administered once daily throughout all studies.

For PBO, there were 435 patients <65 years of age with 368.0 PYE and 34 patients ≥65 years of age with 19.7 PYE in total. For FIL 100 mg, there were 544 patients <65 years of age with 555.5 PYE and 39 patients ≥65 years of age with 30.4 PYE in total. For FIL 200 mg, there were 906 patients <65 years of age with 2173.7 PYE and 65 patients ≥65 years of age with 178.8 PYE in total.

Abbreviations: CI, confidence interval; cPYE, censored patient-years of exposure; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; MACE, major adverse cardiovascular events; PBO, placebo; PYE, patient-years of exposure.

[a]n = number of patients with at least one event of that category within the specific treatment group and age subgroup.

[b]EAIR per 100 cPYE = (total number of patients with an event/total cPYE) × 100. 95% CIs calculated using the exact Poisson distribution method.

[c]One patient experienced two serious adverse events (myocardial infarction and ischaemic stroke) that led to death.

3.6 | Malignancies

The EAIRs per 100 cPYE for malignancy (excluding NMSC) were 0.51, 1.20 and 0.00 for FIL200, FIL100 and placebo respectively (Table 6A). In the analysis of the EAIRs of malignancy (excluding NMSC) and NMSC analysed by age subgroup, patients receiving either FIL dose who were 65 years of age or older had numerically higher EAIRs than did younger patients (Table 6A). Four of the 19 malignancy (excluding NMSC) events reported (a case each of grade 4 colon cancer, grade 3 bladder carcinoma, grade 3 squamous cell carcinoma of middle rectum and grade 3 endometrial cancer) were considered related to FIL by the investigators. The patient who had grade 4 colon cancer (with onset on day 295) had received a screening colonoscopy prior to entering SELECTION. One NMSC case was reported in a patient younger than 65 years of age who received placebo. Details of malignancy (excluding NMSC) events, including malignancy type and duration of exposure based on the timing of diagnosis, are provided in Table 6B.

3.7 | Deaths

There were a total of eight AEs leading to death in cohort 3, all in patients treated with FIL200. Death from any cause (excluding COVID-19) was reported in four patients. In one of these four patients, death occurred owing to dyspnoea. Following medical review, it was determined that dyspnoea resulted from COVID-19 infection, therefore, the cause of death of this patient was also reported as COVID-19 infection. Three cardiovascular deaths occurred during the studies: two during the maintenance study and one during SELECTIONLTE (Table 5B). Patient 1 (FIL200; maintenance study), 66 years of age, underwent surgery for glaucoma following acute deterioration in visual acuity of the left eye. He died overnight in hospital (day 81 of the maintenance study), and postmortem examination revealed atherosclerotic cardiosclerosis. Patient 2 (FIL200; maintenance study), 65 years of age, reported worsening asthma on day 293 of the maintenance study and was subsequently prescribed treatment for allergy-induced asthma. He died at home 1 week later, with the cause of death adjudicated as being CV by an independent expert committee. Patient 3 (FIL200; SELECTIONLTE), 50 years of age, presented for the SELECTIONLTE week 48 (day 336) visit and was found to have non-Q wave myocardial infarction on ECG, with troponin elevation. He was admitted to hospital for treatment, but his condition worsened and he died 6 days later. Autopsy revealed aortic atherosclerosis without any recorded CV history. None of the deaths that occurred during the maintenance study or SELECTIONLTE

TABLE 5 Details for treatment-emergent MACE, excluding deaths (A) and including deaths (B), in cohort 3.

(A) Treatment (study period)	MACE details			Patient details and risk factors		
	AE	Severity[a]	Day of onset[b]	Age, years[c]/sex	Thrombocyte count[d] (×10³/μL)	Risk factors
PBO (IND)	Cerebrovascular accident	Grade 4	65[e]	37/M	512	No
PBO (IND)/PBO (MNT)	Haemorrhagic infarction	Grade 4	267[f]	35/F	377	No
FIL 100 mg (IND)/FIL 100 mg (MNT)	Transient ischaemic attack	Grade 2	313[f]	40/M	325	Dyslipidaemia; current smoker
PBO (IND)/FIL 200 mg (LTE)	Myocardial infarction	Grade 3	366[g]	70/M	199	Age >50 years; CV disease; dyslipidaemia; hypertension
FIL 100 mg (IND, MNT, LTE)	Spinal cord infarction	Grade 4	506[g]	66/M	202	Age >50 years; asthma; BMI ≥30.0 kg/m²; CV disease; diabetes; dyslipidaemia; hypertension
FIL 100 mg (IND)/FIL 200 mg (LTE)	Putamen haemorrhage	Grade 3	36[g]	43/M	333	Chronic kidney disease; diabetes; dyslipidaemia; hypertension
FIL 200 mg (LTE)	Cerebral artery occlusion	Grade 3	996	35/M	243	Hypertension
FIL 200 mg (LTE)	Thrombotic stroke	Grade 3	798	52/M	283	Age >50 years; DVT/PE; hyperglycaemia

(B) Treatment (study period)	AE leading to death			Patient details and risk factors				Related to study drug[h]
	AE	Severity[a]	Day of onset[b]	Age, years[c]/sex	Cause of death	Description	Risk factors	
FIL 200 mg (MNT)	Arteriosclerosis of coronary artery (autopsy)	Grade 4	81[f]	66/M	Left ventricular heart failure	Died in hospital following surgery for glaucoma	Age >50 years; chronic lung disease; DVT/PE; non-alcoholic fatty liver disease; former smoker	No
	Left ventricular failure (autopsy)	Grade 5						
FIL 200 mg (MNT)	Worsening asthma	Grade 1	293[f]	65/M	Cardiovascular	Died at home on day 302[f] following treatment for allergy-induced asthma	Age >50 years; asthma; BMI ≥30.0 kg/m²; hypertension; former smoker	No
	Exacerbated asthma	Grade 5	298[f]					
FIL 200 mg (LTE)	Myocardial infarction	Grade 5	336[g]	50/M	Myocardial infarction	Found to have non-Q wave myocardial infarction on ECG with troponin elevation (>6× ULN). Admitted to hospital; on day 342[g], developed signs of cerebral infarction and died a few hours later	Age >50 years; asthma; aortic atherosclerosis (autopsy)	No
	Ischaemic stroke	Grade 5	342[g]					

Note: FIL and PBO were administered once daily throughout all studies.

Abbreviations: AE, adverse event; BMI, body mass index; CI, confidence interval; CV, cardiovascular; DVT, deep vein thrombosis; ECG, electrocardiogram; F, female sex at birth; FIL, filgotinib; IND, induction; LTE, long-term extension (SELECTIONLTE study); M, male sex at birth; MACE, major adverse cardiovascular events; MNT, maintenance; PBO, placebo; PE, pulmonary embolism; PYE, patient-years of exposure; ULN, upper limit of normal.

[a]Severity grade was based on Common Terminology Criteria for Adverse Events (version 4.03).

[b]Day was the number of study days relative to the date of the first dose of the study drug for the listed treatment period.

[c]Age was based on induction baseline.

[d]Closest available laboratory value at AE onset.

[e]Induction study period.

[f]Maintenance study period.

[g]LTE study period.

[h]According to investigator.

were considered related to the study drug, as assessed by the investigators.

4 | DISCUSSION

This interim integrated safety analysis included data from 1348 patients with moderately to severely active UC, representing 3326.2 PYE, who were treated with FIL or placebo in the SELECTION study and the ongoing SELECTIONLTE study. Overall, FIL was found to be well tolerated and have an acceptable safety profile. All AEs, serious AEs, AEs leading to hospitalisation or study drug discontinuation, and infections occurred at generally similar rates across treatment groups, and the rates of severe AEs, thromboembolic events and HZ were generally low.

The overall risk of infection (EAIR: 37.07 per 100 cPYE) reported for FIL200 in this integrated analysis, including induction, maintenance and long-term extension data (cohort 3) from SELECTION, is slightly lower than that reported in patients with UC receiving the pan-JAK (JAK1–3) inhibitor tofacitinib (5 and 10 mg; incidence rate [IR]: 50.4 per 100 PYE) and the anti-integrin vedolizumab (EAIR: 56.8 per 100 PYE).[6,19] In the subgroup analysis, the rate of all infections was consistently numerically higher among biologic-experienced patients and patients with prior failed biologic therapy than in biologic-naive patients and patients without prior biologic failure, particularly in the placebo group. Patients with inflammatory bowel disease (IBD) are at an increased risk of infection compared with matched controls, and biologic treatment has been associated with an additional infection risk in these patients.[20] The numerically higher infection rate reported in biologic-experienced placebo-treated patients than in FIL200-treated patients in this study suggests that uncontrolled UC may be a driving factor for infections.[20] It is plausible that the better control of inflammation among FIL-treated patients (as reported by Feagan et al.),[5] as observed with vedolizumab,[6] contributed to this observation in this subgroup of refractory patients.

The low EAIRs of serious infection reported across all treatment groups (EAIR: 2.07–2.41 per 100 cPYE) were in line with the IRs reported for prolonged UC treatment with adalimumab (IR: 3.4 per 100 PYE), vedolizumab (IR: 1.8 per 100 PYE) and tofacitinib (5 and 10 mg; IR: 1.7 per 100 PYE).[19,21,22]

The role of JAK1 and JAK3 in the antiviral response suggests that their inhibition predisposes patients to an increased risk of viral infection.[23] A meta-analysis of 43 controlled studies in patients with an immune-mediated disease, of which seven studies were in patients with IBD, showed that the incidence of HZ per 100 PYE was higher in patients who received a JAK inhibitor (tofacitinib [1.62], baricitinib [2.16], upadacitinib [3.92] or FIL [1.83]) than in those who received placebo and/or an active comparator (1.23).[24] Notably, in patients with UC, the OCTAVE trials reported higher rates of HZ with tofacitinib than with placebo, and real-world data showed this incidence to be 6.9 per 100 PYE.[25,26] Other types of UC treatment have been associated with a higher risk of HZ than JAK inhibitors, including the TNF-α antagonist

adalimumab (EAIR: 4.2 per 100 PYE), suggesting that disease susceptibility factors might influence the HZ risk.[27] Accordingly, recombinant HZ vaccination is now recommended for patients with IBD.[28] Although HZ occurred at a numerically higher rate with FIL200 (EAIR: 1.44 per 100 cPYE) than with placebo (EAIR: 0.26 per 100 cPYE) in the current study, the 95% CIs for the FIL200 group overlapped with those of the placebo group. Together with other studies, the results herein could suggest that preferential JAK1 inhibition by FIL may preserve JAK3 signalling, thereby leading to the low rate of HZ reported for the SELECTION programme.[24,29–31] Further studies are warranted to investigate the interaction between drug selectivity and safety.

A cut-off of 65 years was used in the subgroup analysis to align with recent SmPC changes that recommended the use of filgotinib in patients aged at least 65 years only if alternative treatments are not available.[16,17] An elevated risk of HZ was observed in patients treated with FIL200 who were 65 years of age or older (EAIR: 2.93 per 100 cPYE) compared with younger patients (EAIR: 1.32 per 100 cPYE). Similarly, tofacitinib was previously reported to be associated with a higher incidence of HZ in patients 65 years of age or older (IR: 9.6 per 100 PYE) than in younger patients (IR: 3.7 per 100 PYE).[32] This observation is in line with the well-known phenomenon of increased susceptibility to HZ with increasing age.[32–34]

Another important consideration for the use of JAK inhibitors in patients with UC is the increased risk of HZ reported in Asian patients compared with non-Asian patients.[15] High rates per 100 PYE of HZ have been reported in Asian patients with UC treated with tofacitinib (IR: 6.5) and upadacitinib (EAIR: 10.7 [15 mg] and 17.0 [30 mg]).[32,35] In a post hoc analysis of the phase 2b/3 SELECTION study including 102 Japanese patients, no new safety signals were noted and AEs, including HZ, occurred at similar frequencies in Japanese patients compared with the overall SELECTION population.[36]

Patients with IBD have a 2–3-fold increased risk of thromboembolic events, such as deep vein thrombosis and pulmonary embolism, compared with the general population, highlighting the importance of monitoring this potential risk.[37] In the current analysis, thromboembolic events were limited in number and the rates were similarly low in the placebo and FIL groups, with no indication of an enhanced risk in patients receiving either FIL dose.

Pan-JAK inhibition may be associated with AEs such as MACE and malignancy.[15,18] In the ORAL Surveillance study, the risks of cancer and MACE were higher among patients with RA (50 years or older, with at least one CV risk factor) who received tofacitinib than among those who received TNF-α antagonist therapy.[18] Similar safety signals were not reported for tofacitinib in the overall cohort of the UC clinical programme, and safety profile comparisons of tofacitinib and TNF inhibitors are not available in UC.[38] Herein, all FIL-treated patients who experienced MACE had at least one CV risk factor, and a limited number of malignancy (including NMSC) events were reported in general.

The age of patients seemed to have limited impact on the safety profile of FIL in this analysis. A limitation of our analysis is that patients older than 75 years were excluded from the studies and only 138 patients were above 65 years of age. In the age subgroup analysis,

TABLE 6 EAIRs for treatment-emergent malignancies analysed by age (A), and malignancy (excluding NMSC) event details (B), in cohort 3.

(A)	PBO (n = 469) PYE = 387.8		FIL 100 mg (n = 583) PYE = 585.9		FIL 200 mg (n = 971) PYE = 2352.5	
	n[a] (%)	EAIR (95% CI)[b]	n[a] (%)	EAIR (95% CI)[b]	n[a] (%)	EAIR (95% CI)[b]
Malignancy[c]	0	0.00 (0.0–1.0)	7 (1.2)	1.20 (0.5–2.5)	12 (1.2)	0.51 (0.3–0.9)
<65 years	0	0.00 (0.0–1.0)	6 (1.1)	1.08 (0.4–2.4)	8 (0.9)	0.37 (0.2–0.7)
≥65 years	0	0.00 (0.0–18.7)	1 (2.6)	3.30 (0.1–18.4)	4 (6.2)	2.25 (0.6–5.7)
NMSC	1 (0.2)	0.26 (0.0–1.4)	2 (0.3)	0.34 (0.0–1.2)	14 (1.4)	0.60 (0.3–1.0)
<65 years	1 (0.2)	0.27 (0.0–1.5)	1 (0.2)	0.18 (0.0–1.0)	9 (1.0)	0.42 (0.2–0.8)
≥65 years	0	0.00 (0.0–18.7)	1 (2.6)	3.88 (0.1–21.6)	5 (7.7)	2.96 (1.0–6.9)

(B) Treatment sequence	Patient details Age, years[d]/sex	AE details AE	Severity[e]	Day of onset[f]	Related to study drug[g]
FIL 200 mg	54/F	Breast cancer	Grade 2	53	No
FIL 200 mg/**FIL 200 mg**	36/F	Malignant melanoma	Grade 3	221	No
FIL 200 mg/FIL 200 mg/**FIL 200 mg**	44/F	Uterine leiomyosarcoma	Grade 4	36	No
FIL 200 mg/FIL 200 mg/**FIL 200 mg**	65/M	Metastatic carcinoid tumour	Grade 3	336	No
FIL 200 mg/NA/**FIL 200 mg**	66/M	Prostate cancer	Grade 2	244	No
FIL 200 mg/NA/**FIL 200 mg**	57/F	Adenocarcinoma of colon	Grade 4	260	No
FIL 200 mg/NA/**FIL 200 mg**	66/M	Oesophageal adenocarcinoma	Grade 3	393	No
FIL 200 mg/NA/**FIL 200 mg**	54/M	Squamous cell carcinoma of middle rectum	Grade 3	1137	Yes
FIL 100 mg/NA/**FIL 200 mg**	58/M	Colon cancer	Grade 4	295	Yes
FIL 100 mg/NA/**FIL 200 mg**	68/F	Endometrial cancer	Grade 3	555	Yes
PBO/NA/**FIL 200 mg**	34/F	Clear cell renal cell carcinoma	Grade 3	113	No
PBO/NA/**FIL 200 mg**	21/F	Adenocarcinoma of colon	Grade 3	218	No
FIL 100 mg/FIL 100 mg	64/M	Colon cancer[h]	Grade 2	71	No
FIL 100 mg/FIL 100 mg/**FIL 100 mg**	36/M	Renal cell carcinoma	Grade 3	407	No
FIL 100 mg/FIL 100 mg/**FIL 100 mg**	60/F	Breast cancer	Grade 4	437	No
FIL 100 mg/FIL 100 mg/**FIL 100 mg**	57/F	Bladder transitional cell carcinoma	Grade 3	1108	Yes
FIL 100 mg/PBO/**FIL 100 mg**	71/M	Papillary renal cell carcinoma	Grade 3	166	No
PBO/NA/**FIL 100 mg**	58/M	Plasma cell myeloma	Grade 4	535	No
PBO/NA/**FIL 100 mg**	54/M	Adenocarcinoma of colon	Grade 3	864	No

Note: FIL and PBO were administered once daily throughout all studies.

For PBO, there were 435 patients <65 years of age with 368.0 PYE and 34 patients ≥65 years of age with 19.7 PYE in total. For FIL 100 mg, there were 544 patients <65 years of age with 555.5 PYE and 39 patients ≥65 years of age with 30.4 PYE in total. For FIL 200 mg, there were 906 patients <65 years of age with 2173.7 PYE and 65 patients ≥65 years of age with 178.8 PYE in total.

Bold text indicates the treatment during which the malignancy event occurred.

Abbreviations: AE, adverse event; CI, confidence interval; cPYE, censored patient-years of exposure; EAIR, exposure-adjusted incidence rate; F, female sex at birth; FIL, filgotinib; M, male sex at birth; NA, not applicable; NMSC, nonmelanoma skin cancer; PBO, placebo; PYE, patient-years of exposure.

[a]n = number of patients with at least one event of that category within the specific treatment group and age subgroup.

[b]EAIR per 100 cPYE = (total number of patients with an event/total cPYE) × 100. 95% CIs calculated using the exact Poisson distribution method.

[c]Excluding NMSC.

[d]Age was based on induction baseline.

[e]Severity grade was based on the Common Terminology Criteria for Adverse Events (version 4.03).

[f]Day was the number of study days relative to the date of the first dose of the study drug for the listed treatment period.

[g]According to investigator.

[h]The severity of this colon cancer case changed from grade 2 to grade 3 on day 159 and the patient discontinued treatment.

(Continues)

an increased risk for infections was reported in patients 65 years of age or older compared with younger patients across treatment groups; nonetheless, the risk was numerically lower with FIL than with placebo. There was no increased risk of serious infection among patients receiving FIL200 treatment who were 65 years of age or older compared with younger patients. For FIL100 treatment, the rate of serious infections was numerically higher in patients 65 years of age or older than in younger patients; however, wide CIs were reported. Importantly, age has been reported as one of the main risk factors for malignancy, for example in the Swiss IBD Cohort study, but not for malignancy-related hospitalisations in vedolizumab- and ustekinumab-treated patients with IBD.[39,40] A numerically higher frequency of malignancy (including NMSC) in patients treated with FIL who were 65 years of age or older than in younger patients was also observed in the current study. Age-related increases in the incidences of malignancy and MACE in cohort 3 are in line with previously reported data for the same age groups in the general population, suggesting no drug-related increase in risk in older patients.[41–43] Furthermore, the observed age-related increases in our study appear to be generally consistent with the rates of malignancy (IR: 2.05 [0.56–5.25] per 100 PYE) and MACE (IR: 1.06 [0.13–3.81] per 100 PYE) in the tofacitinib UC clinical programme in patients aged 65 years or older.[44] The incidence of malignancy with other advanced therapies, specifically vedolizumab, was reported as 17.6 per 1000 patient-years in a nationwide retrospective cohort study of patients with IBD aged 65 years or older.[45] Overall, there was no trend observed in the diagnosis of certain types of tumour and four malignant events were considered related to FIL treatment by investigators. Eleven out of 19 malignancies were diagnosed within a short period of exposure (1 year) and, therefore, seem less likely to be related to treatment given the chronic nature of malignancy, suggesting that there was no causality between FIL and malignancy.

Owing to study design constraints leading to shorter exposure durations for the placebo (387.8 PYE) and FIL100 (585.9 PYE) groups than the FIL200 group (2352.5 PYE), it was not feasible to compare EAIRs between treatment groups in the analysed cohort. Furthermore, the findings in the placebo group should be interpreted with caution owing to how AEs were attributed in this study. For example, an AE occurring in the maintenance study in a patient receiving placebo would be attributed to placebo, even though the patient may have received FIL200 or FIL100 for up to 11 weeks in the induction study. Another limitation of this analysis is the small number of patients included in the older age groups, meaning fewer PYE. The population size in this analysis is smaller than in FIL safety studies conducted for non-IBD immune-mediated diseases, including RA. Nonetheless, the results reported herein are consistent with the integrated safety data of FIL in patients with RA.[46] Additional limitations include the rarity of AEs such as serious infections, thromboembolic events, MACE and malignancies, and the type of analysis (interim) conducted. A further limitation is the study being prone to selection bias, meaning that the study population may not necessarily represent the real-world population. A longer follow-up of the SELECTIONLTE patients, studies in high-risk subgroups of patients

and analysis of real-world long-term data, including the registration of comorbidities and concomitant medication, are still warranted to elucidate the relative risks of these events fully in FIL-treated patients.

Our current data suggest that FIL has an acceptable safety profile pertaining to infection risk, which is consistent with JAK1 preferential inhibition. Many of the AEs of special interest associated with the JAK inhibitor class of drugs were not detected in the current dataset. This may reflect that these events are expected to occur infrequently in UC populations and the relatively young population in the SELECTION programme. It may also be due to exposure to doses of FIL that are consistently below the maximum dose (as evaluated in phase 1 studies)[47] while retaining its preferential inhibition of JAK1 versus JAK2/JAK3.[48] Based on in vitro cellular cytokine assays using blood from healthy donors and patients with RA, FIL at a dose of 200 mg inhibited JAK1-mediated signalling similarly to other JAK inhibitors but showed less inhibition of JAK2-dependent and JAK3-dependent signalling pathways.[48] This observation provides a potential mechanistic rationale for the apparently differentiated efficacy:safety profile of FIL as compared with other JAK inhibitors.[48] Future integrated safety analyses will include a longer follow-up period and may be combined with data from FIL in other indications.

5 | CONCLUSION

In summary, this integrated safety analysis of data from SELECTION and SELECTIONLTE demonstrated that FIL was well tolerated and had an acceptable safety profile in patients with moderately to severely active UC, independent of previous biologic exposure or age.

AUTHOR CONTRIBUTIONS

Stefan Schreiber: Conceptualization (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Gerhard Rogler:** Conceptualization (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Mamoru Watanabe:** Conceptualization (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Séverine Vermeire:** Conceptualization (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Christian Maaser:** Conceptualization (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Silvio Danese:** Conceptualization (equal); methodology (equal); writing – review and editing (equal). **Margaux Faes:** Data curation (equal); formal analysis (equal); investigation (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Paul Van Hoek:** Writing – review and editing (equal). **Jeremy Hsieh:** Conceptualization (equal); writing – review and editing (equal). **Ulrik Moerch:** Conceptualization (equal); writing – review and editing (equal). **Yan Zhou:** Data curation (equal); formal analysis (equal); investigation (equal); validation (equal); visualization (equal); writing – review and editing (equal). **Angela de Haas:** Conceptualization (equal); methodology (equal); writing – review and editing (equal). **Christine Rudolph:** Conceptualization (equal); methodology (equal); writing – review and editing (equal).

Alessandra Oortwijn: Conceptualization (equal); methodology (equal); writing – review and editing (equal). **Edward V. Loftus Jr:** Conceptualization (equal); investigation (equal); methodology (equal); writing – review and editing (equal). All authors approved the final version.

CONFLICT OF INTEREST STATEMENT

Stefan Schreiber has served as a speaker for AbbVie, Amgen, Arena Pharmaceuticals, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Dr Falk Pharma, Ferring Pharmaceuticals, Fresenius, Galapagos/Gilead, I-Mab, Janssen, Lilly, MSD, Mylan, Pfizer, Protagonist Therapeutics, ProventionBio, Sandoz/Hexal, Takeda, Theravance and UCB. Gerhard Rogler has served as a consultant for AbbVie, Arena Pharmaceuticals, Augurix, Boehringer Ingelheim, Bristol Myers Squibb, Calypso, Celgene, Dr Falk Pharma, Ferring Pharmaceuticals, Fisher, Genentech, Gilead Sciences, Janssen, MSD, Novartis, Pfizer, Phadia, Roche, Takeda, Tillotts, UCB, Vifor, Vital Solutions and Zeller; a speaker for AbbVie, AstraZeneca, Bristol Myers Squibb, Celgene, Dr Falk Pharma, Janssen, MSD, Pfizer, Phadia, Takeda, Tillotts, UCB, Vifor and Zeller; and has received educational funding and research funding from AbbVie, Ardeypharm, Augurix, Calypso, Dr Falk Pharma, Flamentera, MSD, Novartis, Pfizer, Roche, Takeda, Tillotts, UCB and Zeller. Mamoru Watanabe has received funding from AbbVie, Alfresa Pharma, EA Pharma, Kissei, Kyorin, Mitsubishi Tanabe Pharma, Mochida, Nippon Kayaku, Takeda and Zeria; has served as a consultant and/or speaker for AbbVie, EA Pharma, Eli Lilly Japan, Gilead Sciences, Janssen, JIMRO, Kissei, Mitsubishi Tanabe Pharma, Mochida, Nippon Boehringer Ingelheim, Pfizer Japan, Takeda and Zeria. Séverine Vermeire has received funding from AbbVie, Galapagos, Johnson & Johnson, Pfizer and Takeda; has served as a consultant and/or speaker for AbbVie, AbolerIS Pharma, AgomAb, Alimentiv, Arena Pharmaceuticals, AstraZeneca, Avaxia, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, CVasThera, CytoKi Pharma, Dr Falk Pharma, Ferring Pharmaceuticals, Galapagos, Genentech-Roche, Gilead Sciences, GSK, Hospira, IMIdomics, Janssen, Johnson & Johnson, Lilly, Matéria Prima, MiroBio, Morphic, MRM Health, MSD, Mundipharma, Pfizer, Prodigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Surrozen, Takeda, Theravance, Tillotts and Zealand Pharma. Christian Maaser has served as a consultant and/or speaker for AbbVie, Biogen, Dr Falk Pharma, Ferring Pharmaceuticals, Galapagos, Gilead Sciences, Janssen, Pfizer, Takeda and Vifor. Silvio Danese has served as a consultant for AbbVie, Alimentiv, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Dr Falk Pharma, Enthera, Ferring Pharmaceuticals, Gilead Sciences, Hospira, Inotrem, Janssen, Johnson & Johnson, Lilly, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, TiGenix, UCB and Vifor. Edward V. Loftus Jr has served as a consultant for AbbVie, Alvotech, Amgen, Arena Pharmaceuticals, Avalo Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion Healthcare, Fresenius Kabi, Genentech, Gilead Sciences, GSK, Gossamer Bio, Iterative Scopes, Janssen, KSL Diagnostics, Lilly, Morphic Therapeutic, Ono Pharma, Pfizer, Protagonist Therapeutics, Scipher Medicine, Sun Pharma, Surrozen, Takeda and UCB; and has received research funding from AbbVie, Bristol Myers Squibb, Celgene, Genentech, Gilead Sciences, Gossamer Bio, Janssen, Pfizer, Receptos, Robarts Clinical Trials, Takeda, Theravance and UCB. Margaux Faes, Paul Van Hoek, Angela de Haas, Christine Rudolph and Alessandra Oortwijn are employees and shareholders of Galapagos NV. Jeremy Hsieh, Ulrik Moerch and Yan Zhou are employees and shareholders of Gilead Sciences.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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