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Safety and Efficacy of Filgotinib: Up to 4-year Results From an Open-label Extension Study of Phase II Rheumatoid Arthritis Programs

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ABSTRACT. ***Objective.*** The long-term safety and efficacy of filgotinib (from phase II studies), with or without methotrexate (MTX), for the treatment of patients with rheumatoid arthritis was assessed in DARWIN 3, a long-term, open-label extension study (ClinicalTrials.gov: NCT02065700).

Methods. Eligible patients completing the 24-week DARWIN 1 (filgotinib + MTX) and DARWIN 2 (filgotinib monotherapy) studies entered DARWIN 3, where they received filgotinib 200 mg/day, except for 15 men who received filgotinib 100 mg/day. Safety analyses were performed using the safety analysis set and the exposure-adjusted incidence rate (EAIR) of treatment-emergent adverse events (TEAEs) was calculated. Efficacy was assessed from baseline in the parent studies.

Results. Of 790 patients completing the phase II parent studies, 739 enrolled in the study. Through April 2019, 59.5% of patients had received ≥ 4 years of the study drug. Mean (SD) exposure to filgotinib was 3.55 (1.57) years in the filgotinib + MTX group and 3.38 (1.59) years in the filgotinib monotherapy group. EAIR per 100 patient-years of exposure for TEAEs was 24.6 in the filgotinib + MTX group and 25.8 in the filgotinib monotherapy group, and for serious TEAEs, the EAIR was 3.1 and 4.3, respectively. American College of Rheumatology 20/50/70 responses among patients remaining in the study could be maintained through 4 years, with 89.3%/69.6%/49.1% of the filgotinib + MTX group and 91.8%/69.4%/44.4% of the monotherapy group maintaining ACR20/50/70 responses, respectively, based on observed data.

Conclusion. Filgotinib was well tolerated with a 4-year safety profile comparable to that of the parent trials, both in patients receiving combination therapy with MTX or as monotherapy.

Key Indexing Terms: ACR improvement criteria, inflammation, methotrexate, rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent joint inflammation, and if insufficiently treated, may lead to loss of joint function, disability, and decreased quality of life. The aim of RA treatment is to achieve persistent remission or low disease activity by inhibiting inflammation and preventing joint damage and disability.[1,2] Conventional synthetic and biologic disease-modifying antirheumatic drugs (csDMARDs and bDMARDs) used to treat RA may have limitations for some patients, including slow and incomplete responses, loss of efficacy over time, and/or side effects.[3,4] Inhibition of the Janus kinase (JAK) pathway, which blocks intracellular signaling of cytokine pathways implicated in

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RA pathogenesis, has been shown to be effective in patients with RA. Three JAK inhibitors are approved globally for the treatment of RA: tofacitinib, baricitinib, and upadacitinib.[5,6,7,8,9,10]

Filgotinib, an orally administered, preferential JAK1 inhibitor, is approved in the European Union and Japan for the treatment of RA and is currently under investigation for other chronic inflammatory diseases. In 2 prior phase IIb studies, filgotinib, in combination with methotrexate (MTX) and as monotherapy,[11,12] was shown to be effective in treating RA. The DARWIN 3 study (ClinicalTrials.gov: NCT02065700) is an ongoing, open-label, long-term extension (LTE) study of the phase IIb parent studies evaluating the long-term safety and tolerability of filgotinib. Safety and efficacy data through 4 years are presented here.

METHODS

Study patients. Patients rolled over to the LTE included 84.3% of patients who were treated and 93.5% who completed the 24-week parent studies. Patients from DARWIN 1 were aged ≥ 18 years with a diagnosis of RA according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism criteria for ≥ 6 months. They were ACR functional class I–III with ≥ 6 of swollen joint count in 66 joints, ≥ 8 of tender joint count in 68 joints, C-reactive protein (CRP) ≥ 0.7 times the upper limit of normal (ULN); and were taking MTX for ≥ 6 months and corticosteroids ≤ 10 mg/day at stable doses for ≥ 4 weeks prior to screening. Patients with a prior history of bDMARD treatment and/or taking csDMARDs other than MTX were excluded.[12] Eligibility criteria for patients from DARWIN 2 were similar, with the exceptions of higher screening CRP (≥ 1.2× ULN), allowance of antimalarials, and required MTX washout.[11]

Study design. Patients in DARWIN 1 were randomized to placebo or filgotinib (total 50–200 mg/day, given either once or twice daily) plus MTX (15–25 mg/week).[12] In DARWIN 2, patients were randomized to placebo or filgotinib monotherapy (50, 100, or 200 mg daily).[11] Patients were allowed to start or stop MTX during LTE according to the investigator's judgment. All patients enrolled in the LTE received filgotinib 200 mg, either as 200 mg daily or 100 mg twice daily, except for 15 men in the United States who received 100 mg daily due to a requirement by the U.S. Food and Drug Administration (7 analyzed as filgotinib + MTX and 8 as filgotinib monotherapy). Dose adjustment between 100 mg and 200 mg daily was allowed for safety/tolerability issues. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by our US central institutional review board (approval no. INC1-14-016). Patients provided written informed consent to participate in the study and had the right to withdraw at any time.

Assessments. Safety variables included all events that occurred after patients received their first dose of filgotinib (in either the parent or LTE study). Safety assessments included monitoring of adverse events (AEs) and laboratory abnormalities according to National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) 4.03 toxicity grade. Major adverse cardiac events (MACE; defined as cardiovascular [CV] death, myocardial infarction, stroke) and thromboembolic events were adjudicated by an independent committee. For AEs, relatedness to study drug was assessed by the investigator. Annual tuberculosis (TB) testing was performed using the 3-tube QuantiFERON-TB Gold assay in the parent studies; in the LTE study, a newer, more sensitive 4-tube QuantiFERON-TB Gold Plus assay was utilized. All newly positive TB tests resulted in study exit until March 2018, at which time patients with latent TB could remain in the study with appropriate latent TB treatment initiation and completion.

Efficacy was measured as the change from baseline in the parent studies and assessed every 12 weeks, except for Functional Assessment of Chronic Illness Therapy Fatigue scale and 36-item Short Form health survey questionnaires.

Statistical analyses. Patients were grouped as filgotinib + MTX and filgotinib monotherapy based on their parent study designation. There were 22 patients from DARWIN 2 who started MTX and 1 patient from DARWIN 1 who did not receive MTX in the LTE. The analysis included all data from the parent studies through April 26, 2019, when all remaining patients (53.3% and 56.2% in the filgotinib + MTX and filgotinib monotherapy groups, respectively) had at least 4 years of filgotinib exposure (Supplementary Figure 1, available with the online version of this article). The safety analysis included all patients who received at least 1 dose of study drug. Treatment-emergent AEs (TEAEs) were defined as an AE that occurred on or after the first dose of filgotinib, up to 30 days after the last dose. Exposure-adjusted incidence rates (EAIRs) for TEAEs were calculated as total number of patients with the specific event divided by total patient-years of exposure (PYE) to filgotinib. Laboratory assessments were performed every 12 weeks. Changes in laboratory values were derived relative to the date of the first dose of filgotinib in either the parent studies or LTE. Treatment-emergent laboratory abnormalities were defined as values that increased by ≥ 1 toxicity grade from baseline at any postbaseline timepoint, up to the last dose of filgotinib plus 30 days.

Efficacy analyses included all patients who received ≥ 1 dose of study drug. For the analysis using observed cases (OC), missing data were not imputed. For the analysis using nonresponder imputation (NRI), missing data were imputed as nonresponder. For binary endpoints, both OC and NRI data were summarized using descriptive statistics (counts and proportions of patients) by treatment and visit. For continuous endpoints, the change scores were derived relative to the baseline value collected on the first dose date of any study drug in the parent studies.

RESULTS

Demographics/baseline characteristics. A total of 739 patients at 114 centers in 22 countries were enrolled in the LTE. A summary of demographics and baseline characteristics at the start of the parent studies is shown in Table 1. The majority of patients were female (81.5%, 81.8%) and White (75.3%, 74.8%), with a mean age of 53 and 52 years, in the filgotinib + MTX and filgotinib monotherapy groups, respectively. The mean MTX dose in the filgotinib + MTX group remained stable from the parent to LTE baseline (16.8–16.9 mg/week). At the LTE baseline, a majority were taking oral MTX (82.8% oral vs 17.2% other). Approximately half of the patients were on corticosteroids at the parent and LTE baseline with a mean dose of 6.1 mg/day in the LTE.

The total PYE to filgotinib was 2582 with mean ± SD exposure of 3.55 ± 1.57 years in the filgotinib + MTX group and 3.38 ± 1.59 years in the filgotinib monotherapy group with maximum exposure of 5.6 years (293.4 weeks) and 5.4 years (280.6 weeks), respectively. At the time of this analysis, 440 (59.5%) patients had received ≥ 4 years of filgotinib with 401 (54.3%) patients still remaining in the study. A total of 338 (45.7%) patients discontinued treatment prematurely: 232 (46.7%) in the filgotinib + MTX group and 106 (43.8%) in the filgotinib monotherapy group. The majority of patients who discontinued treatment prematurely (n = 299, 88.5%) had < 4 years of filgotinib exposure (Figure 1; Supplementary Figure 1, available with the online version of this article). The most common reasons for discontinuation were AEs (n = 212, 28.7%, with latent TB/positive TB test accounting for 46.7% of the 212 patients) and patient requests (n = 78, 10.6%). All but 12 discontinuations due to latent TB were protocol mandated prior to the protocol

Table 1. Demographics and baseline characteristics (all data represent characteristics at entry into the parent studies).

	Filgotinib + MTX, n = 497	Filgotinib Monotherapy, n = 242	Total, n = 739
Demographics at parent study baseline			
Age, yrs	53 ± 11.7	52 ± 12.2	53 ± 11.9
Female	405 (81.5)	198 (81.8)	603 (81.6)
Race			
White	374 (75.3)	181 (74.8)	555 (75.1)
Other	119 (23.9)	56 (23.1)	175 (23.7)
Black or African American	3 (0.6)	3 (1.2)	6 (0.8)
Asian	1 (0.2)	1 (0.4)	2 (0.3)
Native Hawaiian or Pacific Islander	0	1 (0.4)	1 (0.1)
BMI, kg/m^2	28.3 ± 5.74	27.6 ± 5.55	28.1 ± 5.69
Geographic region			
Latin America	186 (37.4)	75 (31.0)	261 (35.3)
Central and Eastern Europe, EU	136 (27.4)	53 (21.9)	189 (25.6)
Central and Eastern Europe, non-EU	79 (15.9)	73 (30.2)	152 (20.6)
West and Asia Pacific	96 (19.3)	41 (16.9)	137 (18.5)
Disease characteristics at parent study baseline			
Duration of RA from diagnosis, yrs[a]	8.3 ± 7.1	8.9 ± 7.1	8.5 ± 7.1
RF-positive	382 (76.9)	180 (74.4)	562 (76.0)
Anti-CCP–positive	402 (80.9)	192 (79.3)	594 (80.4)
Prior exposure to bDMARD[b]	48 (9.7)	19 (7.9)	67 (9.1)
Concurrent corticosteroids on first dosing date	239 (48.1)	143 (59.1)	382 (51.7)
Concurrent MTX dose on first dosing date, mg/mL	16.8 ± 4.2	NA	16.8 ± 4.2

Values are expressed as n (%) or mean ± SD. [a]Duration of RA (yrs) = (first dose date in core studies – date of initial diagnosis + 1)/365.25. [b]Patients were excluded from the parent studies if they had previous RA treatment with a bDMARD. The only exception to this was if the biologic agent had been received in a single clinical study > 6 months prior to enrollment and if the drug had been effective. bDMARD: biologic disease-modifying antirheumatic drug; CCP: cyclic citrullinated peptide; EU: European Union; MTX: methotrexate; NA: not applicable; RA: rheumatoid arthritis; RF: rheumatoid factor.

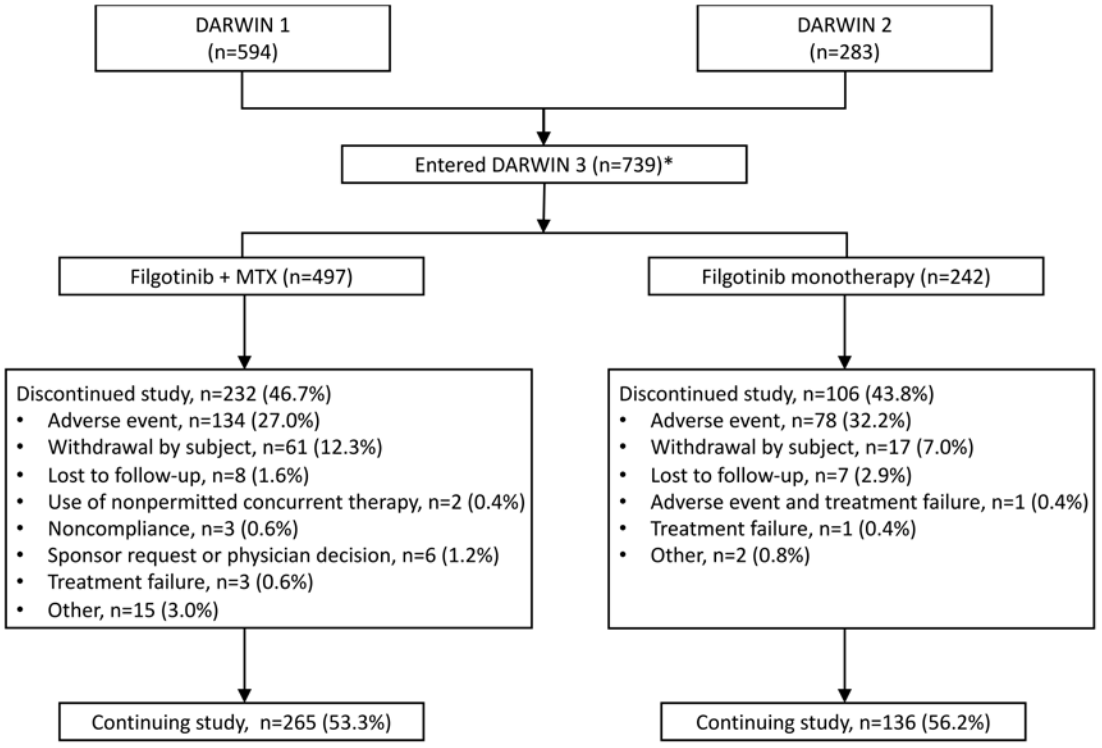

Figure 1. Patient disposition (April 26, 2019). * Patients were assigned to filgotinib + MTX or filgotinib monotherapy groups based on their parent study designation. Patients from DARWIN 1 were analyzed as filgotinib + MTX and patients from DARWIN 2 as filgotinib monotherapy. MTX: methotrexate.

amendment in March 2018. No active TB cases were reported by the investigators among patients who exited with a newly positive test. Dose reductions occurred in 31 patients due to AEs/intolerance (n = 24) or unknown reasons (n = 8), of which 11 increased back to 200 mg (Supplementary Table 1).

AEs. The number of TEAEs and EAIRs per 100 PYE are shown in Table 2. A total of 434 (EAIR 24.6) patients in the filgotinib + MTX group and 211 (EAIR 25.8) in the filgotinib monotherapy group experienced TEAEs, of which nearly half were considered treatment-related. Most TEAEs were mild or moderate in severity. The EAIRs for TEAEs that led to study discontinuation were 7.4 and 9.4 in the filgotinib + MTX and filgotinib monotherapy groups, respectively (Table 2).

Six deaths (3 in each group) occurred during the study, of which 4 were reported as study drug related (1 due to meningococcal meningitis, 2 due to non-Hodgkin lymphomas [NHL], and 1 due to pneumonia). The remaining deaths were due to 1 case of simultaneous deep vein thrombosis (DVT) and pulmonary embolism (PE) occurring > 30 days after the last filgotinib dose, and 1 case of metastatic leiomyosarcoma of cutaneous origin occurring 15 days after the last filgotinib dose.

Infectious and serious infectious AEs. The EAIRs for any infectious AEs were 16.3 and 15.9 in the filgotinib + MTX and filgotinib monotherapy groups, respectively. Twenty-four (EAIR 1.4) patients in the filgotinib + MTX and 16 (EAIR 2.0) in the filgotinib monotherapy group discontinued filgotinib due to infectious TEAEs. Most infectious TEAEs were mild or moderate in severity. The EAIRs for any serious infectious AEs were 0.6 and 1.7 in the filgotinib + MTX and filgotinib monotherapy groups, respectively (Table 2). The EAIRs for both infection categories were similar in patients with and without leukopenia (Supplementary Figure 2, available with the online version of this article). There were no cases of active TB. Twelve patients with latent TB who remained in the study received isoniazid for 3–10 months or a combination of rifampin and isoniazid for 3 months.

Herpes zoster virus infections. The EAIRs for herpes zoster virus (HZV) infections were 1.3 and 1.5 in the filgotinib + MTX and filgotinib monotherapy groups, respectively (Table 2). Except for 1 serious ophthalmic HZV case, all HZV infections were cutaneous, and mild or moderate in severity. Of 35 patients with HZV infections, 13 temporarily interrupted filgotinib, 6 exited the study, and 16 continued with filgotinib. One patient in the filgotinib + MTX group had a recurrent HZV infection; treatment was interrupted during the first event and discontinued after the second event. All but 5 patients were treated with antivirals. The EAIR of HZV infection was similar in patients with and without lymphopenia (defined as grade ≥ 1 per CTCAE definition). Four patients experienced lymphopenia (grade 1–2) within 30 days of HZV diagnosis (2 on corticosteroid doses of 4.0 and 7.5 mg/d prednisone, both on MTX) and 12 patients > 30 days from infection (Supplementary Figure 2, available with the online version of this article).

Malignancies. Malignancies were reported among 9 (EAIR 0.5) patients in the filgotinib + MTX and 5 (EAIR 0.6) in the filgotinib monotherapy group, excluding nonmelanoma skin cancer (NMSC). Six (EAIR 0.3) patients in the filgotinib + MTX and 1 (EAIR 0.1) in the filgotinib monotherapy group had NMSC (Table 2). Thirteen patients had treatment-emergent malignancies: 4 hematologic (3 NHL, 1 diffuse large B-cell lymphoma) and 9 solid tumors. One case of NHL was considered related to study drug.

Gastrointestinal perforation. One patient (EAIR 0.1) in the filgotinib + MTX group experienced a small bowel perforation during hysterectomy for uterine adenomyosis.

DVT/PE. One patient with a recent foot infection (EAIR 0.1) in the filgotinib + MTX group, previously captured under "death" experienced DVT and PE simultaneously (Table 2).

MACE. There was 1 CV death from DVT/PE and 4 nonfatal cases of stroke. All patients who experienced a stroke had ≥ 1 CV risk factor (hypertension, coronary artery disease). The EAIR was 0.2 for both groups; these events were considered not related to the study drug (Table 2).

Laboratory variables. The majority of laboratory abnormalities were grade 1 or 2 TEAEs (Table 3; Supplementary Table 2, available with the online version of this article). Mean values at baseline (first dose of filgotinib in parent study or LTE) and at Week 204, along with details of patients experiencing shifts to grade ≥ 3 through Week 204 are listed in the sections that follow.

Anemia. Mean (SD) hemoglobin (Hb; g/dL) values were 12.7 (1.4) and 12.8 (1.5) at baseline, and 13.7 (1.5) and 13.6 (1.4) at Week 204 in the filgotinib + MTX and filgotinib monotherapy groups, respectively. Five patients with normal Hb or mild anemia at baseline experienced severe anemia through Week 204 (3 in the filgotinib + MTX group; 2 resolved without intervention, 3 discontinued from the study).

Neutropenia. Mean (SD) neutrophil counts ($\times 10^3/\mu L$) were 6.1 (2.5) and 6.4 (2.5) at baseline, and 4.3 (1.7) and 4.2 (1.6) at Week 204 in the filgotinib + MTX and filgotinib monotherapy groups, respectively. Three patients had an increase in severity to grade 3 through Week 204; all resolved without intervention. Two patients had an increase from grade 0 to grade 4; 1 resolved after temporary interruption of filgotinib and filgotinib was resumed without recurrence, and 1 discontinued from the study.

Lymphopenia. Mean (SD) lymphocyte counts ($\times 10^3/\mu L$) were 1.9 (0.7) and 2.1 (0.8) at baseline, and 1.5 (0.6) and 1.5 (0.5) at Week 204 in the filgotinib + MTX and filgotinib monotherapy groups, respectively. Sixteen patients had an increase in severity to grade 3 through Week 204 (8 normalized on repeat assessment without any change in MTX or filgotinib dose, 3 had concurrent infections and/or started antibiotics at the time of lymphopenia, 4 exited the study, and 1 continued to fluctuate throughout the study). One patient with an increase to grade 4 remained in the study with continued grade 0–3 fluctuation.

Thrombocytopenia. Mean (SD) platelet counts ($\times 10^3/\mu L$) were 321 (95) and 314 (88) at baseline, and 278 (72) and 275 (74) at Week 204 in the filgotinib + MTX and filgotinib monotherapy groups, respectively. One patient had thrombocytopenia from grade 0 to 4, which normalized on repeat assessment.

Elevated creatinine. Mean (SD) serum creatinine (mg/dL) levels

Table 2. Summary of AEs and AEs of special interest through Week 204.

	Filgotinib + MTX	Filgotinib Monotherapy
Exposure		
Patients, n	497	242
Total patient-yrs	1764.0	817.7
Mean (SD), yrs	3.55 (1.57)	3.38 (1.59)
TEAEs	n (EAIR/100 PYE)	n (EAIR/100 PYE)
Any TEAE	434 (24.6)	211 (25.8)
Any TEAE leading to premature discontinuation of study drug or study	131 (7.4)	77 (9.4)
Any TEAE leading to temporary interruption of any study drug	111 (6.3)	44 (5.4)
Serious TEAE	54 (3.1)	35 (4.3)
Treatment-related TEAE	242 (13.7)	116 (14.2)
Treatment-related serious TEAE[a]	9 (0.5)	10 (1.2)
Death[b]	3 (0.2)	3 (0.4)
Most common TEAEs (≥ 5% in either treatment group)[c]		
Mycobacterium tuberculosis complex test positive	53 (3.0)	38 (4.6)
Upper respiratory tract infection	52 (2.9)	35 (4.3)
Urinary tract infection	56 (3.2)	26 (3.2)
Nasopharyngitis	56 (3.2)	20 (2.4)
Hypertension	52 (2.9)	21 (2.6)
Bronchitis	51 (2.9)	17 (2.1)
Hypercholesterolemia	36 (2.0)	28 (3.4)
Headache	28 (1.6)	26 (3.2)
Dyslipidemia	32 (1.8)	13 (1.6)
Rheumatoid arthritis	32 (1.8)	13 (1.6)
Back pain	31 (1.8)	11 (1.3)
Influenza	30 (1.7)	10 (1.2)
Lymphopenia	29 (1.6)	11 (1.3)
Pharyngitis	28 (1.6)	10 (1.2)
Diarrhea	28 (1.6)	9 (1.1)
Gastroenteritis	27 (1.5)	9 (1.1)
HZV	22 (4.4)	12 (5.0)
Blood creatinine increased	11 (2.2)	18 (7.4)
Hypertriglyceridemia	16 (3.2)	12 (5.0)
Blood cholesterol increased	8 (1.6)	17 (7.0)
Lymphocyte count decreased	11 (2.2)	14 (5.8)
Adverse events of special interest[d]		
Any infections	288 (16.3)	130 (15.9)
Serious infections	11 (0.6)	14 (1.7)
HZV	23 (1.3)	12 (1.5)
Malignancy, excluding NMSC[e]	9 (0.5)	5 (0.6)
NMSC	6 (0.3)	1 (0.1)
MACE[f]	3 (0.2)	2 (0.2)
DVT and/or PE[f]	1 (0.1)[g]	0
GI perforation	1 (0.1)[h]	0
Active tuberculosis	0	0

[a] Filgotinib + MTX: pneumonia (2), HZV infection (2), asthenia (1), abdominal wall infection (1), breast cancer (1), colon adenoma (1), diffuse large B cell lymphoma (1); filgotinib monotherapy: pneumonia (2), NHL (2); *Escherichia* urinary tract infection (1), jaw abscess (1), liver hemangioma (1), squamous cell carcinoma (1), spontaneous abortion (1), renal cyst (1). [b] Filgotinib + MTX: meningococcal meningitis, leiomyosarcoma, DVT/PE; filgotinib monotherapy: pneumonia, NHL (2). [c] Occurring in ≥ 5% of a proportion of patients in either treatment group. [d] Includes TEAEs and non-TEAEs. [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). [f] Positively adjudicated events. [g] Patient had simultaneous DVT and PE. [h] Procedural small bowel perforation. AE: adverse event; DVT: deep vein thrombosis; EAIR: exposure-adjusted incidence rate; GI: gastrointestinal; HZV: herpes zoster virus; MACE: major adverse cardiovascular event; MTX: methotrexate; NHL: non-Hodgkin lymphoma; NMSC: nonmelanoma skin cancer; PE: pulmonary embolism; PYE: patient-years of exposure; TEAE: treatment-emergent adverse event.

Table 3. Treatment-emergent laboratory abnormalities through April 2019 data cut.

	Filgotinib + MTX, n = 497	Filgotinib Monotherapy, n = 242
Patients With Postbaseline Value, n	496	242
Anemia		
Grade 1	89 (17.9)	50 (20.7)
Grade 2	35 (7.1)	18 (7.4)
Grade 3	7 (1.4)	2 (0.8)
Grade 4	NA	NA
Neutropenia		
Grade 1	38 (7.7)	18 (7.4)
Grade 2	29 (5.8)	14 (5.8)
Grade 3	4 (0.8)	2 (0.8)
Grade 4	2 (0.4)	1 (0.4)
Lymphopenia		
Grade 1	29 (5.8)	9 (3.7)
Grade 2	106 (21.4)	41 (16.9)
Grade 3	23 (4.6)	7 (2.9)
Grade 4	2 (0.4)	0 (0)
Leukopenia		
Grade 1	67 (13.5)	37 (15.3)
Grade 2	19 (3.8)	6 (2.5)
Grade 3	2 (0.4)	1 (0.4)
Grade 4	0 (0)	0 (0)
Thrombocytopenia		
Grade 1	24 (4.8)	5 (2.1)
Grade 2	2 (0.4)	1 (0.4)
Grade 3	1 (0.2)	0 (0)
Grade 4	1 (0.2)	0 (0)
Cr elevation		
Grade 1	11 (2.2)	7 (2.9)
Grade 2	12 (2.4)	14 (5.8)
Grade 3	1 (0.2)	0 (0)
Grade 4	0 (0)	0 (0)
Cholesterol, fasting (increased)[a]		
Grade 1	196 (43.3)	93 (43.7)
Grade 2	51 (11.3)	36 (16.9)
Grade 3	3 (0.7)	1 (0.5)
Grade 4	0 (0)	0 (0)
ALT elevation		
Grade 1	131 (26.4)	54 (22.3)
Grade 2	14 (2.8)	2 (0.8)
Grade 3	4 (0.8)	1 (0.4)
Grade 4	0 (0)	0 (0)
AST elevation		
Grade 1	139 (28.0)	45 (18.6)
Grade 2	10 (2.0)	2 (0.8)
Grade 3	1 (0.2)	1 (0.4)
Grade 4	0 (0)	0 (0)

Values are n (%) unless otherwise indicated. For each individual laboratory test, the most severe graded abnormality for that test was counted for a patient. [a]Severity grades were defined as: Grade 1 (> ULN–300 mg/dL [7.75 mmol/L]), Grade 2 (> 300–400 mg/dL [7.75–10.34 mmol/L]), Grade 3 (> 400–500 mg/dL [10.34–12.92 mmol/L]), Grade 4 (> 500 mg/dL [12.92 mmol/L]). ALT: alanine aminotransferase; AST: aspartate aminotransferase; Cr: creatinine; MTX: methotrexate; NA: not applicable; ULN: upper limit of normal.

were 0.68 (0.15) and 0.69 (0.17) at baseline, and 0.79 (0.17) and 0.79 (0.17) at Week 204 in the filgotinib + MTX and filgotinib monotherapy groups, respectively. One patient in the filgotinib + MTX group experienced an increase to grade 3 through Week 204, which normalized over 4 months, during which filgotinib was withheld for 12 days.

Hyperlipidemia. Mean (SD) total cholesterol levels (mg/dL) were 191 (40) and 196 (41) at baseline, and 212 (47) and 225 (42) at Week 204 in the filgotinib + MTX and filgotinib monotherapy groups, respectively. Eighteen and 14 patients had an increase in severity from desirable to high in the filgotinib + MTX and filgotinib monotherapy groups, respectively, through Week 204. Twenty-three and 14 patients had an increase in low-density lipoprotein/high-density lipoprotein severity from optimal to high in the filgotinib + MTX and filgotinib monotherapy groups, respectively, through Week 204. Twenty-two patients had an increase from optimal to high multiple times through Week 204.

Aspartate aminotransferase and alanine aminotransferase elevation. Mean (SD) values (U/L) for aspartate aminotransferase (AST)/alanine aminotransferase (ALT) were 20 (9)/18 (12) and 19 (9)/17 (11) at baseline, and 26 (15)/24 (17) and 25 (9)/22 (14) at Week 204, for the filgotinib + MTX and filgotinib monotherapy groups, respectively. Six patients (1 filgotinib monotherapy and 5 filgotinib + MTX) had an increase in AST or ALT to > 5–10× ULN from normal baseline values through Week 204: 4 normalized on repeat assessment without medication changes, 1 exited the study, and 1 continued to have fluctuations.

Efficacy. At Week 204, ACR20/50/70 responses were 89.3%/69.6%/49.1% and 91.8%/69.4%/44.4% in the filgotinib + MTX and filgotinib monotherapy groups, respectively, based on the "as observed" analysis. The ACR20/50/70 responses increased from baseline through Week 96 and remained stable thereafter. The remission rates, defined as Disease Activity in 28 joints based on CRP < 2.6 at Week 204, were 57.5% and 49.6% for the filgotinib + MTX and filgotinib monotherapy groups, respectively, and were maintained through Week 204 (Figure 2). NRI analysis followed a similar pattern of response, with lower overall response rates (Supplementary Figure 3, available with the online version of this article). Changes in other efficacy measures are listed in Supplementary Table 3.

DISCUSSION

The data from DARWIN 3 with a mean (SD) of 3.5 (1.6) years of filgotinib treatment and 2582 PYE demonstrates long-term safety, tolerability, and sustained response to filgotinib either in combination with MTX or as monotherapy in patients with moderately to severely active RA and an inadequate response to MTX. There were no meaningful safety differences between patients receiving filgotinib 200 mg as monotherapy or in combination with MTX. In this longest observational data on filgotinib to date, no additional safety signals were identified within these RA populations treated with filgotinib.[13,14,15] A positive *Mycobacterium tuberculosis* test and latent TB, both protocol-mandated criteria for discontinuation, were among

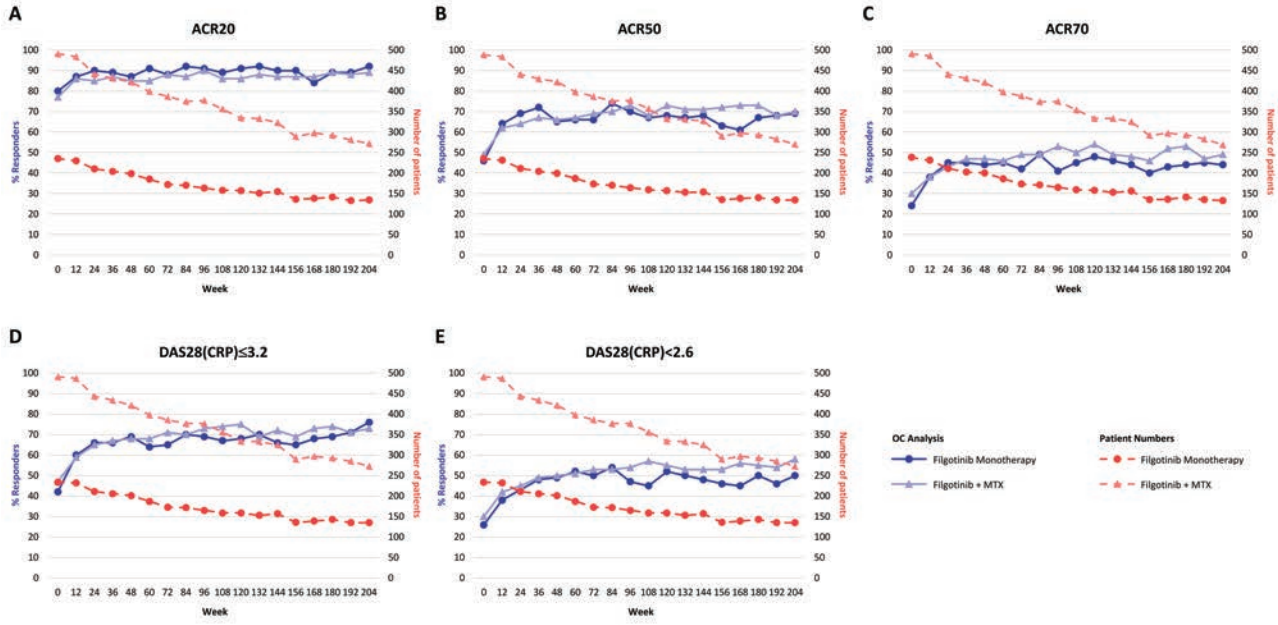

Figure 2. Efficacy variables in patients receiving filgotinib monotherapy or filgotinib + MTX using observed case analysis. (A) ACR20 response rates; (B) ACR50 response rates; and (C) ACR70 response rates; (D) DAS28(CRP) ≤ 3.2 response rates; and (E) DAS28(CRP) < 2.6 response rates. Percent responders are relative to baseline in parent study. ACR: American College of Rheumatology; DAS28(CRP): Disease Activity Score in 28 joints based on C-reactive protein; MTX: methotrexate; OC: observed case.

the most common AEs leading to discontinuation. The high enrollment in regions where TB is prevalent, along with a switch to a more sensitive QuantiFERON-TB Gold assay, may have contributed to higher-than-expected rates of positive TB tests (Table 1). In addition, improved disease control later during the study, with presumably less anergy, may have resulted in more positive QuantiFERON-TB Gold assay results. Last, with longer follow-up, it is expected that patients will have increased risk for exposure and new infections. No active TB cases were reported.

Patients with RA have an increased risk of HZV infection compared with the general population.[16,17,18] A metaanalysis of phase II and III randomized controlled trials for JAK inhibitors reported incidence rates for HZV infection that were higher than expected in the RA population.[19] The incidence rates of HZV infections in this study were relatively low (1.3 and 1.5 per 100 PYE in the filgotinib + MTX and monotherapy groups, respectively) and similar in patients with and without lymphopenia. While the exact causes of HZV reactivation have not yet been fully elucidated, suppression of cell-mediated immunity by drugs such as corticosteroids has been postulated to play a role in patients with RA.[20] Additionally, the risk of viral infections, such as HZV reactivation, might be associated with JAK1- and JAK3-mediated intracellular signaling and survival of immune cells and cytokines relevant to HZV control.[21] Although HZV reactivation appears to be a class effect, some emerging data suggest that there may be relative differences among the various JAK inhibitors regarding the risk of HZV.[22,23] However, additional data (e.g., from head-to-head studies) are needed to draw any conclusions regarding potential differences in the risk of HZV infection between filgotinib and other JAK inhibitors.

Studies have shown that the risk for malignancies in patients with RA is increased, especially in those on immunosuppressive therapy, compared with the general population.[24] The incidence rates for malignancy (excluding NMSC) were 0.5 and 0.6 per 100 PYE in the filgotinib + MTX and monotherapy groups, respectively, and were similar to those reported for other JAK inhibitors[25,26] and bDMARDs.[27,28]

Patients with RA have a 2- to 3-fold increased risk of DVT and PE compared to the general population, with reported incidence rates ranging from 0.3 to 0.8 per 100 PYE.[29,30] One patient (on filgotinib + MTX) experienced simultaneous DVT and PE 62 days after the last dose of filgotinib (0.1 per 100 PYE), which was fatal. The number of DVT/PE events from DARWIN 3 was small and appears comparable to the background risk observed in patients with RA. Although incompletely understood, some observational data suggest that the increased risk for DVT/PE may be a class effect for JAK inhibitors.[31] Additional data, including long-term postmarketing observational studies, are needed to quantify the risk associated with JAK inhibitors, including filgotinib.

The risk of CV disease is also increased among patients with RA.[32] The incidence rates for MACE in this study were low (0.2 per 100 PYE in both groups), and comparable with rates reported for other JAK inhibitors[26,33] and tumor necrosis factor inhibitors[34,35,36] in RA.

There was no evidence of progressive worsening of laboratory abnormalities over time. A small percentage of patients experienced an increase in severity from baseline, most from grade 0–1, with few experiencing an increase to grade ≥ 3 through 4 years. The majority of grade 3 and 4 changes were transient and normalized without intervention and/or with resolution of concurrent

illness. Mean Hb, neutrophil, lymphocyte, and platelet counts remained relatively stable over 4 years in both treatment groups. Creatine phosphokinase levels were not monitored during the study. Overall, these results were not unexpected given prior studies suggesting the role of JAK2 inhibition on hematopoiesis and erythropoiesis.[37] Additional data are needed to fully understand the effect of preferential JAK targeting on changes in biochemistry measures.

Limitations of LTE data analysis include potential bias related to open-label design and inclusion of patients who are more likely to have responded to and tolerated filgotinib. In this study, the majority of the patients from parent studies (83% DARWIN 1 and 85% DARWIN 2) entered the LTE with > 50% remaining through 4 years. Also, analyses related to infections as a function of leukocyte and lymphocyte counts were of patients with a history of leukopenia or lymphopenia during the study and not necessarily at time of infection. A full assessment of the effect of leukopenia and lymphopenia on infections will be further explored in the integrated safety analysis of filgotinib.

This analysis conducted for up to 4 years of filgotinib exposure demonstrated a consistent safety profile and sustained efficacy for filgotinib when administered as 200 mg daily either alone or in combination with MTX.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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