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Integrated safety analysis of filgotinib in patients with moderately to severely active rheumatoid arthritis receiving treatment over a median of 1.6 years

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ABSTRACT

Objective To characterise safety of the Janus kinase-1 preferential inhibitor filgotinib in patients with moderately to severely active rheumatoid arthritis.

Methods Data were integrated from seven trials (NCT01668641, NCT01894516, NCT02889796, NCT02873936, NCT02886728, NCT02065700, NCT03025308). Results are from placebo (PBO)-controlled (through week (W)12) and long-term, as-treated (all available data for patients receiving ≥1 dose filgotinib 200 (FIL200) or 100 mg (FIL100) daily) datasets. We calculated exposure-adjusted incidence rates (EAIRs)/100 patient-years filgotinib exposure (100PYE) for treatment-emergent adverse events (TEAEs).

Results 3691 patients received filgotinib for 6080.7 PYE (median 1.6, maximum 5.6 years). During the PBO-controlled period, TEAEs, including those of grade ≥3, occurred at comparable rates with filgotinib or PBO; long-term EAIRs of TEAEs grade ≥3 were 6.4 and 7.6/100PYE for FIL200 and FIL100. EAIRs for deaths were 0.6/100PYE for FIL200, FIL100 and PBO; long-term EAIRs were 0.5 and 0.3/100PYE for FIL200 and FIL100. EAIRs for serious infection were 3.9, 3.3 and 2.4/100PYE for FIL200, FIL100 and PBO; long-term EAIRs were 1.6 and 3.1/100PYE for FIL200 and FIL100. EAIRs for herpes zoster were 0.6, 1.1, and 1.1/100PYE for FIL200, FIL100 and PBO; long-term EAIRs were 1.8 and 1.1/100PYE for FIL200 and FIL100. EAIRs for major adverse cardiovascular events were 0, 1.7 and 1.1/100PYE for FIL200, FIL100 and PBO; long-term EAIRs were 0.4 and 0.6/100PYE for FIL200 and FIL100. No venous thromboembolism occurred during the PBO-controlled period; long-term EAIRs were 0.2 and 0/100PYE for FIL200 and FIL100.

Conclusions Over a median of 1.6 and maximum of 5.6 years of exposure, safety/tolerability of FIL200 and FIL100 were similar, with a lower incidence of infections with FIL200 among the long-term, as-treated dataset.

Key messages

What is already known about this subject?

- Filgotinib is an oral, preferential Janus kinase-1 inhibitor approved in Europe and Japan for treatment of rheumatoid arthritis (RA).
- In previous clinical trials, filgotinib treatment resulted in improvement in RA signs and symptoms, improvement in physical function, reduced radiographic progression, and improvement in quality of life for patients across the spectrum, from methotrexate-naïve to biologic-refractory RA.
- Filgotinib was generally well tolerated in previous trials and had safety similar to active comparators methotrexate and adalimumab up to 52 weeks.

What does this study add?

- This integrated analysis of safety data from seven clinical trials characterises both the short-term safety compared with placebo (PBO) for 777 and 788 patients receiving filgotinib 200 and 100 mg and long-term safety of filgotinib 200 and 100 mg in patients with RA exposed for 4047.7 and 2032.9 patient-years (median 1.6 and 1.3 years; maximum 5.6 and 4.7 years).
- Overall, both filgotinib 200 and 100 mg were generally well tolerated. Proportions of patients treated with filgotinib 200 and 100 mg who developed infections and serious infections were higher versus PBO. Opportunistic infections, herpes zoster infections, major adverse cardiac events, and venous thromboembolism were infrequently reported. Longer-term study of filgotinib will further elucidate this safety profile.

INTRODUCTION

The oral, Janus kinase-1 (JAK1) preferential inhibitor filgotinib has demonstrated efficacy in rheumatoid arthritis (RA) in phase 2 and 3 trials up to 52 weeks.[1–5] Treatment with filgotinib 200 and 100 mg once daily improved RA signs and symptoms, improved physical function, reduced radiographic progression and improved health-related quality of life across patient populations.[1–5] Filgotinib safety up to 52 weeks was comparable to active comparators (methotrexate, adalimumab) in phase

Key messages

How might this impact on clinical practice or future developments?

- This integrated analysis of PBO-controlled and as-treated extension-study datasets describes the safety of filgotinib as treatment of RA.
- Over a median of 1.6 and maximum of 5.6 years of exposure, safety/tolerability of filgotinib 200 and 100 mg were similar, with a lower incidence of infections with filgotinib 200 mg among the long-term, as-treated dataset.

3 trials.[4 5] Most events occurred in similar proportions across treatments.[1–5]

It has been hypothesised that selectivity for JAK1 may preserve the efficacy benefit seen with less selective JAK inhibitors, while limiting the JAK2- and JAK3-mediated safety and tolerability concerns.[6] Based on a study of in vitro cellular assays and clinical pharmacokinetics of filgotinib, baricitinib, tofacitinib and upadacitinib, filgotinib demonstrated reduced JAK2 and JAK3 activity while maintaining comparable inhibition of JAK1. However, the clinical relevance of JAK selectivity remains unclear.[6]

Here, we use an integrated analysis across seven trials, including long-term extensions (LTEs), to evaluate the safety of filgotinib among patients with RA treated for a median of 1.6 (and up to 5.6) years, with attention to adverse events of special interest (AESIs) with JAK inhibition.

METHODS

Study designs

Patient-level data were integrated from two phase 2 (NCT01668641, NCT01894516), three phase 3 (NCT02889796, NCT02873936, NCT02886728) and phases 2 and 3 LTE trials (NCT02065700, NCT03025308) (table 1). Data from patients receiving monotherapy and concomitant conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) were combined per filgotinib dose. Trials are summarised in online supplemental methods, and the phase 3 LTE protocol is available as supplemental file 2.[1–5 7] All data from patients receiving filgotinib 200 or 100 mg once a day or placebo from completed trials were included. Data from ongoing phase 2 and 3 LTEs were included through 26 April 2019 and 16 September 2019.

Eligible patients were aged ≥18 years with a diagnosis of RA per European League Against Rheumatism/American College of Rheumatology 2010 criteria.[8] Eligible patients were to have swollen and tender joint counts ≥6 and, depending on the study, either documented erosions or elevated serum C reactive protein (CRP).[1–5] Exclusion criteria included recent or active infections, major adverse cardiovascular events (MACE) within 6 months prior to screening, and specified abnormal laboratory results at screening.[1–5] Interruption of study drug was to be considered for any patient who developed an infection during the studies; those with specific laboratory abnormalities (eg, sequential elevations of aspartase aminotransferase or alanine aminotransferase >3× the upper limit of normal with either elevated bilirubin or with symptoms of hepatic injury) were to have study drug discontinued. The protocols for the phase 2 studies required study drug discontinuation for any QuantiFERON (QF) tuberculosis (TB) test positivity during the study, independent of clinical diagnosis. Also, in the phase 2 trials only, lymphopaenia (two sequential lymphocyte counts <500/mm^3) and elevated creatinine (two sequential increases in serum creatinine >50% over the average of screening and baseline values) were criteria for study drug discontinuation. In the phase 3 studies, drug interruption was required per local standard of care for QF TB-positive tests and newly diagnosed latent TB.

Patient and public involvement

Patients were not involved in research design, conduct or reporting. Patients were recruited by individual sites and provided written, informed consent.

Table 1 Key features of filgotinib RA phases 2 and 3 studies

	Required background medication			Control		Protocol-defined rerandomisation to FIL
	None	MTX	csDMARD(s)	PBO	Active comparator	
Phase 3 studies						
FINCH 1 NCT02889796		X		24 weeks	52 weeks (ADA)	PBO patients at week 24
FINCH 2 NCT02873936			X	24 weeks		
FINCH 3* NCT02886728	X			NA	52 weeks (MTX)	
FINCH 4 (LTE) NCT03025308	X†			NA		At study entry‡
Phase 2 Studies						
DARWIN 1 NCT01668641		X		24 weeks		Non-responders at week 12
DARWIN 2 NCT01894516	X			12 weeks		PBO patients and nonresponders at week 12
DARWIN 3 (LTE) NCT02065700	X§			NA		At study entry¶

*In addition to filgotinib 200 mg +MTX and filgotinib 100 mg +MTX, this trial included a filgotinib 200 mg monotherapy treatment arm.
†Patients continued to receive parent study protocol-approved background medication; patients in FINCH 3 receiving MTX discontinued on enrolment in FINCH 4.
‡All patients who received FIL at the time of completion of parent study continued to receive blinded FIL dose (100 mg once a day or 200 mg once a day). Patients who received ADA, PBO or MTX monotherapy, or who completed FINCH 2 on standard of care, were rerandomised at LTE entry to receive either FIL 100 mg or FIL 200 mg. Patients from FINCH 1 and FINCH 3 who completed parent study on standard of care were not eligible.
§Patients were permitted to restart background MTX therapy if deemed necessary by the investigator.
¶Patients who received FIL 200 mg once a day or FIL 100 mg two times per day at the time of completion of parent study continued to receive the same FIL dose in the LTE study. Patients who received FIL 25 mg two times per day, FIL 50 mg once a day, FIL 50 mg two times per day or FIL 100 mg at the time of completion of parent study were assigned either FIL 200 mg once a day or FIL 100 mg two times per day at LTE entry. Patients who received PBO at the time of completion of parent study were rerandomised at LTE entry to receive either FIL 200 mg once a day or FIL 100 mg two times per day. In the USA, dosing in male subjects was restricted to FIL 100 mg once a day.
ADA, adalimumab; csDMARD, conventional synthetic disease-modifying antirheumatic drug; FIL, filgotinib; LTE, long-term extension; MTX, methotrexate; NA, not applicable; PBO, placebo; RA, rheumatoid arthritis.

Analysis sets

The placebo-controlled safety analysis dataset included patients in four placebo-controlled trials randomised to filgotinib 200 or 100 mg once a day or placebo up to 12 weeks (online supplemental figure S1). Treatment-emergent AEs (TEAEs) were defined as any AE with an onset date on or after the first dose of study drug and no later than the earliest date of either 30 days after the last dose of study drug or the first dose date of the switched treatment minus 1 day. Safety of filgotinib relative to active comparators adalimumab and methotrexate was reported by Combe *et al*[4] and Westhovens *et al*[5] and is not presented as part of this analysis.

The long-term, as-treated analysis dataset included all available data from patients in all seven trials who received ≥1 dose of filgotinib 200 or 100 mg once a day. Data were included from the original assigned treatment and after rerandomisation/reassignment to filgotinib. Therefore, patients may have contributed exposure time to more than one treatment group. Events were assigned to treatment received at time of event, with a 30-day window after last dose. The long-term, as-treated analysis dataset was the largest. It included patients with the longest exposure and was used to describe long-term, exposure-adjusted incidence rates (EAIRs). Data are presented through 96 weeks; beyond 96 weeks, the numbers of events and the numbers of patients still exposed to study drug were small, rendering interpretation difficult.

Safety was assessed through TEAEs, TEAEs leading to treatment discontinuation, serious AEs (SAEs), deaths, AE severity, AESIs and laboratory abnormalities coded according to Medical Dictionary for Regulatory Activities.

AESIs included infections, serious infections, opportunistic infections (OIs), active TB, herpes zoster (HZ) reactivation, MACE, venous thromboembolism (VTE), arterial thrombotic events (ATE; not including stroke or myocardial infarctions (MI)), malignancies, non-melanoma skin cancers (NMSC) and gastrointestinal perforation. Serious infections were infections meeting SAE criteria. Mucocutaneous candidiasis and superficial fungal infections were not considered OIs; TB and genital, disseminated and ophthalmic HZ were considered OIs. Herpes simplex virus (HSV) infection was also monitored. MACE, VTE and ATE positively adjudicated by an independent committee were included. MACE included cardiovascular (CV) death, MI and stroke, while ATEs were defined as all arterial events other than MI or stroke. VTE included pulmonary embolism and deep vein thrombosis (DVT). All deaths, including those that occurred off study drug, are reported.

Statistical methods

Baseline demographics and disease characteristics were summarised by descriptive statistics. For the placebo-controlled dataset, the proportion of patients with an event was described (n (%)) during the 12-week, placebo-controlled period.

For each exposure-group in the as-treated dataset, filgotinib patient-years of exposure (PYE) were calculated as (last dose date − first dose date +1)/365.25. If patients had multiple events, only the first event was counted. EAIRs per 100 PYE (100PYE) and 95% CIs were calculated using Poisson regression model including treatment and study as covariates to account for different study sizes and log of PYE as offset. If a specific event was not observed in any study, data were integrated across all studies, and the Poisson regression model only included treatment without adjusting by study. If a specific event was not observed in a treatment after studies were integrated, crude EAIRs and their differences were calculated. For crude EAIRs, 95% CIs were derived using an exact method[9] and based on confidence limits of individual point estimates.[10]

RESULTS

Patient population and exposure

Demographics and disease characteristics at baseline were well balanced and similar across treatment groups. Nineteen percent of patients were aged ≥65 years. At baseline, 91% and 88% of patients received csDMARDs concomitantly with treatment in the placebo-controlled and as-treated datasets; 39% and 38% of patients in the placebo-controlled and as-treated datasets received corticosteroids concomitantly with treatment (table 2). Across datasets, mean baseline Disease Activity Score with 28 joints using CRP was 5.7–5.9. Forty percent to 45% of patients had ≥1 traditional CV risk factor.

The placebo-controlled dataset included 777, 788 and 781 patients receiving filgotinib 200, 100 mg and placebo. In the as-treated dataset, 2267 patients received filgotinib 200 mg for 4047.7 PYE, 1647 patients received filgotinib 100 mg for 2032.9 PYE. Median filgotinib treatment duration was 1.6 years; 2740 (74.2%) patients received treatment for ≥1 year (table 3). As of the data cut-off, 16 September 2019, the longest individual exposure to filgotinib was up to 5.6 years.

Overall AEs

During the 12-week, placebo-controlled period, rates of TEAEs, grade ≥3 TEAEs, serious TEAEs and TEAEs leading to study drug discontinuation were comparable for filgotinib and placebo (table 3). Most common TEAEs were nasopharyngitis, upper respiratory tract infection (URTI) and nausea (table 4). Most common TEAE leading to discontinuation was pneumonia (n=3 (0.4%) filgotinib 200 mg, n=2 (0.3%) filgotinib 100 mg, n=2 (0.3%) placebo), followed by RA flare (among placebo patients only, n=5 (0.6%)) and gamma-glutamyltransferase increased (n=1 (0.1%) filgotinib 200 mg, n=2 (0.3%) filgotinib 100 mg). EAIRs of grade ≥3 TEAEs, SAEs and TEAEs leading to discontinuation were comparable between doses.

Twenty-five deaths were reported in filgotinib groups (table 3). During the placebo-controlled period, four patients died (figure 1A). Long-term, more deaths occurred in the filgotinib 200 mg group than the 100 mg group; EAIRs (95% CI) of all deaths did not change over 96 weeks (figure 1B). Most deaths in the long-term analysis were due to CV events, serious infection, and malignancies (online supplemental table S1); all fatal MI (n=2; one each in filgotinib 200 and 100 groups) and strokes (n=3; 2 with filgotinib 200 and 1 with filgotinib 100 mg) occurred in patients with ≥1 CV risk factor. Acute DVT was the cause of death for one patient receiving filgotinib 200.

AEs of special interest

During the placebo-controlled period, infections were more frequent in both filgotinib groups versus placebo (figure 1C, table 3). Long-term, EAIRs of infections decreased over time (figure 1D). Overall, the most commonly reported infections were URTI, nasopharyngitis and urinary tract infection (UTI). EAIRs were similar between the two doses. During the placebo-controlled period, serious infections occurred in 20 patients (figure 1E). Long-term, EAIRs for serious infections did not vary over time (figure 1F). The most common serious infections were pneumonia, cellulitis and bronchitis; each occurred at similar rates between the filgotinib 200 and 100 groups.

Nine OIs were reported with filgotinib. No OIs or active TB occurred during the placebo-controlled period (table 3). Long term, EAIRs for OIs were 0.1 (0.1–0.3) and 0.2 (0.1–0.5)/100PYE for filgotinib 200 and 100 mg. Active TB was reported in three patients receiving filgotinib 100 mg from endemic areas (Hong Kong, Poland, India).

Table 2 Baseline demographics, disease characteristics and cardiovascular risk factors

	PBO controlled			Long term, as-treated	
	FIL 200 mg N=777	FIL 100 mg N=788	PBO N=781	FIL 200 mg N=2267	FIL 100 mg N=1647
Age, mean±SD years	53±12.6	53±12.4	54±12.6	53±12.8	53±12.8
≥65 years	135 (17.4)	151 (19.2)	158 (20.2)	410 (18.1)	327 (19.9)
≥75 years	26 (3.3)	27 (3.4)	25 (3.2)	76 (3.4)	67 (4.1)
Female	633 (81.5)	636 (80.7)	638 (81.7)	1828 (80.6)	1319 (80.1)
Race					
Asian	137 (17.6)	136 (17.3)	124 (15.9)	372 (16.4)	286 (17.4)
Black or African American	21 (2.7)	20 (2.5)	35 (4.5)	63 (2.8)	53 (3.2)
White	543 (69.9)	548 (69.5)	528 (67.6)	1568 (69.2)	1137 (69.0)
Other	76 (9.8)	83 (10.5)	90 (11.5)	262 (11.6)	170 (10.3)
Hispanic or Latino	151 (19.4)	169 (21.4)	173 (22.2)	525 (23.2)	355 (21.6)
BMI, mean±SD kg/m^2	27.6±6.25	27.4±6.28	27.7±6.28	27.6±6.20	27.6±6.20
≥25 kg/m^2	472 (60.7)	496 (62.9)	482 (61.7)	1402 (61.8)	1034 (62.8)
≥30 kg/m^2	229 (29.5)	234 (29.7)	235 (30.1)	668 (29.5)	498 (30.2)
Duration of RA from diagnosis, mean±SD years	8.6±8.2	9.1±8.0	8.6±8.1	6.3±7.6	7.4±7.8
Range, years	0.3–49.7	0.1–41.8	0.1–51.4	0.0–52.3	0.0–51.4
hsCRP, mean±SD mg/L	18.2±21.4	19.3±25.9	18.0±24.4	18.9±24.5	18.6±25.6
DAS28 (CRP), mean±SD	5.9±0.9	5.8±1.0	5.9±0.9	5.8±0.9	5.8±1.0
CDAI, mean±SD	40.5±12.38	39.9±12.59	40.4±11.69	40.4±12.26	39.7±12.23
HAQ-DI, mean±SD	1.65±0.611	1.61±0.637	1.66±0.600	1.62±0.623	1.62±0.618
Concurrent oral corticosteroids*	300 (38.6)	305 (38.7)	297 (38.0)	781 (34.5)	631 (38.3)
Mean±SD mg/day				6.3±2.69	6.3±2.57
Concurrent csDMARDs*	710 (91.4)	721 (91.5)	712 (91.2)	1843 (81.3)	1500 (91.1)
Concurrent MTX*	685 (88.2)	692 (87.8)	678 (86.8)	1219 (53.8)	1100 (66.8)
Prior exposure to bDMARDs	181 (23.3)	179 (22.7)	164 (21.0)	276 (12.2)	255 (15.5)
Concurrent oral contraceptive*	51 (6.6)	53 (6.7)	31 (4.0)	127 (5.7)†	97 (6.1)†
Concurrent statin*	68 (8.8)	95 (12.1)	93 (11.9)	213 (9.4)	186 (11.3)
Nicotine use‡					
Current	84 (13.5)	95 (15.0)	88 (14.1)	244	193
Former	85 (13.7)	81 (12.8)	80 (12.8)	236	174
Medical history	310 (39.9)§	349 (44.3)§	331 (42.4)§	950 (41.9)¶	740 (44.9)¶
Diabetes‡	76 (12.2)	61 (9.6)	69 (11.1)	221 (9.7)	158 (9.6)
Hypertension	263 (33.8)	276 (35.0)	274 (35.1)	766 (33.8)	560 (34.0)
Dyslipidaemia	118 (15.2)	130 (16.5)	147 (18.8)	336 (14.8)	280 (17.0)
CVD	47 (6.0)	30 (3.8)	44 (5.6)	111 (4.9)	69 (4.2)
Ischaemic CNS vascular conditions	17 (2.2)	17 (2.2)	19 (2.4)	51 (2.2)	34 (2.1)
Peripheral vascular disease	–	–	–	5 (0.2)	6 (0.4)
DVT/PE	6 (0.8)	7 (0.9)	11 (1.4)	18 (0.8)†	14 (0.9)†

Data are n (%) unless otherwise indicated. DVT/PE were unadjudicated.
*On first dosing date in parent study.
†For FIL 200 mg and FIL 100 mg, n=2227 and 1600.
‡PBO-controlled group includes patients enrolled in phase 3 trials only. For FIL 200 mg, FIL 100 mg, and PBO, n=622, 633 and 623.
§Excluding diabetes and peripheral vascular disease.
¶Excluding DVT/PE.
bDMARD, biological DMARD; BMI, body mass index; CDAI, Clinical Disease Activity Index; CNS, central nervous system; CRP, C reactive protein; csDMARD, conventional synthetic DMARD; CVD, cardiovascular disease; DAS28(CRP), Disease Activity Score with 28 joints using CRP; DMARD, disease-modifying antirheumatic drug; DVT, deep vein thrombosis; FIL, filgotinib; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high sensitivity CRP; MTX, methotrexate; PBO, placebo; PE, pulmonary embolism; RA, rheumatoid arthritis.

In the placebo-controlled period, HZ occurred in 5 patients (figure 1G; table 3). Long term, EAIRs of HZ were higher for filgotinib 200 vs 100 mg and remained stable over time (figure 1H). EAIRs of HZ infection/reactivation were generally higher among Asian patients than among the overall population based on the long-term, as-treated analysis set (online supplemental figure S2). Most HZ infections were mild to moderate, monodermatomal or adjacent dermatomal and nonvisceral. Most patients recovered after treatment interruption and could continue treatment on recovery. Six SAEs of HZ were reported by five patients receiving filgotinib 200 mg and one receiving filgotinib 100 mg. All six patients were aged ≥53 years, four of six were of Asian descent, three of six were taking concomitant corticosteroids and methotrexate, while one of six was taking only concomitant corticosteroids; one of six was known to have been vaccinated against HZ. All six were hospitalised for their HZ event, and all events resolved. One of these cases was cutaneous disseminated HZ in a patient receiving filgotinib 200 mg who was hospitalised and discontinued from the study.

During the placebo-controlled period, four patients reported HSV (table 3). Long term, EAIRs of HSV were 0.6 (0.4–1.1) and 0.9 (0.6–1.4)/100PYE for filgotinib 200 and 100 mg.

During the placebo-controlled period, five patients reported MACE; patients who had MI or stroke all had ≥1 CV risk factor (figure 1I; table 3). EAIRs of MACE for filgotinib 200 and 100 mg remained stable over time (figure 1J). One ATE, a grade 4 SAE of peripheral artery thrombosis, was reported in a 64-year-old patient with hypertension and body mass index of 29.7 who was receiving filgotinib 200 mg.

Nine patients experienced VTEs; none occurred in the placebo-controlled period (figure 1K; table 3). EAIRs remained stable over time (figure 1L). All patients reporting VTEs had ≥1 traditional risk factor.

Table 3 Exposure to study drug and rates of safety events

	PBO-controlled analysis set			Long term, as-treated analysis set	
	FIL 200 mg N=777	FIL 100 mg N=788	PBO N=781	FIL 200 mg N=2267 PYE=4047.7	FIL 100 mg N=1647 PYE=2032.9
Exposure to study drug, years					
Mean±SD	0.4±0.1	0.4±0.1	0.4±0.1	1.8±1.2	1.2±0.7
Median (Q1, Q3)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.3, 0.5)	1.6 (1.0, 2.1)	1.3 (0.5, 1.8)
Cumulative n (%) exposed to study drug					
Week 12	748 (96.3)	754 (95.7)	649 (83.1)	2165 (95.5)	1547 (93.9)
Week 52	NA	NA	NA	1731 (76.4)	1001 (60.8)
Week 96	NA	NA	NA	799 (35.2)	360 (21.9)
Rates of safety events	EAIR (95% CI) per 100 PYE			EAIR (95% CI) per 100 PYE	
TEAE	195.4 (173.7 to 219.8) n=354	176.3 (156.0 to 199.2) n=323	175.9 (155.5 to 198.9) n=316	40.4 (38.3 to 42.7) n=1771	64.2 (58.9 to 69.9) n=1140
TEAE Grade ≥3	12.0 (7.4 to 19.5) n=31	11.5 (7.0 to 18.7) n=30	10.6 (6.4 to 17.5) n=27	6.4 (5.6 to 7.4) n=309	7.6 (5.3 to 10.8) n=206
TE SAE	10.9 (6.7 to 17.8) n=21	12.8 (8.1 to 20.4) n=25	8.9 (5.2 to 15.2) n=17	6.1 (5.4 to 7.0) n=254	7.5 (5.6 to 10.1) n=166
TEAE leading to premature discontinuation	8.7 (4.9 to 15.3) n=15	6.3 (3.3 to 12.0) n=11	8.8 (5.0 to 15.4) n=15	6.0 (5.3 to 6.9) n=239	6.8 (5.4 to 8.6) n=93
TEAE leading to temporary interruption	27.3 (19.7 to 37.8) n=58	25.6 (18.3 to 35.6) n=55	21.9 (15.4 to 31.1) n=46	12.5 (11.3 to 13.8) n=576	14.8 (11.9 to 18.5) n=364
All deaths	0.6 (0.1 to 3.9) n=1	0.6 (0.1 to 3.9) n=1	0.6 (0.1 to 4.0) n=2	0.5 (0.3 to 0.7) n=19	0.3 (0.1 to 0.7) n=6
Infectious AEs	76.9 (63.7 to 92.9) n=139	67.3 (55.2 to 82.1) n=123	58.0 (47.0 to 71.7) n=104	24.8 (23.1 to 26.5) n=1074	34.4 (30.4 to 38.8) n=648
Serious infectious AEs	3.9 (1.6 to 9.1) n=8	3.3 (1.4 to 8.2) n=7	2.4 (0.9 to 6.7) n=5	1.6 (1.2 to 2.1) n=67	3.1 (2.1 to 4.5) n=51
Opportunistic infections	0	0	0	0.1 (0.1 to 0.3) n=5*	0.2 (0.1 to 0.5) n=4†
Active TB	0	0	0	0	0.1 (0.0 to 0.5) n=3
Herpes zoster	0.6 (0.1 to 3.9) n=1	1.1 (0.3 to 4.4) n=2	1.1 (0.3 to 4.5) n=2	1.8 (1.4 to 2.3) n=74	1.1 (0.8 to 1.7) n=23
Herpes simplex virus	1 (0.1)	1 (0.1)	2 (0.3)	0.6 (0.4 to 1.1) n=33	0.9 (0.6 to 1.4) n=18
Adjudicated MACE	0	1.7 (0.3 to 4.8) n=3	1.1 (0.1 to 4.0) n=2	0.4 (0.2 to 0.7) n=19	0.6 (0.4 to 1.1) n=13
CV death	0	0.6 (0.0 to 3.1) n=1	0	0.1 (0.1 to 0.3) n=6	0.2 (0.1 to 0.5) n=4
Nonfatal MI	0	1.1 (0.1 to 4.0) n=2	0.6 (0.0 to 3.1) n=1	0.1 (0.0 to 0.3) n=4	0.2 (0.1 to 0.6) n=5
Nonfatal stroke	0	0	0.6 (0.0 to 3.1) n=1	0.2 (0.1 to 0.5) n=10	0.2 (0.1 to 0.5) n=4
Adjudicated ATE	0	0	0	0.0 (0.0 to 0.2) n=1	0
Adjudicated VTE	0	0	0	0.2 (0.1 to 0.4) n=8	0.0 (0.0 to 0.3) n=1
PE	0	0	0	0.1 (0.1 to 0.3) n=6	0.0 (0.0 to 0.3) n=1
DVT	0	0	0	0.1 (0.1 to 0.3) n=6	0
Malignancy excluding NMSC	0	0.6 (0.0 to 3.1) n=1	0.6 (0.0 to 3.1) n=1	0.6 (0.4 to 0.9) n=22	0.5 (0.3 to 1.0) n=11
NMSC	0	0	0	0.2 (0.1 to 0.4) n=9	0.1 (0.0 to 0.5) n=3
Gastrointestinal perforations	0	0	0	0.1 (0.0 to 0.2) n=3	0

The PBO-controlled analysis set only included data up to 12 weeks.
*Two patients reported oesophageal candidiasis, one patient reported pneumonia cryptococcal, one patient reported herpes zoster disseminated and one patient reported both oesophageal candidiasis and pneumonia cryptococcal.
†One patient reported oesophageal candidiasis, one patient reported TB, one patient reported lymph node TB, one patient reported meningitis TB and one patient reported pulmonary TB.
AE, adverse event; ATE, arterial thrombotic event; CV, cardiovascular; DVT, deep vein thrombosis; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; MACE, major adverse cardiovascular event; MI, myocardial infarction; NA, not applicable; NMSC, non-melanoma skin cancer; PBO, placebo; PE, pulmonary embolism; PYE, patient-years exposure; SAE, serious adverse event; TB, tuberculosis; TE, treatment-emergent; TEAE, treatment-emergent adverse event; VTE, venous thromboembolism.

During the placebo-controlled period, one malignancy each was reported with filgotinib 100 mg (cervix carcinoma) and placebo (malignant glioma) (figure 1M; table 3). Long term, EAIR of all non-NMSC malignancies for filgotinib 200 and 100 mg remained stable over time (figure 1N). In patients receiving filgotinib 200 mg, one diffuse large B-cell lymphoma and three non-Hodgkin's lymphomas were reported; 1 T-cell lymphoma and one central nervous system lymphoma were reported with filgotinib 100 mg. During the placebo-controlled period, no NMSCs were reported (figure 1O, table 3). EAIRs for NMSC were 0.2 (0.1–0.4) and 0.1 (0–0.5)/100PYE for filgotinib 200 and 100 mg (figure 1P).

No gastrointestinal perforations occurred during the placebo-controlled period (table 3). Gastrointestinal perforations were reported for three patients receiving filgotinib 200 mg with risk factors of concomitant non-steroidal anti-inflammatory (one

Table 4 Common TEAEs (≥3% in any treatment group) in the PBO-controlled period up to week 12

	FIL 200 mg N=777	FIL 100 mg N=788	PBO N=781
Nasopharyngitis, n (%)	27 (3.5)	19 (2.4)	19 (2.4)
Upper respiratory tract infection, n (%)	26 (3.3)	20 (2.5)	14 (1.8)
Nausea, n (%)	27 (3.5)	18 (2.3)	13 (1.7)

FIL, filgotinib; PBO, placebo; TEAE, treatment-emergent adverse event.

patient) and corticosteroid (one patient) use; EAIR was 0.1 (0–0.2)/100PYE.

Graded laboratory abnormalities occurring during the placebo-controlled period are reported in online supplemental table S2.

DISCUSSION

We evaluated the safety of filgotinib as treatment for RA with an integrated analysis encompassing seven trials that included 3691 patients, treated for a median of 1.6 years (maximum exposure, 5.6 years in <3% of patients). In the placebo-controlled analysis dataset, proportions of patients with TEAEs, SAEs and AESIs were similar between those receiving filgotinib 200, 100 mg or placebo. The long-term, as-treated dataset revealed similar incidence between doses for most AESIs, with the exception of numeric differences in serious infection (higher incidence with filgotinib 100 vs 200 mg) and in VTE and HZ (higher incidence with filgotinib 200 vs 100 mg). Incidence of malignancy, MACE, and other serious events were similar between doses.

A numeric increase in mortality among the long-term, as-treated dataset was observed for filgotinib 200 (0.5/100PYE) vs 100 mg (0.3/100PYE) and appeared to remain stable over time; however, rates were similar overall with overlapping CIs. Mortality rates were not adjusted for demographic factors or ageing over the study period, but they appear to fall within reported RA population rates and were consistent with those observed with other RA therapeutics.[11–13] The leading causes of death for patients receiving filgotinib were those most frequently reported in patients with RA: CV death, infections and malignancies.[12 14–16] All fatal MI and strokes occurred in patients with ≥1 CV risk factor.[17]

Patients with RA have increased risk for infection due to underlying disease and many of the immunosuppressive therapies used to treat it.[18 19] Compared with csDMARDs, JAKi are associated with greater risk of serious infection, with observed incidence rates from RA clinical trials (generally 3–5/100PYE) similar between JAKi and biological DMARDs.[19 20] The most common serious infections observed were those common among patients with RA (eg, pneumonia, skin and soft tissue infection, UTI).[21] Though incidence of serious infection for the placebo-controlled dataset was 1.0% with filgotinib 200 mg and 0.9% with filgotinib 100 mg, serious infection EAIRs were higher for filgotinib 100 mg (3.1/100PYE) vs 200 mg (1.6/100PYE). Overall infection rates decreased over time, while rates of serious infections appeared to remain stable. Though cross-trial comparisons are fraught with limitations and potential bias, the EAIR for serious infections with filgotinib 100 mg was similar to those reported for other JAKi (including over LTE periods), which range from 2.7 to 6.2/100PYE, while the EAIR with filgotinib 200 mg was slightly lower.[13 22–24] It is possible this lower EAIR with filgotinib 200 mg may be explained, at least partially, by reduced inhibition of JAK2 and JAK3 relative to other JAKi.[6]

RA confers elevated risk for HZ, and corticosteroids and JAKi can further increase this risk.[25] Reactivation of latent varicella zoster virus by tofacitinib, baricitinib and upadacitinib has been described.[13 23 24 26] From the placebo-controlled dataset, there were five cases of HZ: 1 (0.1%) with filgotinib 200 mg and 2 (0.3%) with filgotinib 100 mg and with placebo. For filgotinib 200 and 100 mg, EAIRs of HZ were 1.8 and 1.1/100PYE, and EAIRs were higher among Asian populations than among the overall population. As in other JAKi programmes, most HZ cases were monodermatomal and not serious.[13 23 24] Among the six patients who had SAEs of HZ, three were receiving concomitant corticosteroids and methotrexate, while one was receiving concomitant corticosteroid alone.

In the filgotinib programme, OIs—including active TB—were infrequent; however, QF status was carefully monitored, and patients with changes in QF status discontinued the phase 2 LTE or had to pause study drug and start treatment for latent TB if applicable in the phase 3 LTE. Longer-term, real-world and population-based data are needed to better understand the potential TB risk of filgotinib and other JAKi.

VTE risk is elevated for patients with RA compared with the general population[27 28]; risk with JAKi is incompletely understood,[29 30] as is a potential mechanism for JAKi to cause VTE. Here, VTEs were infrequently reported (none from the placebo-controlled data set and EAIRs of 0.2/100PYE and 0.0/100PYE for filgotinib 200 and 100 mg), and their incidence did not increase over time. EAIR of VTEs was 0.5/100PYE for all doses in an integrated safety analysis of baricitinib[22] and 0.6/100PYE for upadacitinib 15 mg.[13] While real-world and population-based data are needed to better understand the potential risk of VTE associated with JAKi, our findings with filgotinib suggest a risk no greater than that reported from real-world studies showing background rates of VTE in RA of 0.3–1.0/100PYE.[27 28]

Patients with RA are also at increased risk for MACE compared with the general population.[31 32] As expected, 40%–45% patients had a medical history of CV risk factors at baseline. MACE were infrequent, and EAIRs (0.4/100PYE and 0.6/100PYE for filgotinib 200 and 100 mg) remained stable over time.

Patients with RA experience higher rates of malignancies, due to underlying disease and immunosuppressive treatments, compared with the general population.[33] In this analysis, malignancies were uncommon, and EAIRs did not increase with time exposed to filgotinib. Rates of malignancy excluding NMSC with filgotinib treatment (0.6 and 0.5/100PYE for filgotinib 200 and 100 mg) appeared to fall within the range reported from large registries of patients with RA.[34] In integrated analyses of baricitinib and tofacitinib, EAIRs of malignancy excluding NMSC were 0.8 and 0.9/100PYE.[22 23]

Filgotinib was associated with decreases in mean neutrophil, lymphocyte and platelet counts and increases in mean lipid, CK and creatinine levels, as previously reported.[1–5 7] There were small numerical differences in frequencies of Grade 3/4 neutropenia and lymphopenia in patients treated with filgotinib versus placebo.

Limitations of this analysis include comparatively short follow-up for rare and long-latency events, especially malignancies. Relative to other JAKi, the filgotinib RA programme has included fewer patients. The short placebo-controlled period limited the assessment of filgotinib against the background of rare events, such as VTE. Filgotinib was also evaluated against active comparators for only 52 weeks.[4 5] The LTE trials did not have a control group, and clinicians were permitted to modify background therapy per clinical judgement, as they would in real-world treatment plans. Another limitation is survival bias: patients who had intolerable AEs or lack of efficacy were discontinued from their studies. Longer-term, adequately powered studies with greater numbers of patients and events are needed to better understand the safety of filgotinib, describe the incidence of uncommon events over time, and assess its safety relative to other JAKi.

AESI incidence is generally similar between filgotinib 200 and 100 mg. Serious infection risk is likely elevated with filgotinib vs

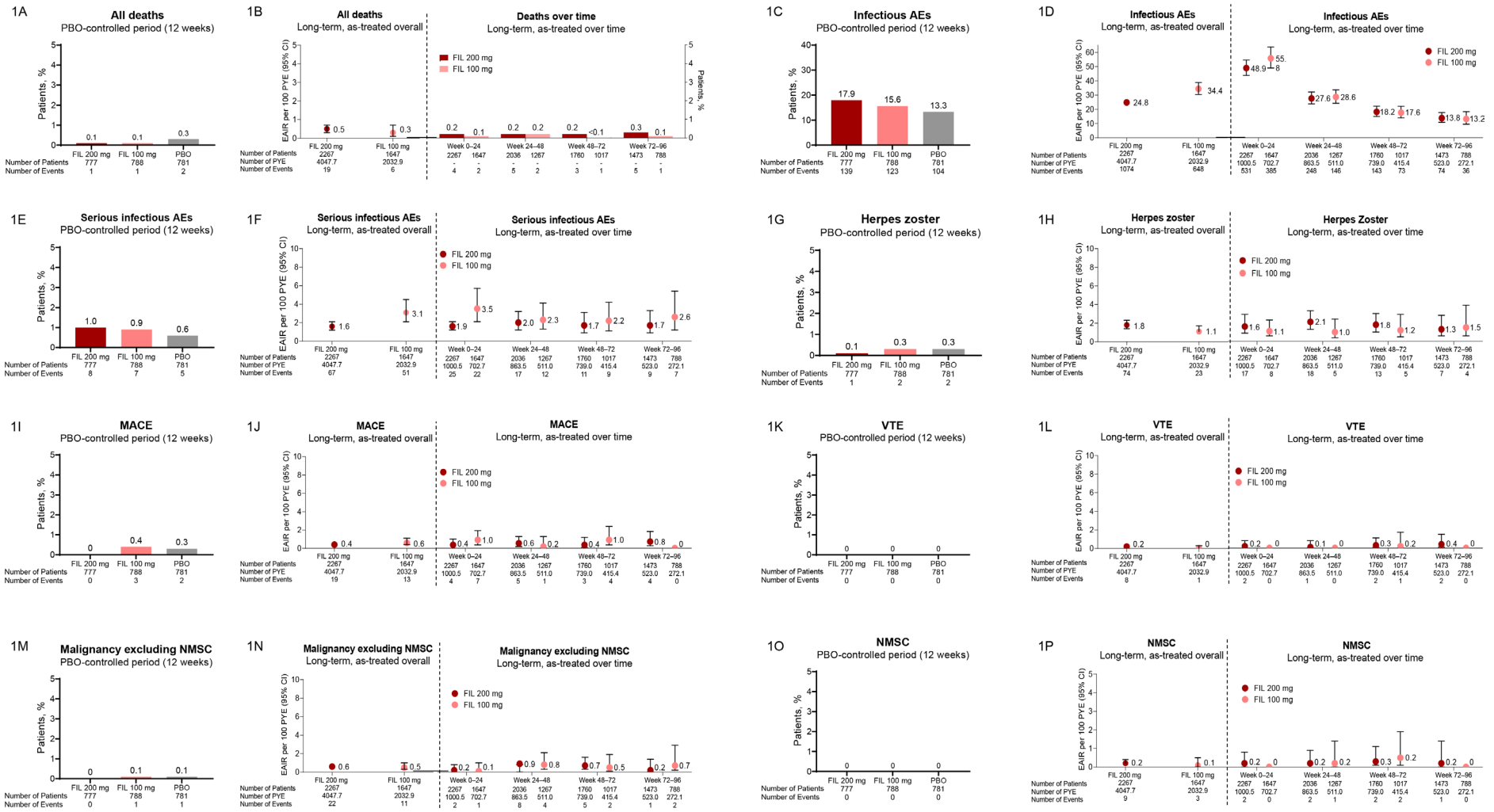

Figure 1 Summary safety event rates. (A) All deaths during the PBO-controlled period; (B) all deaths in the long-term, as-treated set and over time; (C) infectious AEs during the PBO-controlled period; (D) infectious AEs in the long-term, as-treated set and over time; (E) serious infectious AEs in the PBO-controlled period; (F) serious infectious AEs in the long-term, as-treated set and over time; (G) herpes zoster during the PBO-controlled period; (H) herpes zoster in the long-term, as-treated set and over time; (I) MACE during the PBO-controlled period; (J) MACE in the long-term, as-treated set and over time; (K) VTEs during the PBO-controlled period; (L) VTEs in the long-term, as-treated set and over time; (M) non-NMSC malignancy during the PBO-controlled period; (N) non-NMSC malignancy in the long-term, as-treated set and over time; (O) NMSC malignancy during the PBO-controlled period; (P) NMSC malignancy in the long-term, as-treated set and over time. MACE and VTEs were positively adjudicated. AE, adverse event; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; MACE, major adverse cardiovascular events; NMSC, nonmelanoma skin cancer; PBO, placebo; PYE, patient-years exposure; VTE, venous thromboembolism.

placebo, as is risk of HZ. Rates of VTE were low; malignancy and MACE were low and similar to that reported in population-based studies of RA. Over a median of 1.6 and maximum of 5.6 years of exposure, safety/tolerability of FIL200 and FIL100 were similar, with a lower incidence of infections with FIL200 among the long-term, as-treated dataset.

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