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REVIEW

Long-Term Safety, Efficacy, and Patient-Centered Outcomes of Filgotinib in the Treatment of Rheumatoid Arthritis: Current Perspectives

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Abstract: Filgotinib is an orally administered, preferential Janus kinase (JAK) inhibitor indicated for the treatment of moderate-to-severe rheumatoid arthritis (RA). The short-term safety, efficacy, and patient-reported outcomes (PROs) with filgotinib from Phase 2b/3 clinical trials (DARWIN 1 and 2; FINCH 1, 2, and 3) are described in patients who inadequately responded to methotrexate (MTX) and biologic disease-modifying antirheumatic drugs or who were naïve to MTX. This article reviews the safety and efficacy from the long-term extension (LTE) trials, DARWIN 3 (N=739) and FINCH 4 (N=2731), and PROs across the filgotinib development program in RA. Overall, in the DARWIN clinical trials (conducted from 2013–2023), patients received their LTE treatment for ≤8 years, while in the FINCH trials (ongoing from 2016–2025), patients received filgotinib treatment for ≤6 years in the LTE. The longer-term safety profile and consistent, sustained efficacy (American College of Rheumatology 20/50/70, Clinical Disease Activity Index, and Disease Activity Scale in 28 joints with C-reactive protein response rates) of filgotinib were largely similar to those observed in the shorter-term parent trials ≤52 weeks. PRO results from the parent trials showed improvements in patients' quality of life with filgotinib treatment, which compared to or exceeded improvements seen with placebo and active comparators (adalimumab, MTX). Filgotinib has a higher specificity for JAK1 compared with other therapeutic treatments, leading to reduced inhibition of JAK2/3–dependent pathways, potentially providing a distinct safety profile. Filgotinib is approved in Europe and Japan for treatment of people with moderate-to-severe RA, though it has not been approved by the US Food and Drug Administration, due to concerns around the benefit/risk profile of the filgotinib 200-mg dosage and the potential impact on semen parameters.

Keywords: Janus kinase inhibitors, selectivity, JAKi, disease-modifying antirheumatic drug, DMARD, RA

Introduction

Approximately 0.5% of the world's population has rheumatoid arthritis (RA).[1,2] RA is a chronic, systemic, autoimmune, and inflammatory disease characterized by tender, swollen, and stiff joints; high morbidity and mortality; and progressive disability.[3–5] While the full spectrum of signaling pathways involved in the pathogenesis of RA remains unclear, abnormalities in cytokines involved in immune and inflammation responses, including interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-alpha, are implicated in the progression of RA and are targets of disease-modifying antirheumatic drugs (DMARDs).[5–10] Janus kinase (JAK) inhibitors (JAKis)—the first class of targeted synthetic DMARDs to gain marketing authorizations—work by blocking JAK-dependent cytokine signaling pathways, interfering with inflammatory responses and subsequently disrupting the pathogenesis of RA.[4,5,7,10,11] Filgotinib, an orally administered medication, has been extensively studied for the treatment of moderate-to-severe RA in a series of Phase 2b and 3 clinical trials: DARWIN 1, 2, and 3 and FINCH 1, 2, 3, and 4.[12–22] The Phase 2b DARWIN trials were filgotinib dose-finding studies, while the Phase 3 FINCH trials assessed the safety and efficacy of the treatment modality.[23–29] The DARWIN and FINCH trials both required an RA diagnosis defined by the 2010 American College of Rheumatology

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(ACR)/European League Against Rheumatism (EULAR) criteria for RA and an ACR functional class I–III.[23–29] These trials included RA patients who had inadequate response (IR) to other treatments, including methotrexate (MTX) and biologic DMARDs (bDMARDs), and those who were naïve to MTX treatment.[12–21] Based on the evidence generated by these trials, filgotinib is approved for the treatment of moderately to severely active RA in the European Union, the United Kingdom, and Japan.[30–32] This review describes the safety, efficacy, tolerability, and patient-reported outcomes (PROs) of filgotinib treatment in patients with RA.

Filgotinib + MTX (DARWIN 1; NCT01888874) and filgotinib monotherapy (DARWIN 2; NCT01894516) were evaluated in patients with active RA and IR to previous MTX treatment.[15,18] Patients meeting key inclusion criteria for DARWIN 1 were ≥18 years of age, had a diagnosis of RA ≥6 months and met the 2010 ACR/EULAR criteria of RA and ACR function class I–III, had ≥6 swollen joints from a 66-joint count and ≥8 tender joints from a 68-joint count at screening and at baseline, had a screening serum C-reactive protein (CRP) ≥0.7 × upper limit of laboratory normal range, and had received MTX for ≥6 months and were on a stable dose of MTX for ≥4 weeks prior to screening and were willing to continue their current treatment regimen for the duration of the study.[18,26] Inclusion criteria for DARWIN 2 were the same as DARWIN 1 with the exception that patients were required to have an IR in terms of either lack of efficacy or toxicity to MTX and were required to have an MTX washout period of ≥4 weeks before or during the screening period.[15,25] DARWIN 3 (NCT02065700), an open-label extension study, evaluated the long-term safety and efficacy of filgotinib (200 mg once daily or 100 mg twice daily) in eligible patients who had completed either DARWIN 1 (filgotinib and MTX) or DARWIN 2 (filgotinib monotherapy).[16] Overall, the DARWIN clinical trials were conducted internationally across 23 countries from 2013 to 2023, and patients received their long-term extension (LTE) treatment in DARWIN 3 for ≤8 years.[23,25,26]

FINCH 1 (NCT02889796) investigated filgotinib 200 mg or 100 mg once daily, subcutaneous adalimumab (ADA; 40 mg) every 2 weeks, or placebo all in combination with MTX in patients who were MTX-IR.[12] Key inclusion criteria for FINCH 1 were patients ≥18 years of age, a diagnosis of RA based on the 2010 ACR/EULAR criteria of RA and ACR function class I–III, ≥6 swollen joints from a 66-joint count and ≥6 tender joints from a 68-joint count at screening and day 1, and ongoing treatment with a stable dose of MTX.[12] FINCH 2 (NCT02873936) included adult patients with moderately to severely active RA, similar to FINCH 1; however, additional inclusion criteria were an IR to 1 or more prior bDMARDs (tumor necrosis factor inhibitor [TNFi] bDMARD exposure: ADA, etanercept, infliximab, golimumab, and certolizumab; non-TNFi bDMARD exposure: tocilizumab, abatacept, rituximab, and anakinra) and had active RA despite ongoing treatment with conventional synthetic DMARDs (csDMARDs; 1 or 2 of the following: MTX, hydroxychloroquine or chloroquine, sulfasalazine, and/or leflunomide; however, the combination of leflunomide and MTX was not allowed).[14] These patients were treated with once-daily filgotinib (200 mg or 100 mg) or placebo, in combination with csDMARDs.[14] Inclusion criteria for FINCH 3 (NCT02886728) were similar to FINCH 1 and 2, with the exception that FINCH 3 required that eligible patients be naïve to MTX and during the trial were treated with either filgotinib 200 mg or 100 mg daily + MTX, filgotinib 200 mg monotherapy, or MTX monotherapy.[4,17,21] Patients who completed any of the FINCH parent trials were eligible to enroll in the LTE study FINCH 4 (NCT03025308).[24] Patients who had been assigned to filgotinib continued their originally assigned filgotinib dosage while those who had been assigned to control groups in the parent trials were rerandomized (blinded) to filgotinib 200 or 100 mg once daily.[20,21,33] Overall, the FINCH clinical trials have been conducted internationally across 34 countries beginning in 2016, with FINCH 4 currently ongoing, with projected completion in 2025.[24] Patients received their LTE treatment in FINCH 4 for ≤6 years.[24]

Filgotinib was safe and well tolerated and showed consistent efficacy for clinical and PRO measures, with significant improvements vs controls ≤52 weeks in the DARWIN and FINCH parent trials.[4,12–15,17–21] The LTE studies (DARWIN 3 and FINCH 4) are ongoing as of December 2022, with DARWIN 3 collecting data for ≤8 years and FINCH 4 for ≤6 years.[23,24] This paper reviews the findings to date from DARWIN 3 and FINCH 4 regarding long-term safety, tolerability, and efficacy of filgotinib, along with adherence to treatment and PROs, among patients with RA who are MTX-IR, bDMARD-IR, or MTX-naïve. Table 1 summarizes study characteristics of the DARWIN and FINCH clinical trials; Table 2 summarizes patient demographics of the DARWIN and FINCH clinical trial populations.

Table 1 Trial Characteristics of DARWIN and FINCH

Study		DARWIN			FINCH			
		1	2	3	1	2	3	4
Patient population		MTX-IR			MTX-IR	bDMARD-IR	MTX-naïve	MTX-IR, bDMARD-IR, MTX-naïve
Treatment arms								
Filgotinib 50 mg	Monotherapy		Once daily					
	Combination	Once daily + MTX Twice daily + MTX						
Filgotinib 100 mg	Monotherapy		Once daily	Once daily[a]				Once daily
	Combination	Once daily + MTX Twice daily + MTX			Once daily + MTX	Once daily + csDMARD	Once daily + MTX	
Filgotinib 200 mg	Monotherapy		Once daily	200 mg once daily or 100 mg twice daily			Once daily	Once daily
	Combination	Once daily + MTX Twice daily + MTX		200 mg once daily + MTX or 100 mg twice daily + MTX	Once daily + MTX	Once daily + csDMARD	Once daily + MTX	
Comparator		PBO + MTX	PBO		PBO + MTX; ADA + MTX	PBO + csDMARD	MTX	
Duration (weeks)		24	24		52	24	52	

Notes: [a]Includes 15 men in the United States who received 100 mg daily due to a requirement by the US Food and Drug Administration (7 analyzed as filgotinib + MTX and 8 as filgotinib monotherapy). Data from these studies.[12,14–18,24]

Abbreviations: ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; IR, inadequate response; MTX, methotrexate; PBO, placebo.

Table 2 Patient Demographics in the DARWIN and FINCH Programs

Study	DARWIN			FINCH			
	1	2	3	1	2	3	4
Prior treatment	MTX-IR			MTX-IR	bDMARD-IR	MTX-naïve	MTX-IR, bDMARD-IR, MTX-naïve
Number of patients enrolled	594	283	739	1755	448	1249	2731
Age, years, mean (range or SD)	53 (18–84)	52 (18–79)	53 (11.9)	53 (12.7)	56 (12.2)	53 (13.6)	NR
Female, n (%)	481 (81.0)	231 (81.6)	603 (81.6)	1435 (81.8)	360 (80.4)	961 (77.0)	NR
Male, n (%)	113 (19.0)	52 (18.4)	136 (18.4)	320 (18.2)	88 (19.6)	288 (23.1)	NR
RA duration, years, mean (range or SD)[a]	8.3 (0.5–43.2)	8.8 (0.5–49.6)	8.5 (7.1)	7.8 (7.6)	NR	2.2 (5.0)	NR

Notes: [a]Duration of RA (years) = (first dose date in core studies − date of initial diagnosis + 1)/365.25. Data from these studies.[12,16,17,24–27]

Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; IR, inadequate response; MTX, methotrexate; NR, not reported; RA, rheumatoid arthritis; SD, standard deviation.

Long-Term Safety and Tolerability of Filgotinib

Filgotinib was generally well tolerated in previous clinical trials, with similar safety profiles ≤52 weeks with active comparators MTX and ADA.[12–21,33–35] Safety endpoints such as adverse events (AEs), treatment-emergent AEs (TEAEs)

and their exposure-adjusted incidence rates (EAIRs), infections, malignancies, major adverse cardiovascular events (MACE), venous thromboembolisms, and deaths were included for both the FINCH and DARWIN clinical trials.[16,19,33–35] EAIRs, representing the number of patients with AEs of interest per patients' total exposure time, were calculated for TEAEs.[16,19,33–35] An integrated safety analysis of data from patients treated a median of 1.6 years (maximum, 5.6 years) in the DARWIN and FINCH studies and a subsequent update at 2.2 years (maximum, 6.8 years) demonstrated that the safety and 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, and no new safety concerns were identified (Table 3).[19,36] EAIRs of TEAEs, including deaths and AEs of special interest (AESIs), decreased or remained stable since the earlier report, while slight increases were noted in rates of nonmelanoma skin cancer (NMSC) and non-NMSC malignancies.[36]

Filgotinib in Patients with Inadequate Responses to Methotrexate

DARWIN 3 evaluated safety and tolerability of filgotinib through ≤204 weeks among patients who had IR to MTX. Patients continuing from DARWIN 1 received 200 mg/day of filgotinib in combination with MTX, while patients continuing from DARWIN 2 received 200 mg/day of filgotinib monotherapy (Table 1).[16] Overall, DARWIN 3 reported that filgotinib was well tolerated and had a similar safety profile when compared to the 2 parent trials, and the EAIRs for TEAEs were similar between patients receiving filgotinib as a monotherapy or combination therapy.[15,16,18] MACE and herpes zoster (HZ) have been reported to be associated with other JAKi treatments; however, the incidence rates for these events are similar to placebo (Table 4).[16,19,37–40]

RA patients were eligible to enroll in the LTE FINCH 4 study if they had completed 1 of the FINCH parent studies. Among patients who were MTX-IR and were rerandomized for the LTE from ADA + MTX to filgotinib + MTX or those who continued their parent-trial treatment with filgotinib 100 or 200 mg with MTX, incidence of TEAEs, serious AEs (SAEs), and ≥3-grade AEs were largely comparable (Table 5).[34] Overall incidence of AEs appeared to be lowest among patients who were on ADA + MTX in the parent trial (FINCH 1) and rerandomized to 100 mg of filgotinib + MTX in the LTE (Table 5).[34] AESIs occurred at similar rates between treatment groups, with the exception of a higher EAIR of HZ among patients treated with 200 mg filgotinib during the LTE compared with those treated with 100 mg filgotinib, which was also seen in DARWIN 3 (Table 5).[34] Deep vein thrombosis, opportunistic infections, and NMSC occurred only in

Table 3 Summary of Safety Results from DARWIN 1–3 and FINCH 1–4 Trials

	200 mg of Filgotinib n=2267 PYE=4047.7	100 mg of Filgotinib n=1647 PYE=2032.9
TEAE, n (%)	1771 (78.1)	1140 (69.2)
EAIR (95% CI)	40.4 (38.3–42.7)	64.2 (58.9–69.9)
≥3-grade TEAE, n (%)	309 (13.6)	206 (12.5)
EAIR (95% CI)	6.4 (5.6–7.4)	7.6 (5.3–10.8)
TE serious AE, n (%)	254 (11.2)	166 (10.1)
EAIR (95% CI)	6.1 (5.4–7.0)	7.5 (5.6–10.1)
TEAE leading to study drug discontinuation, n (%)	239 (10.5)	93 (5.6)
EAIR (95% CI)	6.0 (5.3–6.9)	6.8 (5.4–8.6)
All deaths, n (%)	19 (0.8)	6 (0.4)
EAIR (95% CI)	0.5 (0.3–0.7)	0.3 (0.1–0.7)

Notes: Patients received treatment for a median of 1.6 years in the 200 mg of filgotinib group and 1.3 years for the 100 mg of filgotinib group. EAIR data represented as EAIR/100 PYE. Adapted with permission from BMJ Publishing Group Limited. Winthrop KL, Tanaka Y, Takeuchi T, et al. Integrated safety analysis of filgotinib in patients with moderately to severely active rheumatoid arthritis receiving treatment over a median of 1.6 years. Annals of the Rheumatic Diseases, volume 81, issue 2, pages 184–192, 2022.[19]
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate; PYE, patient-years exposure; TE, treatment-emergent; TEAE, treatment-emergent AE.

Table 4 Safety Results Among MTX-IR Patients from DARWIN 3

	Filgotinib + MTX n=497	Filgotinib Monotherapy n=242
TEAEs	434 (24.6)	211 (25.8)
Treatment-related TEAEs	242 (13.7)	116 (14.2)
TE serious AEs	54 (3.1)	35 (4.3)
Treatment-related serious TEAEs	9 (0.5)	10 (1.2)
Discontinuation due to TEAEs	131 (7.4)	77 (9.4)
Deaths[a]	3 (0.2)	3 (0.4)
Infections[b]	288 (16.3)	130 (15.9)
Serious infections	11 (0.6)	14 (1.7)
Herpes zoster	23 (1.3)	12 (1.5)
Opportunistic infections	NR	NR
MACE[b,c]	3 (0.2)	2 (0.2)
VTE	NR	NR
DVT and/or PE[b,c]	1 (0.1)[d]	0
Malignancy (excluding NMSC)[b,e]	9 (0.5)	5 (0.6)
NMSC[b]	6 (0.3)	1 (0.1)

Notes: Patients received treatment for a mean exposure of 3.55 ± 1.57 years in the filgotinib + MTX group and 3.38 ± 1.59 years in the filgotinib monotherapy group. Data represented as n (EAIR/100 PYE) unless otherwise noted. [a]Filgotinib + MTX: meningococcal meningitis, leiomyosarcoma, DVT/PE; filgotinib monotherapy: pneumonia, NHL (2). [b]Includes TEAEs and non-TEAEs. [c]Positively adjudicated events. [d]Patient had simultaneous DVT and PE. [e]Of the 13 patients with treatment-emergent malignancies, 4 were hematologic (3 NHL and 1 diffuse large B-cell lymphoma) and 9 were solid tumors (2 lung cancer, 2 breast cancer, 1 each colon cancer, gallbladder adenocarcinoma, metastatic leiomyosarcoma, melanoma, and renal cancer). Adapted with permission from The Journal of Rheumatology Publishing Co. Ltd. Kavanaugh A, Westhovens RR, Winthrop KL, et al. Safety and efficacy of filgotinib: up to 4-year results from an open-label extension study of Phase II rheumatoid arthritis programs. Journal of Rheumatology, volume 48, issue 8, pages 1230–1238, 2021. Permission conveyed through Copyright Clearance Center, Inc.[16]

Abbreviations: AE, adverse event; DVT, deep vein thrombosis; EAIR, exposure-adjusted incidence rate; IR, inadequate response; MACE, major adverse cardiovascular events; MTX, methotrexate; NHL, non-Hodgkin lymphoma; NMSC, nonmelanoma skin cancer; NR, not reported; PE, pulmonary embolism; PYE, patient-years exposure; TE, treatment-emergent; TEAE, treatment-emergent AE; VTE, venous thromboembolism.

Table 5 Safety Results Among MTX-IR Patients from FINCH 4

Number of Events (EAIR, 95% CI)	Patients Continuing 100 mg of Filgotinib (n=570)	Patients Rerandomized from ADA and MTX to 100 mg of Filgotinib and MTX (n=130)	Patients Continuing 200 mg of Filgotinib (n=571)	Patients Rerandomized from ADA and MTX to 200 mg of Filgotinib (n=128)
TEAEs	443 (52.0, 47.4–57.0)	88 (45.7, 37.1–56.3)	429 (49.9, 45.4–54.9)	91 (46.0, 37.5–56.5)
TE serious AEs	60 (7.0, 5.5–9.1)	9 (4.7, 2.4–9.0)	52 (6.1, 4.6–7.9)	13 (6.6, 3.8–11.3)
Deaths	3 (0.4, 0.1–1.1)	2 (1.0, 0.3–4.2)	3 (0.3, 0.1–1.1)	2 (1.0, 0.3–4.0)
Infections	249 (29.2, 25.8–33.1)	43 (22.3, 16.6–30.1)	243 (28.3, 24.9–32.1)	52 (26.3, 20.0–34.5)
Serious infections	13 (1.5, 0.9–2.6)	1 (0.5, 0.1–3.7)	7 (0.8, 0.4–1.7)	2 (1.0, 0.3–4.0)

(*Continued*)

Table 5 (Continued).

Number of Events (EAIR, 95% CI)	Patients Continuing 100 mg of Filgotinib (n=570)	Patients Rerandomized from ADA and MTX to 100 mg of Filgotinib and MTX (n=130)	Patients Continuing 200 mg of Filgotinib (n=571)	Patients Rerandomized from ADA and MTX to 200 mg of Filgotinib (n=128)
Herpes zoster	13 (1.5, 0.9–2.6)	1 (0.5, 0.1–3.7)	16 (1.9, 1.1–3.0)	5 (2.5, 1.1–6.1)
Opportunistic infections	2 (0.2, 0.0–0.8)	0 (0.0, 0.0–1.9)	2 (0.2, 0.0–0.8)	0 (0.0, 0.0–1.9)
MACE (adjudicated)	3 (0.4, 0.1–1.1)	3 (1.6, 0.5–4.8)	1 (0.1, 0.0–0.6)	0 (0.0, 0.0–1.9)
VTE	NR	NR	NR	NR
DVT/PE (adjudicated)	3 (0.4, 0.1–1.0)	0 (0.0, 0.0–1.9)	3 (0.3, 0.1–1.0)	0 (0.0, 0.0–1.9)
Malignancy (excluding NMSC)	4 (0.5, 0.1–1.2)	0 (0.0, 0.0–1.9)	5 (0.6, 0.2–1.4)	3 (1.5, 0.5–4.7)
NMSC	2 (0.2, 0.0–0.8)	0 (0.0, 0.0–1.9)	3 (0.3, 0.1–1.0)	0 (0.0, 0.0–1.9)

Notes: Patients received treatment for a median of 2.2 years. Data presented as number of events (EAIR/100 PYE, 95% CI) unless otherwise noted. EAIR and 95% CI were estimated using Poisson regression model including treatment group with an offset of natural log of exposure time. If any treatment had 0 events, exact Poisson method was applied. Adapted with permission from John Wiley and Sons. Combe B, Tanaka Y, Emery P, et al. Clinical outcomes up to week 48 of filgotinib treatment in an ongoing long-term extension trial of RA patients with inadequate response to MTX initially treated with filgotinib or adalimumab during the Phase 3 parent trial. Arthritis & Rheumatology, volume 73, supplement 9, 2021.[34]

Abbreviations: ADA, adalimumab; AE, adverse event; CI, confidence interval; DVT, deep vein thrombosis; EAIR, exposure-adjusted incidence rate; IR, inadequate response; MACE, major adverse cardiovascular events; MTX, methotrexate; NMSC, nonmelanoma skin cancer; NR, not reported; PE, pulmonary embolism; PYE, patient-years exposure; TE, treatment-emergent; TEAE, treatment-emergent AE; VTE, venous thromboembolism.

patients who started on and continued filgotinib treatment throughout the entire parent and LTE study (Table 5).[34] Overall, the long-term safety of filgotinib in MTX-IR patients was largely comparable and consistent with that observed in FINCH 1, and the safety profiles established in the DARWIN and FINCH trials were similar.[16,34]

Filgotinib in Patients with Inadequate Responses to bDMARDs

In the FINCH 2 trial, patients who had not met predefined response criteria by week 14 were switched to standard-of-care (SOC) therapy for the rest of the controlled period.[14] Patients from FINCH 2 who had been assigned to a filgotinib arm remained on their blinded filgotinib dose (100 mg or 200 mg once daily) for FINCH 4, while those who had been receiving placebo or SOC treatment were rerandomized to 100 mg or 200 mg filgotinib.[14,33]

In FINCH 4, the safety profile of filgotinib among patients who were bDMARD-IR showed minor deviations from that of patients who were MTX-IR and MTX-naïve. The numbers of SAEs, malignancies, and infections were higher among the bDMARD-IR patient population than what was seen in the MTX-IR or MTX-naïve populations (Table 6).[33–35] These differences may be due to longer disease duration, prior immunosuppressive exposures, and the smaller size of the bDMARD-IR population (n=369) compared with the MTX-IR (n=1399) and MTX-naïve (n=960) populations.[33–35] EAIRs for SAEs, TEAEs, infections, and serious infection AEs were all higher among patients who had received SOC treatment in the parent trial than among those who received placebo or filgotinib during the parent trial.[33] Up to week 48, five deaths were reported in the bDMARD-IR patient groups despite the smaller population size (Table 6).[33] Overall, safety profiles were largely consistent between the parent trial and LTE.[14,33]

Filgotinib in Methotrexate-Naïve Patients

Patients naïve to MTX enrolled into FINCH 4 from the parent trial FINCH 3.[17] Patients randomized to MTX in the parent trial underwent a 4-week MTX washout followed by blinded rerandomization to 100 or 200 mg filgotinib.[35] The LTE safety profile of filgotinib among the MTX-naïve subpopulation was largely comparable to the parent trial and across treatment arms (Table 7).[17,35,36] Six deaths and 5 MACE were reported among patients receiving filgotinib 200 mg in the parent trial and LTE, but there were no deaths or MACE among patients receiving

Table 6 Safety Results Among bDMARD-IR Patients from FINCH 4

	Patients Continuing 100 mg of Filgotinib with csDMARDs (n=110)	Patients Rerandomized from PBO and csDMARDs to 100 mg of Filgotinib with csDMARDs (n=46)	Patients Rerandomized from SOC and csDMARDs to 100 mg of Filgotinib with csDMARDs (n=22)	Patients Continuing 200 mg of Filgotinib with csDMARDs (n=121)	Patients Rerandomized from PBO with csDMARDs to 200 mg of Filgotinib with csDMARDs (n=47)	Patients Rerandomized from SOC with csDMARDs to 200 mg of Filgotinib with csDMARDs (n=23)
TEAEs	90 (40.3, 32.8–49.5)	37 (40.6, 29.4–56.1)	19 (49.8, 31.8–78.0)	107 (46.9, 38.8–56.6)	38 (38.7, 28.2–53.2)	22 (52.2, 34.4–79.3)
TE serious AEs	18 (8.1, 5.1–12.8)	12 (13.2, 7.5–23.2)	8 (21.0, 10.5–41.9)	28 (12.3, 8.5–17.8)	12 (12.2, 6.9–21.5)	9 (21.4, 11.1–41.1)
Deaths	1 (0.4, 0.1–3.2)	0 (0.0, 0.0–4.0)	0 (0.0, 0.0–9.7)	3 (1.3, 0.4–4.1)	1 (1.0, 0.0–5.7)	0 (0.0, 0.0–8.8)
Infections	50 (22.4, 17.0–29.5)	24 (26.3, 17.7–39.3)	15 (39.3, 23.7–65.2)	78 (34.2, 27.4–42.6)	22 (22.4, 14.8–34.1)	15 (35.6, 21.5–59.1)
Serious infections	2 (0.9, 0.2–3.6)	2 (2.2, 0.5–8.8)	3 (7.9, 2.5–24.4)	8 (3.5, 1.8–7.0)	2 (2.0, 0.5–8.2)	3 (7.1, 2.3–22.1)
Herpes zoster	0 (0.0, 0.0–1.7)	2 (2.2, 0.5–8.8)	1 (2.6, 0.1–14.6)	5 (2.2, 0.7–5.1)	1 (1.0, 0.1–7.2)	0 (0.0, 0.0–8.8)
Opportunistic infections	0 (0.0, 0.0–1.7)	0 (0.0, 0.0–4.0)	0 (0.0, 0.0–9.7)	0 (0.0, 0.0–1.6)	0 (0.0, 0.0–3.8)	0 (0.0, 0.0–8.8)
MACE (adjudicated)	2 (0.9, 0.2–3.6)	1 (1.1, 0.2–7.8)	0 (0.0, 0.0–9.7)	3 (1.3, 0.4–4.1)	1 (1.0, 0.1–7.2)	0 (0.0, 0.0–8.8)
VTE	NR	NR	NR	NR	NR	NR
DVT/PE (adjudicated)	1 (0.4, 0.1–3.2)	0 (0.0, 0.0–4.0)	0 (0.0, 0.0–9.7)	2 (0.9, 0.2–3.5)	0 (0.0, 0.0–3.8)	1 (2.4, 0.1–13.2)
Malignancy (excluding NMSC)	4 (1.8, 0.7–4.8)	3 (3.3, 1.1–10.2)	0 (0.0, 0.0–9.7)	3 (1.3, 0.4–4.1)	3 (3.1, 1.0–9.5)	2 (4.7, 0.6–17.2)
NMSC	0 (0.0, 0.0–1.7)	0 (0.0, 0.0–4.0)	0 (0.0, 0.0–9.7)	0 (0.0, 0.0–1.6)	0 (0.0, 0.0–3.8)	2 (4.7, 0.6–17.2)

Notes: Data presented as number of events (EAIR/100 PYE, 95% CI) unless otherwise noted. EAIR and 95% CI were estimated using Poisson regression model including treatment group with an offset of natural log of exposure time. If any treatment had 0 events, exact Poisson method was applied. Adapted with permission from John Wiley and Sons. Buch M, Takeuchi T, Rajendran V, et al. Clinical outcomes up to week 48 of ongoing filgotinib RA long-term extension trial of biologic DMARD inadequate responders initially on filgotinib or placebo in a Phase 3 trial. Arthritis & Rheumatology, volume 73, supplement 9, 2021.[33]

Abbreviations: AE, adverse event; bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DVT, deep vein thrombosis; EAIR, exposure-adjusted incidence rate; IR, inadequate response; MACE, major adverse cardiovascular events; NMSC, nonmelanoma skin cancer; NR, not reported; PBO, placebo; PE, pulmonary embolism; PYE, patient-years exposure; SOC, standard-of-care; TE, treatment-emergent; TEAE, treatment-emergent AE; VTE, venous thromboembolism.

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Table 7 Safety Results Among MTX-Naïve Patients from FINCH 4

	Patients Rerandomized from 100 mg of Filgotinib + MTX to 100 mg of Filgotinib (n=169)	Patients Rerandomized from MTX to 100 mg of Filgotinib (n=151)	Patients Continuing 200 mg of Filgotinib (n=167)	Patients Rerandomized from 200 mg of Filgotinib + MTX to 200 mg of Filgotinib (n=325)	Patients Rerandomized from MTX to 200 mg of Filgotinib (n=148)
TEAEs	118 (49.9, 41.7–59.8)	100 (46.4, 38.2–56.5)	109 (46.9, 38.9–56.6)	236 (49.7, 43.8–56.5)	108 (50.6, 41.9–61.1)
TE serious AEs	21 (8.9, 5.8–13.6)	14 (6.5, 3.9–11.0)	14 (6.0, 3.6–10.2)	28 (5.9, 4.1–8.5)	14 (6.6, 3.9–11.1)
Deaths	0 (0.0, 0.0–1.6)	0 (0.0, 0.0–1.7)	1 (0.4, 0.1–3.1)	5 (1.1, 0.3–2.5)	0 (0.0, 0.0–1.7)
Infections	65 (27.5, 21.6–35.1)	59 (27.4, 21.2–35.4)	69 (29.7, 23.4–37.6)	135 (28.5, 24.0–33.7)	61 (28.6, 22.2–36.7)
Serious infections	6 (2.5, 1.1–5.7)	4 (1.9, 0.7–4.9)	7 (3.0, 1.4–6.3)	5 (1.1, 0.4–2.5)	4 (1.9, 0.7–5.0)
Herpes zoster	2 (0.8, 0.2–3.4)	2 (0.9, 0.2–3.7)	4 (1.7, 0.6–4.6)	4 (0.8, 0.3–2.2)	4 (1.9, 0.7–5.0)
Opportunistic infections	2 (0.8, 0.2–3.4)	0 (0.0, 0.0–1.7)	0 (0.0, 0.0–1.6)	1 (0.2, 0.0–1.5)	0 (0.0, 0.0–1.7)
MACE[a]	0 (0.0, 0.0–1.6)	0 (0.0, 0.0–1.7)	2 (0.9, 0.2–3.4)	3 (0.6, 0.1–1.8)	0 (0.0, 0.0–1.7)
VTE[b]	0 (0.0, 0.0–1.6)	0 (0.0, 0.0–1.7)	1 (0.4, 0.1–3.1)	1 (0.2, 0.0–1.2)	0 (0.0, 0.0–1.7)
DVT/PE	NR	NR	NR	NR	NR
Malignancy (excluding NMSC)	4 (1.7, 0.6–4.5)	0 (0.0, 0.0–1.7)	0 (0.0, 0.0–1.6)	3 (0.6, 0.2–2.0)	1 (0.5, 0.0–2.6)
NMSC	2 (0.8, 0.2–3.4)	0 (0.0, 0.0–1.7)	1 (0.4, 0.1–3.1)	3 (0.6, 0.2–2.0)	1 (0.5, 0.0–2.6)

Notes: Data presented as number of events (EAIR/100 PYE, 95% CI) unless otherwise noted. EAIR and 95% CIs were estimated using Poisson regression model including treatment group with an offset of natural log of exposure time. [a]Positively adjudicated. [b]VTE adjudicated for DVT and PE. Adapted with permission from John Wiley and Sons. Aletaha D, Westhovens R, Atsumi T, et al. Clinical outcomes of MTX-naïve RA patients on filgotinib long-term extension trial initially on FIL or MTX during Phase 3 parent trial. Arthritis & Rheumatology, volume 73, supplement 9, 2021.[35]

Abbreviations: AE, adverse event; CI, confidence interval; DVT, deep vein thrombosis; EAIR, exposure-adjusted incidence rate; MACE, major adverse cardiovascular events; MTX, methotrexate; NMSC, nonmelanoma skin cancer; NR, not reported; PE, pulmonary embolism; PYE, patient-years exposure; TE, treatment-emergent; TEAE, treatment-emergent AE; VTE, venous thromboembolism.

100 mg filgotinib or among those rerandomized from MTX to 200 mg filgotinib for the LTE (Table 7).[35] Incidence of TEAEs, AEs of Grade 3 or higher, SAEs, and infections did not appear to increase among patients rerandomized from MTX to filgotinib for the LTE, while EAIRs of HZ were comparable across treatment arms among MTX-naïve patients, regardless of parent-trial treatment (Table 7).[17,35] In general, the rates of AESIs among MTX-naïve patients were low; however, they tended to be higher among patients maintained on filgotinib from the parent study.[35]

Summary of Long-Term Safety and Tolerability of Filgotinib

The safety profile of filgotinib in RA remained broadly consistent with that of the parent trials in each of the LTE studies. RA inflammation leads to increased cardiac abnormalities and physiologic changes, such as increased arterial stiffness, changes in lipid salvage, and destabilized plaque, leading to an increased risk of cardiovascular events among patients with RA.[41–49] MACE were infrequently reported in the LTE studies of filgotinib, which is of particular importance, as careful consideration of cardiovascular risk must inform medication choices for patients with RA.[16,33–35,41] Most deaths in the LTE studies were due to cardiovascular events, serious infection, and malignancies.[19] All fatal myocardial infarction and strokes reported in the LTE occurred in patients with ≥1 cardiovascular risk factor.[19] Patients with RA treated with JAKis can be susceptible to latent viral infections, such as HZ, because JAKis block intracellular signals on the cytokine level modulating the immune response; therefore, HZ infections remain a safety risk for the long-term use of filgotinib.[12–21,33–35,50] However, given that other JAKis (tofacitinib, baricitinib, and upadacitinib) are reported to be associated with an increased risk of infection, as well as of reactivation of HZ, it is likely such risk is a class effect rather than unique to filgotinib.[19,51–54] A 2020 meta-analysis by Harrington et al suggested that filgotinib had the lowest incidence of HZ among the JAKis.[55]

Long-Term Efficacy of Filgotinib

The efficacy of filgotinib was measured using the ACR20/50/70 response rate, the Disease Activity Score in 28 joints with CRP (DAS28[CRP]) response rate, and Clinical Disease Activity Index (CDAI) across the clinical trials.[12–18,20,21,33–35] The ACR20/50/70 responses are commonly used criteria for measuring response rate and are reported as at least a 20%, 50%, and 70% improvement in at least 3 of 5 ACR core set measures (patient's pain, patient's global assessment of disease activity, physician's global assessment of disease activity, physical function, and highly sensitive quantification of CRP concentration).[56] In patients with RA using JAKis, significant advantages for improving the quality of life, reducing inflammation, and efficacy in reducing disease activity have been shown.[57] In a meta-analysis of patients treated with JAKis, ACR response rates were considerably higher, and JAKis showed a significant advantage in all disease activity parameters (DAS28[CRP], DAS28-erythrocyte sedimentation rate, simplified disease activity index, and CDAI).[57] Improvements in efficacy parameters are seen likely because JAKis interfere with inflammatory responses and disrupt the pathogenesis of RA.[4,5,7,10,11] These outcomes were analyzed in the parent trials using the nonresponder imputation (NRI) approach, whereas the outcomes reported from the LTEs are observed cases (OC). As such, the as-observed data from the LTEs may report values higher than that of the parent trials. Data cannot be directly compared between parent trials and LTEs, because the higher values seen in the LTE studies may overestimate the effect of filgotinib.

Filgotinib in Patients with Inadequate Responses to Methotrexate

The ACR20/50/70 responses in DARWIN 3 at week 204, based on the OC analysis, were 89.3%/69.6%/49.1% in the filgotinib + MTX group and 91.8%/69.4%/44.4% in the filgotinib monotherapy group, respectively (Figure 1).[16] The observed ACR response rates in the LTE were slightly higher than those reported in the parent trials at week 24.[15,18] The proportions of patients who achieved DAS28(CRP) <2.6 were sustained over time: 57.5% of the filgotinib + MTX groups and 49.6% of the filgotinib monotherapy group achieved DAS28(CRP) <2.6 at week 204 of the LTE, suggesting long-term efficacy for those remaining on filgotinib (Figure 1).[16]

In FINCH 4, numerically greater proportions of patients met response criteria (ACR20/50/70, DAS28[CRP], and CDAI) at week 48 of the LTE in the filgotinib 200-mg once-daily group compared with the filgotinib 100-mg group, regardless of their treatment in the parent trial, FINCH 1 (Figure 2).[34] ACR20/50/70 response rates among ADA patients rerandomized to 200 mg of filgotinib were slightly higher at LTE week 48 than that achieved with ADA in the parent trial

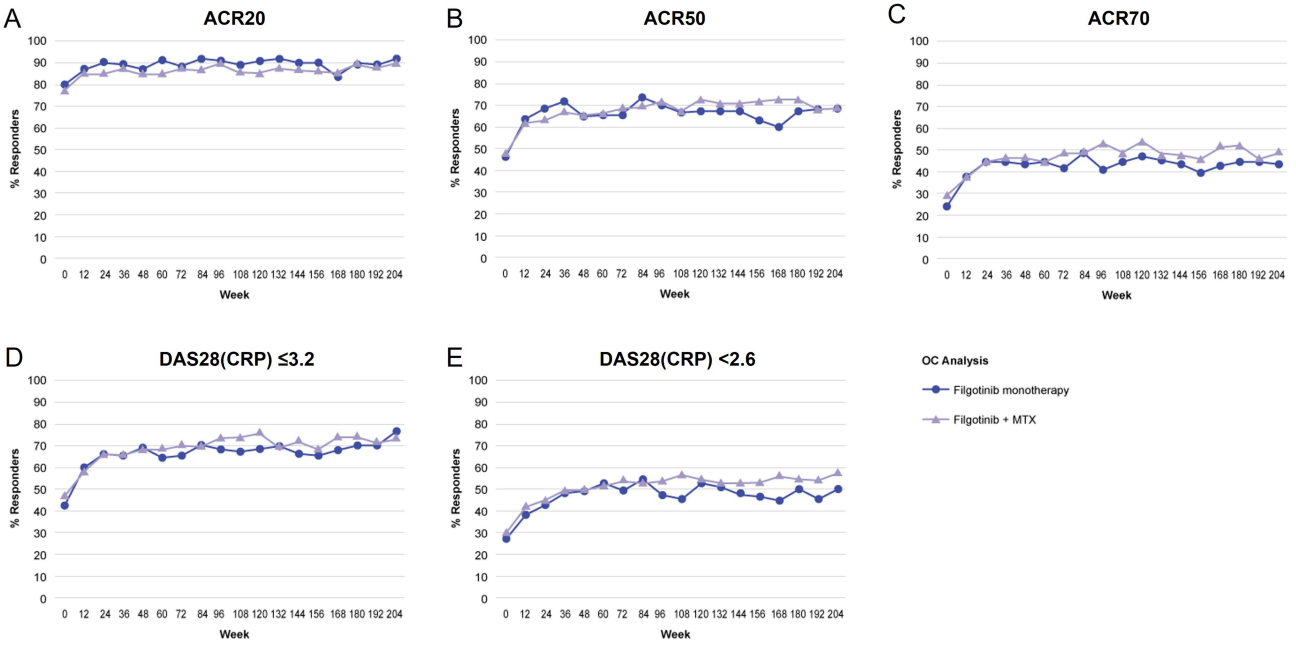

Figure 1 Efficacy results among MTX-IR patients from DARWIN 3.
Notes: ACR20/50/70 response rates (**A**–**C**) and DAS28(CRP) response rates (**D** and **E**) of MTX-IR patients in DARWIN 3 for the filgotinib monotherapy and filgotinib in combination with MTX treatment arms have been plotted from baseline to week 204 (week 156 of the LTE). Adapted with permission from The Journal of Rheumatology Publishing Co. Ltd. Kavanaugh A, Westhovens RR, Winthrop KL, et al. Safety and efficacy of filgotinib: up to 4-year results from an open-label extension study of Phase II rheumatoid arthritis programs. Journal of Rheumatology, volume 48, issue 8, pages 1230–1238, 2021. Permission conveyed through Copyright Clearance Center, Inc.[16]
Abbreviations: ACR, American College of Rheumatology; DAS28(CRP), Disease Activity Score for 28 joint count using C-reactive protein; IR, inadequate response; LTE, long-term extension; MTX, methotrexate; OC, observed cases.

to week 52, and for those who had not achieved CDAI remission at LTE baseline, 22% and 18% were able to achieve such remission with filgotinib 200 or 100 mg, respectively.[12,34] Broadly speaking, the proportions of patients achieving ACR20/50/70, DAS28(CRP) ≤3.2 and <2.6, and CDAI ≤10 and ≤2.8 were maintained in all treatment arms up to week 48 of the FINCH 4 LTE, suggesting maintenance of long-term efficacy.[4,34]

Filgotinib in Patients with Inadequate Responses to bDMARDs

In general, the ACR20/50/70 response rates in bDMARD-IR patients were similar between week 24 of the FINCH 2 parent trial and week 48 of the LTE.[14,33] The proportions of DAS28(CRP) responders were maintained among patients continuing filgotinib treatment from the parent trial into the LTE and increased among patients who were rerandomized from placebo or SOC in the parent trial to filgotinib treatment up to week 48 of the LTE (Figure 3).[33] However, despite increasing efficacy among patients who had been on SOC in the parent trial, the proportion who achieved DAS28(CRP) response at LTE week 48 was lower than among other groups, potentially revealing a difficult-to-treat population.[33] The total number of such patients included in FINCH 4 was low (n=45).[33] Further research into this specific subpopulation of patients is warranted, as they may respond differently to therapeutic treatment.

Filgotinib in Methotrexate-Naïve Patients

Overall, response rates (ACR20/50/70, DAS28[CRP], and CDAI) from LTE baseline slightly decreased to week 12 and then stabilized to week 48 among MTX-naïve patients treated with filgotinib in the FINCH 3 parent trial (Figure 4).[35] Patients who were rerandomized from MTX monotherapy (FINCH 3) to filgotinib (FINCH 4) showed increased response rates during the LTE. Further, independent of initial treatment group in the parent study, the response rates at LTE week 48 were comparable across groups.[35]

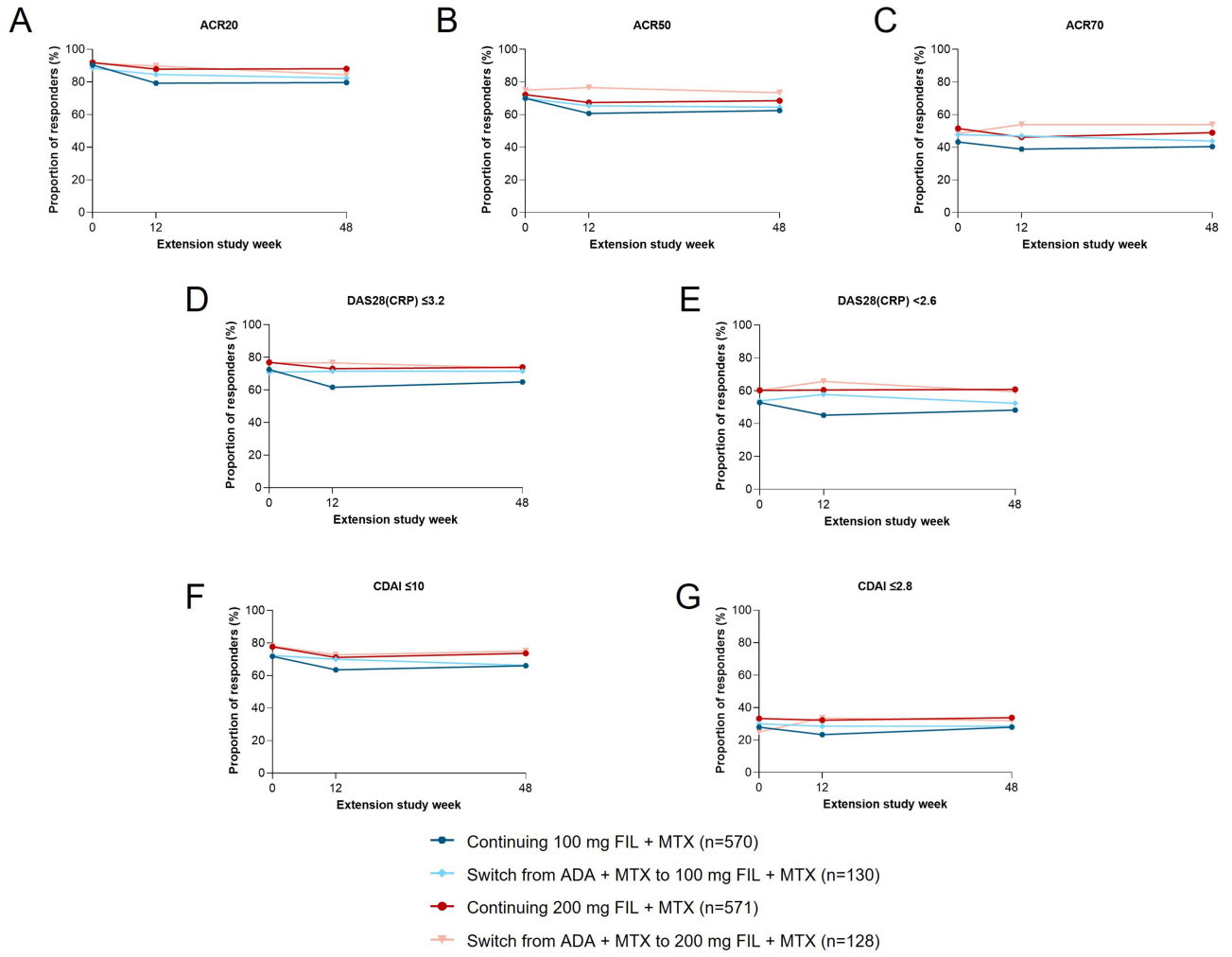

Figure 2 Efficacy results among MTX-IR patients from FINCH 4.

Notes: ACR20/50/70 response rates (**A**–**C**), DAS28(CRP) response rates (**D** and **E**), and CDAI response rates (**F** and **G**) of MTX-IR patients in FINCH 4 for the 4 different treatment arms have been plotted from baseline to week 48 of the LTE (FINCH 4). ACR20 is calculated based on parent study baseline. Analyzed using the logistic regression model including treatment group and stratification factors; no formal comparison of efficacy outcomes was performed. DAS28(CRP) <2.6 or CDAI ≤2.8 signify remission and DAS28(CRP) ≤3.2 or CDAI ≤10 signify low disease activity. Data from Combe et al.[34]

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CDAI, Clinical Disease Activity Index; DAS28(CRP), Disease Activity Score for 28 joint count using C-reactive protein; FIL, filgotinib; IR, inadequate response; LTE, long-term extension; MTX, methotrexate.

Summary of Long-Term Efficacy of Filgotinib

In summary, filgotinib efficacy was mostly maintained across MTX-IR, MTX-naïve, and bDMARD-IR patient groups in the longer term for those who remained on treatment.[16,20,33–35] Improvements in the efficacy outcomes measured during the LTE trials were comparable to those in the parent trials.[12–18,20,21,33–35] However, the response rates among bDMARD-IR patients were lower relative to those observed among the MTX-IR and MTX-naïve populations.[14,16,20,33–35]

Persistence and Patient-Reported Outcomes with Filgotinib

Patient completion of the FINCH parent trials was similar and independent of patient characteristics.[59] Completion rates were 82.1%, 86.4%, 85.0% among MTX-naïve, MTX-IR, and bDMARD-IR patients, respectively.[59] Of the patients followed into the LTE from the MTX-IR parent study, 91% of patients who continued 200 mg filgotinib, 88% of those who continued 100 mg filgotinib, 92% of those rerandomized from ADA to 200 mg filgotinib, and 89% of those randomized from ADA to 100 mg filgotinib were still on study drug as of June 2020.[34] Of patients who entered the LTE from the MTX-naïve parent study, 89% from the filgotinib 200-mg groups and 85% from the filgotinib 100-mg groups were still on study treatment, as were 89% of those rerandomized from MTX to filgotinib 200 mg and 88% of those rerandomized to filgotinib 100 mg.[35]

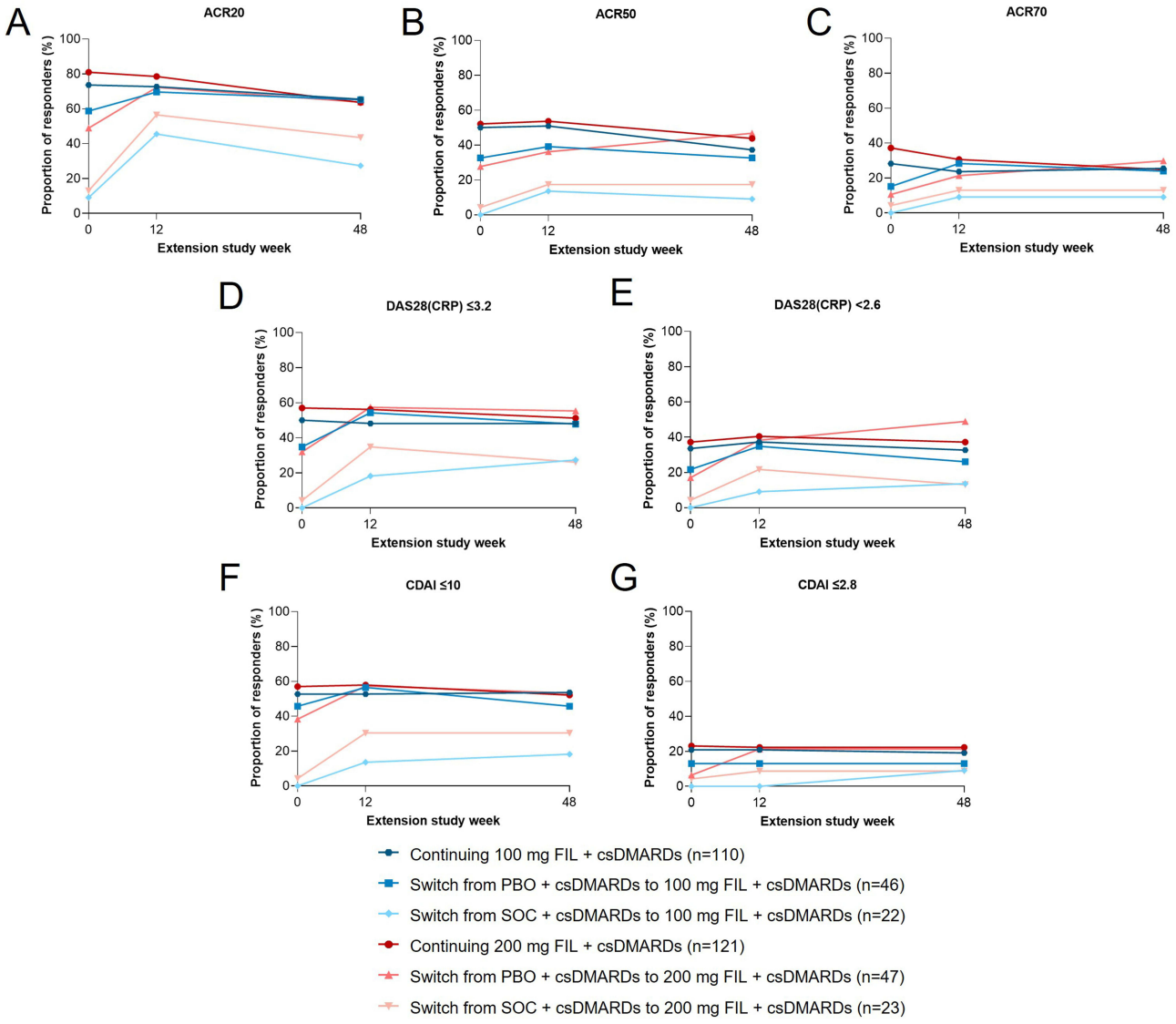

Figure 3 Efficacy results among bDMARD-IR patients from FINCH 4.
Notes: ACR20/50/70 response rates (**A**–**C**), DAS28(CRP) response rates (**D** and **E**), and CDAI response rates (**F** and **G**) of bDMARD-IR patients in FINCH 4 for the 4 different treatment arms have been plotted from baseline to week 48 of the LTE (FINCH 4). DAS28(CRP) <2.6 or CDAI ≤2.8 signify remission and DAS28(CRP) ≤3.2 or CDAI ≤10 signify low disease activity. Data from Buch et al.[33]
Abbreviations: ACR, American College of Rheumatology; bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28(CRP), Disease Activity Score for 28 joint count using C-reactive protein; FIL, filgotinib; IR, inadequate response; LTE, long-term extension; PBO, placebo; SOC, standard-of-care.

Lastly, of the bDMARD-IR patients who entered the LTE, 66% of those receiving 200 mg filgotinib and 69% of those receiving 100 mg filgotinib were still on study treatment as of June 2020.[33] Patients still on LTE filgotinib from placebo were 75% for 200 mg filgotinib and 70% for 100 mg filgotinib, while those patients among the SOC group were 57% for 200 mg filgotinib and 59% for 100 mg filgotinib.[33] The proportion of patients continuing filgotinib in the bDMARD-IR subpopulation was lower than the proportions of the MTX-IR and MTX-naïve populations.[33–35] Given that the bDMARD-IR patients experienced more SAEs and infections, as well as had lower efficacy rates than patients with other treatment backgrounds, this may have contributed to lower treatment persistence over the long term.[33–35]

The DARWIN 3 LTE included 93.5% of patients who completed the parent trials.[16] However, the proportion of patients in DARWIN 3 remaining on the study treatment at week 204 was lower (54.3%) than the completion rate of the parent trials.[15,16,18] This may be due to the long duration of the trial for patients on study treatment. The most common reasons for discontinuation

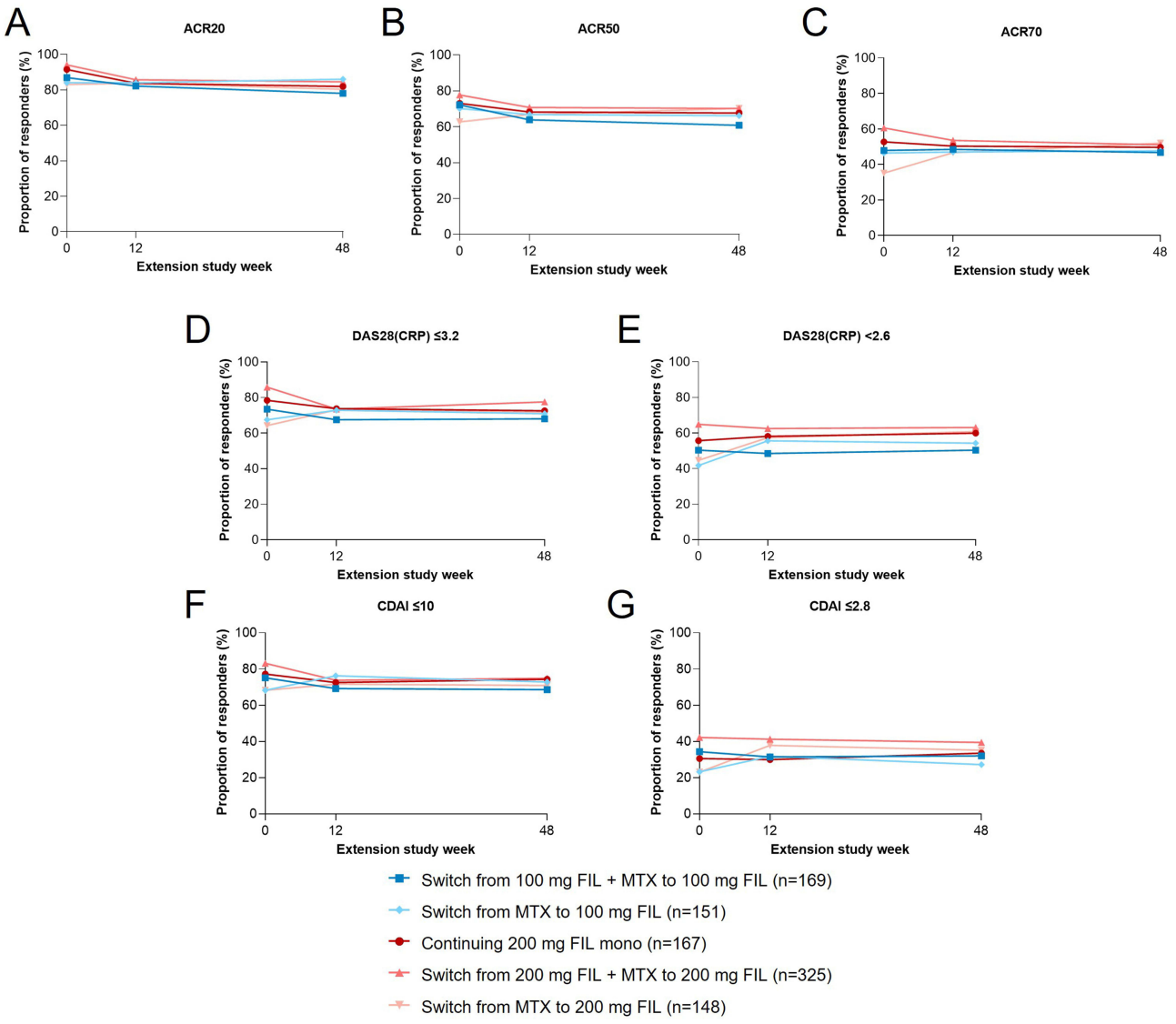

Figure 4 Efficacy results among MTX-naïve patients from FINCH 4.
Notes: ACR20/50/70 response rates (**A**–**C**), DAS28(CRP) response rates (**D** and **E**), and CDAI response rates (**F** and **G**) of MTX-naïve patients in FINCH 4 for the 4 different treatment arms have been plotted from baseline to week 48 of the LTE (FINCH 4). DAS28(CRP) <2.6 or CDAI ≤2.8 signify remission and DAS28(CRP) ≤3.2 or CDAI ≤10 signify low disease activity. Data from Aletaha et al.[58]
Abbreviations: ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; DAS28(CRP), Disease Activity Score for 28 joint count using C-reactive protein; FIL, filgotinib; LTE, long-term extension; mono, monotherapy; MTX, methotrexate.

were AEs (28.7%, n=212) and patients' requests to discontinue (10.6%, n=78).[16] Of the 212 patients with AEs, latent tuberculosis/positive tuberculosis test accounted for 46.7%.[16] The interim data for continuation in FINCH 4 have not yet been reported, and the study is expected to be completed in 2025.[24] It is important to note that for the LTEs, patients were rerandomized from active comparators (MTX, ADA, and csDMARDs) to filgotinib by study design rather than for safety, efficacy, or tolerability.[20,33] More evidence is needed for the tolerability of filgotinib in real-world settings.

Patient perspectives on treatment can also be assessed directly via PRO measures. PROs provide insight into patient quality of life (QoL) and the impact of disease on patient functionality—important measures to consider when making treatment decisions.[60] QoL instruments, including the Short Form Health Survey 36 (SF-36), Health Assessment Questionnaire–Disability Index (HAQ-DI), or Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale, were administered throughout the DARWIN and FINCH programs.[59,60] Though the PROs from the LTEs are not yet available, data collected from patients in the FINCH parent trials have been reported.[59] Outcomes from these trials

show that filgotinib improved patient functional status, QoL, fatigue, work productivity and presenteeism, and assessments of disease activity in multiple patient populations.[59] MTX-IR patients treated with 200 mg filgotinib + MTX showed greater improvements in PRO measures from baseline than those treated with ADA + MTX, while 100 mg filgotinib + MTX and ADA + MTX patients experienced similar improvements in PRO measures throughout the study.[59] Patients treated with either dosage of filgotinib achieved clinically meaningful improvements relative to placebo.[59] In DARWIN 1 and 2, patients treated with filgotinib showed improvements in all PROs, with the exception of the SF-36 mental component in the add-on study, compared to placebo.[60] Improvements in HAQ-DI, FACIT-F, patient's global assessment, and pain were maintained or improved to week 24.[60] While the FINCH and DARWIN randomized controlled trials provide insight into the potential improvements in PROs with filgotinib treatment, analysis of PROs in the LTEs is needed to determine whether these improvements in QoL persist long term.

To supplement the existing PRO data, the Adelphi RA Disease Specific Programme has provided insight into the management of RA using patient-centric outcomes in real-world settings.[61] This large, multinational, point-in-time survey was conducted among rheumatologists and their patients with RA in Europe (Belgium, France, Germany, Italy, Spain, and UK) between January and October 2020.[61] Physicians completed record forms for clinical and treatment data including their rationales for current treatment choices. These were then categorized into clinical or patient-centric reasons.[61] JAKis were prescribed to 18.5% of patients, with 57.4% receiving treatment as monotherapy.[61] When patient-centric, rheumatologist-stated reasons for any advanced therapy choice were investigated, the "acceptability of method of delivery for the patient" was the most commonly selected response at 23%, followed by "ease of product use for the patient" (16%) and "low out-of-pocket cost/affordability for patients" (10%).[61] When looking at patients with RA treated with JAKis, higher rates of "acceptability of method of delivery for the patient" (35%) and "ease of product use for the patient" (24%) were reported by rheumatologists (Figure 5).[61] Furthermore, improvement or maintenance of QoL was listed more often as a common patient-centric reason for physicians to prescribe JAKis (31.0%) than to prescribe other advanced therapies.[61]

Expert Opinions

Filgotinib shows promise to be well tolerated and effective in the long term as a treatment for moderate-to-severe RA. JAKis have similar efficacy in RA with potentially distinct safety profiles, but cross-trial comparisons have inherent

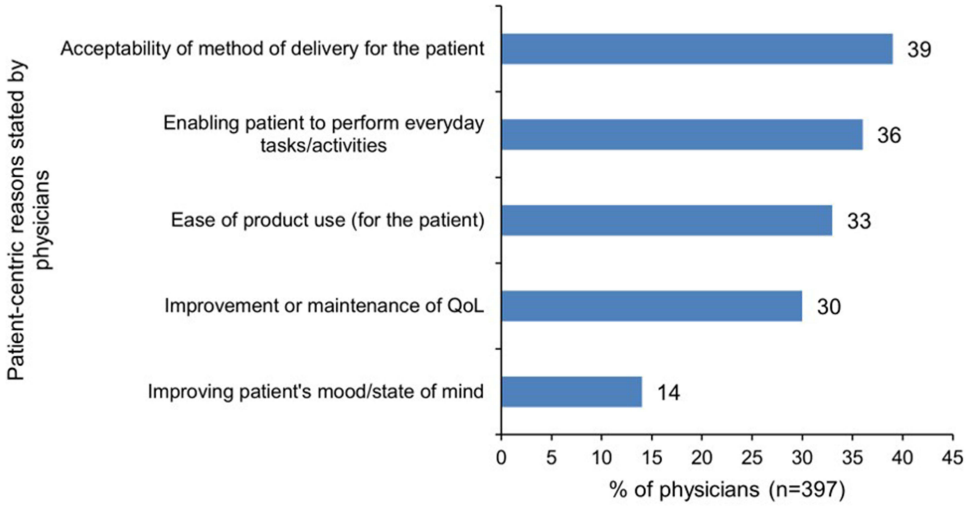

Figure 5 Patient-centric reasons physicians prescribed JAKis to patients with RA.
Notes: The top 5 most commonly reported patient-centric reasons for physicians prescribing JAKis in patients with RA from a large, multinational, point-in-time survey conducted among rheumatologists in Europe (Belgium, France, Germany, Italy, Spain, and UK) between January and October 2020. Reproduced with permission from John Wiley and Sons. Taylor P, Fautrel B, Piette Y, et al. Physicians' reasons for prescribing Janus kinase inhibitors (JAKi) in patients with rheumatoid arthritis, and associated alignment between physicians and patients in a real-world clinical setting. Arthritis & Rheumatology, volume 73, supplement 9, 2021.[62]
Abbreviations: JAKi, Janus kinase inhibitor; QoL, quality of life; RA, rheumatoid arthritis.

limitations and potential biases.[63] The safety profiles of JAKis may differ—regarding incidences of HZ, serious infections, venous thromboembolisms, decreased natural killer cell numbers, thrombocytopenia, and anemia—and these differences could be related to JAKi selectivity/preference for cytokine signaling by distinct JAK pairs.[63] At therapeutic doses, filgotinib showed similar selectivity as other JAKis in the inhibition of the JAK1 pathway in an in vitro analysis.[63]

Filgotinib appears to be well tolerated in the longer term, as 85% to 92% of patients across treatment groups were still on filgotinib treatment after a median of 2.2 years.[34–36] Better understanding of the effects of filgotinib treatment on semen parameters is needed.[64] The Phase 2 MANTA and MANTA-RAy studies are investigating the potential impacts of filgotinib on semen parameters among men with active inflammatory diseases.[65] No differences in semen parameters were noted between treatment groups in the proportion of patients who had a 50% or more decrease from baseline in semen parameters at week 13 (pooled primary endpoint: filgotinib 6.7%, placebo 8.3%) and at week 26.[22]

While controlled clinical trials for filgotinib have provided valuable data, there is an ongoing need to assess whether the trends observed in these settings reflect real-world populations. Ongoing observational studies assessing the safety, effectiveness, persistence, and PROs of filgotinib in real-world settings are underway (FILOSOPHY, NCT04871919; PARROTFISH, NCT05323591).[66,67] These studies aim to assess the persistence rate of patients with moderate-to-severe RA remaining on filgotinib after 24 months of follow-up and to assess disease activity and PROs for pain, fatigue, functional assessment, and work productivity.[66,67]

Conclusion

The international LTEs assessing the efficacy, safety, and tolerability of filgotinib provide a better understanding of filgotinib as a treatment for patients with moderate-to-severe RA. Patients completing one of the parent studies were eligible to participate in the LTEs. Both DARWIN 3 and FINCH 4 demonstrate that the long-term safety and efficacy of filgotinib remain comparable to that shown in short-term data from the parent trials. PROs collected during the parent trials showed marked improvements with filgotinib compared to active comparators, and these PROs are being studied in the FINCH 4 LTE. Patients' persistence in the LTEs suggests that filgotinib remains tolerable over time. Overall, the data collected from short- and long-term clinical trials have shown filgotinib to be a safe, effective, and tolerable option for patients with moderate-to-severe RA with various treatment backgrounds. However, more evidence is needed to assess whether such trends are observed in a real-world setting.

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