

# Effect of Filgotinib vs Placebo on Clinical Response in Patients With Moderate to Severe Rheumatoid Arthritis Refractory to Disease-Modifying Antirheumatic Drug Therapy

## The FINCH 2 Randomized Clinical Trial

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**IMPORTANCE** Patients with active rheumatoid arthritis (RA) despite treatment with biologic disease-modifying antirheumatic drug (bDMARD) therapy need treatment options.

**OBJECTIVE** To evaluate the effects of filgotinib vs placebo on the signs and symptoms of RA in a treatment-refractory population.

**DESIGN, SETTING, AND PARTICIPANTS** A 24-week, randomized, placebo-controlled, multinational phase 3 trial conducted from July 2016 to June 2018 at 114 sites internationally, randomizing 449 adult patients (and treating 448) with moderately to severely active RA and inadequate response/intolerance to 1 or more prior bDMARDs.

**INTERVENTIONS** Filgotinib, 200 mg (n = 148); filgotinib, 100 mg (n = 153); or placebo (n = 148) once daily; patients continued concomitant stable conventional synthetic DMARDs (csDMARDs).

**MAIN OUTCOMES AND MEASURES** The primary end point was the proportion of patients who achieved 20% improvement in the American College of Rheumatology criteria (ACR20) at week 12. Secondary outcomes included week 12 assessments of low disease activity (disease activity score in 28 joints–C-reactive protein [DAS28-CRP]  $\leq 3.2$ ) and change in Health Assessment Questionnaire–Disability Index, 36-Item Short-Form Health Survey Physical Component, and Functional Assessment of Chronic Illness Therapy–Fatigue scores, as well as week 24 assessment of remission (DAS28-CRP  $< 2.6$ ) and adverse events.

**RESULTS** Among 448 patients who were treated (mean [SD] age, 56 [12] years; 360 women [80.4%]; mean [SD] DAS28-CRP score, 5.9 [0.96]; 105 [23.4%] with  $\geq 3$  prior bDMARDs), 381 (85%) completed the study. At week 12, more patients receiving filgotinib, 200 mg (66.0%) or 100 mg (57.5%), achieved ACR20 response (placebo, 31.1%; difference vs placebo: 34.9% [95% CI, 23.5%-46.3%] and 26.4% [95% CI, 15.0%-37.9%], respectively; both  $P < .001$ ), including among patients with prior exposure to 3 or more bDMARDs (70.3%, 58.8%, and 17.6%, respectively; difference vs placebo: 52.6% [95% CI, 30.3%-75.0%] for filgotinib, 200 mg, and 41.2% [95% CI, 17.3%-65.0%] for filgotinib, 100 mg; both  $P < .001$ ). The most common adverse events were nasopharyngitis (10.2%) for filgotinib, 200 mg; headache, nasopharyngitis, and upper respiratory infection (5.9% each) for filgotinib, 100 mg; and RA (6.1%) for placebo. Four uncomplicated herpes zoster cases and 1 retinal vein occlusion were reported with filgotinib; there were no opportunistic infections, active tuberculosis, malignancies, gastrointestinal perforations, or deaths.

**CONCLUSIONS AND RELEVANCE** Among patients with active RA who had an inadequate response or intolerance to 1 or more bDMARDs, filgotinib, 100 mg daily or 200 mg daily, compared with placebo resulted in a significantly greater proportion achieving a clinical response at week 12. However, further research is needed to assess longer-term efficacy and safety.

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Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation, leading to destruction and deformity of joints, disability, and decreased quality of life. Treatment is guided by disease severity and the patient's comorbidities and response to therapy. Pharmacotherapy typically begins with a conventional synthetic disease-modifying antirheumatic drug (csDMARD), such as methotrexate, often plus a short course of glucocorticoids. If response to initial therapy is inadequate, addition of a targeted therapy, either a biologic bDMARD or a targeted synthetic DMARD, such as Janus kinase (JAK)-signal transducer and activator of transcription inhibitors, is the next step.<sup>1,2</sup> The first targeted therapy is often a tumor necrosis factor (TNF) inhibitor; however, patients often discontinue TNF inhibitors due to ineffectiveness and adverse events (AEs).<sup>3</sup> In this setting, treatment guidelines recommend switching to another TNF inhibitor, to a bDMARD with alternative mechanism of action, or to a targeted synthetic DMARD.<sup>1,2</sup>

While the cause of RA is not completely understood, various factors have been implicated in its pathogenesis, including several prominent cytokine pathways. JAK inhibitors block the signaling of multiple cytokines, growth factors, and hormones implicated in autoimmunity.<sup>4</sup> JAK inhibition may, therefore, have potential as a therapeutic option for a range of inflammatory conditions including RA.<sup>5,6</sup> Filgotinib is an oral, small-molecule inhibitor of JAK1 that has demonstrated clinical efficacy, both as a monotherapy and in combination with methotrexate, in phase 2 studies in patients with moderately to severely active RA.<sup>7-9</sup> The multinational, phase 3 FINCH 2 study compared the effects of filgotinib vs placebo for the treatment of patients with moderately to severely active RA and an inadequate response or intolerance to 1 or more prior bDMARDs.

## Methods

### Study Design

This was a randomized, double-blind, placebo-controlled study conducted between July 2016 and June 2018 at 114 sites (hospitals, outpatient clinics, academic centers, and private research sites) internationally. The protocol and statistical analysis plan are included in [Supplement 1](#) and [Supplement 2](#), respectively. The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines and approved by each study center's institutional review board or ethics committee. All patients provided written informed consent.

Patients were 18 years of age or older at the time of consent with a diagnosis of RA,<sup>10</sup> 6 or more swollen joints (swollen joint count [SJC] of 66 joints [SJC66]), and 6 or more tender joints (tender joint count [TJC] of 68 joints [TJC68]) at both screening and baseline, and a serum C-reactive protein (CRP) level of 4 mg/L or greater based on central laboratory assessment at screening. Self-reported patient race and ethnicity (predefined categories) were collected to meet regulatory

## Key Points

**Question** Is filgotinib more effective than placebo in active rheumatoid arthritis refractory to biologic disease-modifying antirheumatic drug therapy?

**Findings** In this randomized clinical trial of 448 patients with active rheumatoid arthritis who had an inadequate response or intolerance to 1 or more biologic disease-modifying antirheumatic drugs, clinical response as measured by American College of Rheumatology 20% response was achieved at week 12 by significantly greater proportions of patients treated with filgotinib, 200 mg (66.0%) or 100 mg (57.5%), compared with placebo (31.1%).

**Meaning** A greater proportion of patients who received filgotinib, compared with those who received placebo, achieved clinical response at 12 weeks, but further research is needed to assess longer-term efficacy and safety.

requirements. Patients had active RA despite ongoing treatment with csDMARDs and an inadequate response or intolerance to 1 or more prior bDMARDs. All bDMARDs were discontinued 4 or more weeks ( $\geq 6$  months for B-cell-depleting bDMARDs) prior to randomization. Patients with evidence of latent tuberculosis could enroll only if appropriate prophylaxis was initiated prior to first dose of study drugs. Main exclusion criteria included previous treatment with a JAK inhibitor, specified abnormal laboratory results, pregnancy, and/or recent or active infection.

### Randomization

Patients were randomized via an interactive web response system in a 1:1:1 ratio to once-daily filgotinib, 200 mg; filgotinib, 100 mg; or placebo tablets (matched in appearance) using a stratified randomization schedule with a block size of 6. The randomization sequence was prepared by an independent statistician; patients were stratified by geographic region, prior exposure to bDMARDs ( $< 3$  or  $\geq 3$ ), and seropositivity (rheumatoid factor or anticyclic citrullinated peptide antibodies) at screening. Study treatment allocation was determined by an interactive web response system.

### Interventions

All patients assigned to once-daily filgotinib, 200 mg; filgotinib, 100 mg; or placebo continued 1 to 2 protocol-specified stable csDMARDs (methotrexate, hydroxychloroquine, sulfasalazine, or leflunomide; methotrexate and leflunomide were not permitted in combination), and dose decreases were permitted only for intolerance/AE and/or laboratory abnormalities but not for change in disease activity. Stable doses of glucocorticoids ( $\leq 10$  mg/d prednisone or equivalent) and/or nonsteroidal anti-inflammatory drugs were permitted. Patients who discontinued study drug for any reason, including those who had not achieved responder status (defined as  $\geq 20\%$  improvement in both SJC66 and TJC68 from day 1 to week 14), were allowed to continue study visits and assessments while receiving standard-of-care therapy (investigator's choice of treatment appropriate for the patient). All patients who attained responder status at week 14 continued

their assigned study drugs in blinded fashion through week 24. Clinical assessments, patient questionnaires, collection of AEs (coded according to Medical Dictionary for Regulatory Activities version 21.0 and using Common Terminology Criteria for Adverse Events version 4.03 criteria), and laboratory tests were performed on day 1 and weeks 2, 4, 8, 12, 14, 16, 20, and 24 (or early termination) to evaluate efficacy and AEs according to the prespecified analysis. Uncomplicated herpes zoster cases limited to the primary dermatome or 2 adjacent dermatomes were not considered opportunistic infections. For patients discontinuing the study, a postdosing visit occurred 4 weeks after the last dose of study drug.

### Outcomes

The primary end point was the proportion of patients with an American College of Rheumatology 20% (ACR20) response at week 12. Key secondary efficacy end points were the change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score, the proportion of patients with disease activity score in 28 joints count using CRP (DAS28-CRP) of 3.2 or less, and the change from baseline in the 36-Item Short-Form Health Survey Physical Component and Functional Assessment of Chronic Illness Therapy-Fatigue scores measured at week 12, as well as the proportion of patients with DAS28-CRP less than 2.6 at week 24. Other secondary end points included ACR50 and ACR70 responses and patient's and physician's global assessments of disease. ACR20, ACR50, and ACR70 response rates are based on patients achieving 20% or more, 50% or more, and 70% or more improvement in TJC68 and SJC66 and 20% or more, 50% or more, or 70% or more 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).<sup>11</sup> SJC66 and TJC68 are counts of swollen and tender joints evaluating a fixed set of 66 and 68 joints, respectively, from both upper and lower body and hands and feet; SJC28 and TJC28 are abbreviated assessments considering a subset of only 28 joints. Patient's pain, patient's global assessment of disease activity, and physician's global assessment of disease activity are measured on 0- to 100-mm visual analog scales, with higher scores representing worse pain or disease. DAS28-CRP is another composite disease activity score factoring in TJC28, SJC28, and CRP levels and a physician's global assessment, and is scored on a range up to 10.0, with scores of 3.2 or lower considered low disease activity and scores less than 2.6 considered remission.<sup>12,13</sup>

The HAQ-DI assesses 8 functional categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities), with scores ranging from 0 (no disability) to 3 (completely disabled), and a change of 0.22 considered the minimally important difference.<sup>14,15</sup> The Short-Form Health Survey is composed of 36 items that group into 8 scales, which can be further summarized as Physical and Mental Component scores; scores range from 0 to 100, representing "least health" to "greatest health."<sup>16</sup> The Functional Assessment of Chronic Illness Therapy-Fatigue is a 13-item questionnaire on fatigue during a patient's usual daily activities over the past

week that is scored from 0 to 52, with higher scores indicating less fatigue.<sup>17</sup>

The Clinical Disease Activity Index and Simplified Disease Activity Index are both composite scores based on TJC28, SJC28, patient's global assessment, and physician's global assessment; the Simplified Disease Activity Index also includes CRP.<sup>18-20</sup> The Clinical Disease Activity Index is scored on a scale of 0 to 76, with higher scores indicating greater disease activity and a score of 10 or lower indicating low disease activity. The Simplified Disease Activity Index is scored on a scale of 0 to 86.0, with higher scores indicating greater disease activity and a score of 11 or lower indicating low disease activity. Other outcomes assessed but not reported herein included ACR-N and European League Against Rheumatism responses, as well as Work Productivity and Activity Impairment Questionnaire for Rheumatoid Arthritis and European Quality of Life-5 Dimensions scores.

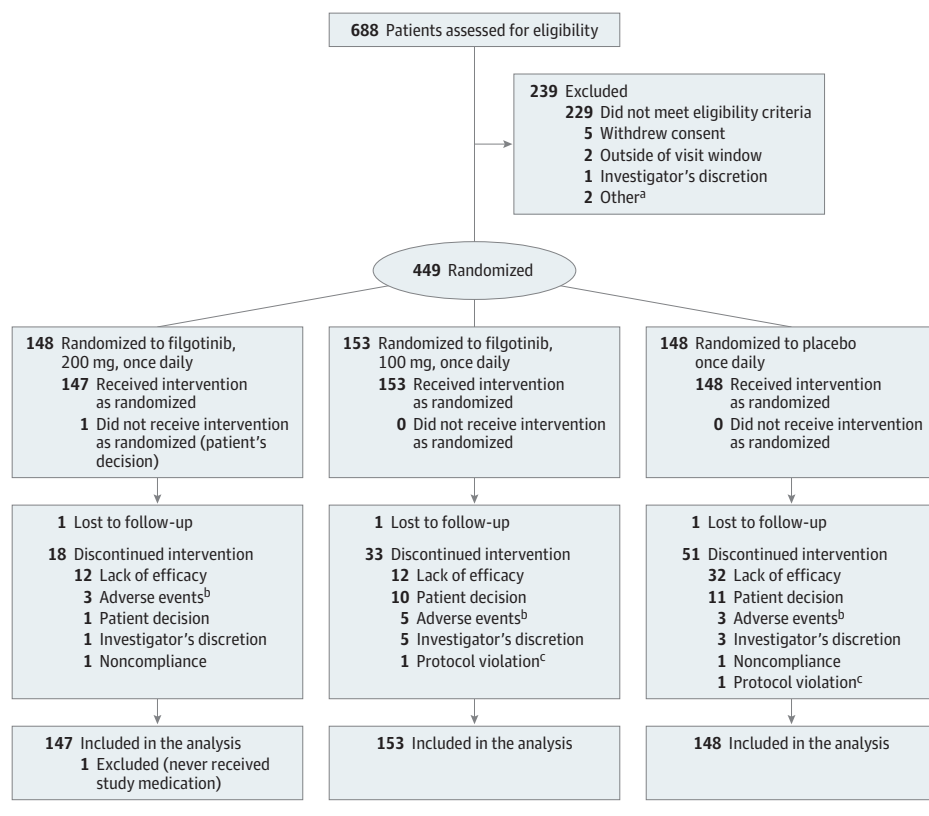
### Statistical Analysis

The key secondary end point, HAQ-DI, required a bigger sample size to ensure adequate power and was used to determine sample size. A sample size of 141 patients in each group (423 total) was targeted to provide 90% power at a 2-sided .05 level to detect a difference of 0.25 between filgotinib and placebo on the change from baseline in HAQ-DI at week 12 and to provide more than 90% power to detect an increase in ACR20 response rate of 25% to 45% between placebo and filgotinib groups.

The primary and key secondary end points were tested according to the hierarchical testing principle (as described in eFigure 1 in Supplement 3) at the 2-sided .05 level to maintain control of type I error. The primary analyses consist of a superiority test of filgotinib, 200 mg, compared with placebo based on the ACR20 response rate at week 12. The hypothesis testing for secondary analyses commenced if the primary analysis reached statistical significance and were tested according to the hierarchical testing principle at the 2-sided .05 level. If a null hypothesis was not rejected, formal sequential testing was to be stopped and only nominal significance was to be reported for the remaining hypotheses.

The full analysis set includes all randomized patients who received at least 1 dose of study drug, and this set was used for efficacy analyses. Comparison of filgotinib vs placebo was made by logistic regression with treatment and stratification factors (geographic region, prior exposure to number of bDMARDs, and presence of rheumatoid factor or anticyclic citrullinated peptide antibody at screening) included in the model with nonresponder imputation for ACR response rate and other binary end points. Patients with missing binary end points were considered to be nonresponders (ie, nonresponder imputation). The *P* value from the logistic regression model is reported. A mixed-effects model with repeated measures that included all available data was used to evaluate treatment effect for continuous end points with baseline value, stratification factors (geographic region, prior exposure to number of bDMARDs, and presence of rheumatoid factor or anticyclic citrullinated peptide antibody at screening), treatment, visit, and treatment by visit interaction included as fixed effects and time being a random effect. Treatment comparison

Figure 1. Study Flow and Patient Disposition



<sup>a</sup> No additional information was provided by the site investigators.

<sup>b</sup> Adverse events in the filgotinib, 200 mg, group included 1 case each (0.7%) of abnormal blood alkaline phosphatase, gastroesophageal reflux disease, and migraine; in the filgotinib, 100 mg, group included 1 case each (0.7%) of anxiety, herpes zoster, hot flush, myocardial ischemia, and osteitis; and in the placebo group included 2 cases of rheumatoid arthritis (1.4%) and 1 case (0.7%) of decreased lymphocyte count.

<sup>c</sup> A patient in the filgotinib, 100 mg, group reported their partner's pregnancy at the week 4 visit that resulted in the patient being removed from the study and recorded as a protocol violation. A patient in the placebo group received protocol-prohibited medication on study day 6 due to severe bodily pain caused by rheumatoid arthritis (dexamethasone intra-articular injection and dexamethasone intravenous drip).

on the other secondary end points was not adjusted for multiplicity, and nominal *P* values are presented and should be interpreted as exploratory.

Sensitivity analyses (eg, multiple imputation and tipping point analyses) were conducted to ensure that conclusions were robust and not dependent on mechanisms used to account for missing data. The multiple imputation procedure replaced each missing value with a set of plausible values that represented the uncertainty about the right value to impute. Fifty imputed data sets were generated based on logistic regression models for binary efficacy end points (eg, ACR20) or linear regression models for continuous efficacy end points (HAQ-DI). These multiple imputed data sets were analyzed using the same method as for the primary analysis. The results from each set of imputed data sets were combined using Rubin's rule. The stratification factors were included in the imputation model as covariates, and all available data at postbaseline visits up to the time point of interest were included in the longitudinal model. A  $\delta$ -adjusting pattern-mixture approach for tipping point analysis was conducted for the primary and key secondary efficacy end points to assess the robustness of analysis results under missing not at random assumption. Specifically, a series of analyses were performed with a range of different values of the shift parameter  $\delta$  applied to the imputed data sets at which the conclusion about the statistical significance of the estimated treatment effect will be altered. Each  $\delta$  value is classified as either "altering the study's conclusion"

or tips from "keeping the study's conclusion unchanged." For each  $\delta$  value, multiple imputed data sets were generated. The same analysis method as for the primary analysis was applied when analyzing adjusted data generated under the different  $\delta$  values. All statistical analyses were done using SAS version 9.4 (SAS Institute).

Subgroup analyses were performed by repeating the analysis within subgroups of patients defined by a subgrouping variable. There was no formal testing for interactions, so effect sizes among subgroups should not be compared.

## Results

### Study Participants

The disposition of the 688 screened patients is shown in Figure 1. Table 1 shows baseline characteristics and eTable 1 in Supplement 3 shows prior bDMARD and concurrent methotrexate and steroid use. Most patients (81.9%) were receiving concomitant methotrexate on the first dosing date and the mean (SD) dose was 15.8 (5.25) mg/week (eTable 1 in Supplement 3). Most of the enrolled patients were from the United States (255 patients; 56.9%) and Europe (103; 23.0%) (eFigure 2 in Supplement 3). Selected baseline characteristics within each region are in eTable 2 in Supplement 3.

Patients who did not attain a 20% or greater decrease in both SJC and TJC at week 14 were to transition to a standard-of-care group. The numbers of nonresponders at week 14 were

Table 1. Demographics, Treatment History, and Baseline Disease Characteristics

Characteristic	No. (%)		
	Filgotinib, 200 mg, Once Daily (n = 147)	Filgotinib, 100 mg, Once Daily (n = 153)	Placebo Once Daily (n = 148)
Age, mean (SD), y	56 (12.5)	55 (12.0)	56 (12.1)
<65	112 (76.2)	117 (76.5)	106 (71.6)
≥65	35 (23.8)	36 (23.5)	42 (28.4)
Sex			
Male	27 (18.4)	34 (22.2)	27 (18.2)
Female	120 (81.6)	119 (77.8)	121 (81.8)
Race/ethnicity			
White	110 (74.8)	109 (71.2)	97 (65.5)
Asian	15 (10.2)	20 (13.1)	15 (10.1)
Black/African American	14 (9.5)	12 (7.8)	21 (14.2)
American Indian/Alaska Native	7 (4.8)	9 (5.9)	10 (6.8)
Other <sup>a</sup>	1 (0.7)	3 (2.0)	2 (1.4)
Not permitted <sup>a</sup>	0	0	3 (2.0)
Geographic region <sup>b</sup>			
Region A	111 (75.5)	110 (71.9)	110 (74.3)
Region B	12 (8.2)	12 (7.8)	11 (7.4)
Region D	12 (8.2)	16 (10.5)	14 (9.5)
Region E	12 (8.2)	15 (9.8)	13 (8.8)
Body mass index, median (IQR) <sup>c</sup>	29.4 (24.2-35.1)	28.7 (25.2-34.2)	28.8 (24.6-33.7)
Duration of rheumatoid arthritis diagnosis, median (IQR), y	9.8 (5.2-19.6)	10.3 (6.4-16.4)	9.9 (5.2-17.2)
High-sensitivity CRP median (IQR), mg/L	11.2 (5.7-22.9)	10.6 (5.5-23.8)	9.7 (5.3-20.0)
Presence of RF only	13 (8.8)	5 (3.3)	8 (5.4)
Presence of anti-CCP antibody only	8 (5.4)	11 (7.2)	11 (7.4)
Presence of RF + anti-CCP antibody	91 (61.9)	102 (66.7)	84 (56.8)
No. of prior biologic DMARD exposures			
<3	110 (74.8)	119 (77.8)	114 (77.0)
≥3	37 (25.2)	34 (22.2)	34 (23.0)
Reason for failure of prior biologic DMARD exposures			
Lack of efficacy	125 (85.0)	129 (84.3)	126 (85.1)
Intolerance	36 (24.5)	34 (22.2)	32 (21.6)
HAQ-DI, mean (SD) <sup>d</sup>	1.70 (0.7)	1.64 (0.7)	1.65 (0.6)
SJC66, mean (SD) <sup>d</sup>	18 (12.5)	17 (12.4)	17 (9.7)
TJC68, mean (SD) <sup>d</sup>	28 (16.1)	26 (15.4)	27 (15.5)
SJC28, mean (SD) <sup>d</sup>	12 (6.3)	12 (6.0)	12 (6.0)
TJC28, mean (SD) <sup>d</sup>	16 (7.7)	15 (6.8)	16 (6.9)
DAS28-CRP, mean (SD) <sup>d</sup>	5.9 (1.03)	5.9 (0.98)	5.9 (0.86)
Functional Assessment of Chronic Illness Therapy-Fatigue, mean (SD) <sup>d</sup>	24.2 (11.5)	23.7 (12.3)	25.4 (10.9)
Patient's pain assessment, mean (SD), mm <sup>d</sup>	66 (21.6)	67 (21.7)	68 (19.9)
Global assessment of disease activity, mean (SD), mm <sup>d</sup>			
Patient's	68 (20.6)	69 (20.2)	70 (18.0)
Physician's	69 (17.6)	68 (18.7)	66 (16.7)
Disease Activity Index, mean (SD) <sup>d</sup>			
Simplified	43.4 (14.64)	42.6 (14.16)	43.0 (12.33)
Clinical	41.7 (14.23)	40.4 (13.23)	41.4 (12.00)

Abbreviations: CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28-CRP, disease activity score for 28 joints using C-reactive protein; DMARD, disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; IQR, interquartile range; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count.

<sup>a</sup> Other races included people whose predominant origins cannot be determined or who are of mixed race and do not identify with a primary race. Not permitted category includes patients whose local regulators did not allow collection of race or ethnicity information.

<sup>b</sup> Region A: Australia, Belgium, France, Germany, Israel, Republic of Korea, Spain, Switzerland, United Kingdom, and United States. Region B: Hungary and Poland. Region C: China; no patients were screened or enrolled in this region. Region D: Argentina and Mexico. Region E: Japan.

<sup>c</sup> Calculated as weight in kilograms divided by height in meters squared.

<sup>d</sup> See the Methods section for descriptions of the scale scores.

12 (8.2%) for filgotinib, 200 mg; 14 (9.2%) for filgotinib, 100 mg; and 23 (18.2%) for placebo. Fifteen (10.2%), 23 (15%), and 29 (19.6%) patients, respectively, missed the week 14 visit for

determination of SJC or TJC, and their responder status was instead evaluated at week 12 or week 16, as specified in the statistical analysis plan (Supplement 2).

Table 2. Key Secondary Efficacy Measures at Weeks 12 and 24<sup>a</sup>

	Filgotinib		Placebo	Difference vs Placebo		P Value for Filgotinib	
	200 mg	100 mg		200 mg	100 mg	200 mg	100 mg
<b>Week 12</b>							
HAQ-DI							
No.	137	140	129				
Mean (SD)	1.15 (0.74)	1.15 (0.71)	1.40 (0.71)				
Mean change from baseline (SD)	-0.55 (0.59)	-0.48 (0.60)	-0.23 (0.55)	-0.32 (-0.45 to -0.19) <sup>b</sup>	-0.27 (-0.40 to -0.14) <sup>b</sup>	<.001	<.001
HAQ-DI reduction ≥0.22							
No. (%)	144 (66.7)	148 (66.2)	144 (44.4)	22.2 (10.3 to 34.1) <sup>c</sup>	21.8 (10.0 to 33.6) <sup>c</sup>	<.001	<.001
DAS28-CRP ≤3.2							
No. (%)	147 (40.8)	153 (37.3)	148 (15.5)	25.3 (14.7 to 35.8) <sup>c</sup>	21.7 (11.4 to 32.0) <sup>c</sup>	<.001	<.001
36-Item Short-Form Health Survey Physical Component score							
No.	141	144	133				
Mean change from baseline (SD)	7.6 (7.68)	6.8 (8.22)	3.6 (8.16)	4.3 (2.5 to 6.1) <sup>b</sup>	7.6 (1.6 to 15.2) <sup>b</sup>	<.001	<.001
DAS28-CRP <2.6							
No. (%)	147 (22.4)	153 (25.5)	148 (8.1)	14.3 (5.6 to 23.1) <sup>c</sup>	17.4 (8.5 to 26.2) <sup>c</sup>	<.001	<.001
Functional Assessment of Chronic Illness Therapy-Fatigue							
No.	140	143	132				
Mean change from baseline (SD)	9.6 (11.24)	8.3 (10.80)	4.5 (10.37)	5.0 (1.19) <sup>d</sup>	3.2 (1.18) <sup>d</sup>	<.001	.007
<b>Week 24</b>							
HAQ-DI							
No.	123	113	92				
Mean (SD)	0.95 (0.71)	1.04 (0.71)	1.22 (0.68)				
Mean change from baseline (SD)	-0.75 (0.62)	-0.60 (0.66)	-0.42 (0.60)	-0.36 (-0.51 to -0.21) <sup>b</sup>	-0.22 (-0.37 to -0.08) <sup>b</sup>	<.001	.003
HAQ-DI reduction ≥0.22							
No. (%)	144 (68.8)	148 (54.1)	144 (35.4)	33.3 (21.8 to 44.9) <sup>c</sup>	18.6 (6.8 to 30.5) <sup>c</sup>	<.001	.001
DAS28-CRP ≤3.2							
No. (%)	136 (48.3)	137 (37.9)	128 (20.9)	27.4 (16.3 to 38.4) <sup>b</sup>	17.0 (6.2 to 27.7) <sup>b</sup>	<.001	.003
DAS28-CRP <2.6							
No. (%)	136 (30.6)	137 (26.1)	128 (12.2)	18.5 (8.6 to 28.3) <sup>c</sup>	14.0 (4.6 to 23.4) <sup>c</sup>	<.001	.003
Functional Assessment of Chronic Illness Therapy-Fatigue							
No.	122	110	90				
Mean change from baseline (SD)	11.6 (11.67)	9.8 (10.39)	7.0 (10.23)	4.6 (1.28) <sup>d</sup>	2.1 (1.30) <sup>d</sup>	<.001	.11

Abbreviations: DAS28-CRP, disease activity score for 28 joints using C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares.

<sup>a</sup> Values are percentage of patients achieving a response unless otherwise noted.

<sup>b</sup> LS mean difference (95% CI).

<sup>c</sup> Percentage difference (95% CI).

<sup>d</sup> LS mean difference (SE).

### Primary and Key Secondary Outcomes

At week 12, the ACR20 response rates (primary end point) were 66.0% (95% CI, 58.0%-74.0%) and 57.5% (95% CI, 49.4%-65.7%) for filgotinib, 200 mg and 100 mg, respectively, vs 31.1% (95% CI, 23.3%-38.9%) for placebo (difference vs placebo: 34.9% [95% CI, 23.5%-46.3%] for filgotinib, 200 mg, and 26.4% [95% CI, 15.0%-37.9%] for filgotinib, 100 mg; both  $P < .001$ ). Sensitivity analyses were consistent with these findings and indicate a good model fit.

Table 2 shows key secondary outcomes. The mean (SD) changes in HAQ-DI from baseline to week 12 were -0.55 (0.59) for filgotinib, 200 mg; -0.48 (0.60) for filgotinib, 100 mg; and -0.23 (0.55) for placebo, with differences vs placebo of -0.32 (95% CI, -0.45 to -0.19) for filgotinib, 200 mg, and -0.27 (95% CI, -0.40 to -0.14) for filgotinib, 100 mg (both  $P < .001$ ).

DAS28-CRP of 3.2 or less at week 12 was achieved by more patients taking filgotinib, 200 mg (40.8% [95% CI, 32.5%-49.1%]), and filgotinib, 100 mg (37.3% [95% CI,

29.3%-45.2%]), compared with placebo (15.5% [95% CI, 9.4%-21.7%]) (difference vs placebo: 24.6% [95% CI, 14.0%-35.2%] for filgotinib, 200 mg, and 21.0% [95% CI, 10.7%-31.4%] for filgotinib, 100 mg; both  $P < .001$ ). At week 24, significant differences between both filgotinib doses and placebo were maintained or improved ( $P \leq .001$ ). More patients also achieved DAS28-CRP less than 2.6 at week 24 with filgotinib, 200 mg (30.6% [95% CI, 22.8%-38.4%], difference vs placebo: 18.5% [95% CI, 8.6%-28.3%];  $P < .001$ ), and filgotinib, 100 mg (26.1% [95% CI, 18.9%-33.4%], difference vs placebo: 14.0% [95% CI, 4.6%-23.4%];  $P = .003$ ), compared with placebo (12.2% [95% CI, 6.6%-17.8%]); significant differences from placebo were also observed from week 4 for both doses of filgotinib.

The changes from baseline in 36-Item Short-Form Health Survey Physical Component score at weeks 12 and 24 were significantly greater for both filgotinib doses than for placebo (all  $P \leq .002$  vs placebo). Statistically significant effects were seen for improvement in Functional Assessment of Chronic Illness Therapy-Fatigue scores with filgotinib, 200 mg (Table 3).

### Other Secondary Outcomes

ACR20, ACR50, and ACR70 responses over time are shown in Figure 2, A-C. Patients receiving filgotinib had significantly greater improvements in DAS28-CRP over time compared with placebo (Figure 2D). Patients receiving filgotinib had significantly better scores on HAQ-DI and other components of the ACR core set of response criteria (eFigure 3 in Supplement 3). Also, week 12 and week 24 ACR responses, Clinical and Simplified Disease Activity Indexes, and indicators of low disease activity and remission showed the greater efficacy of filgotinib compared with placebo (eTable 3 in Supplement 3).

### Subgroup Analyses

ACR20 responses in patients with 1, 2, and 3 or more prior bDMARDs are shown in eFigure 4 in Supplement 3. This analysis showed that the ACR20 response rates of patients with 3 or more prior bDMARDs at week 12 were 70.3%, 58.8%, and 17.6% for patients receiving filgotinib, 200 mg; filgotinib, 100 mg; or placebo, respectively (difference vs placebo: 52.6% [95% CI, 30.3%-75.0%] for filgotinib, 200 mg, and 41.2% [95% CI, 17.3%-65.0%] for filgotinib, 100 mg; both  $P < .001$  vs placebo). eTable 2 in Supplement 3 shows key efficacy and safety data by geographic region.

### AEs

Treatment-emergent AEs were reported in 102 patients (69.4%) receiving filgotinib, 200 mg; 97 (63.4%) receiving filgotinib, 100 mg; and 100 (67.6%) receiving placebo; 30 (6.7%) were grade 3 or greater (by Common Terminology Criteria for Adverse Events) in severity. The most frequently reported AEs were nasopharyngitis, upper respiratory tract infection, nausea, bronchitis, and headache (Table 3). Overall, serious AEs occurred in 6 patients (4.1%) receiving filgotinib, 200 mg; 8 (5.2%) receiving filgotinib, 100 mg; and 5 (3.4%) receiving placebo. AEs leading to study drug discontinuation were reported in 5 patients (3.4%) receiving filgotinib, 200 mg; 6 (3.9%) receiving filgotinib, 100 mg; and 3 (2.0%) receiving placebo.

### AEs of Special Interest

Infections occurred in 53 patients (36.1%) receiving filgotinib, 200 mg; 52 patients (34.0%) receiving filgotinib, 100 mg; and 38 patients (25.7%) receiving placebo; they were serious in 1 (0.7%), 3 (2.0%), and 2 (1.4%) patients, in the filgotinib, 200 mg; filgotinib, 100 mg; and placebo groups, respectively. There were 4 cases of uncomplicated herpes zoster (57- and 62-year-old women with filgotinib, 100 mg, and 62- and 63-year-old women with filgotinib, 200 mg; all cases were  $\leq$ grade 2 in severity). There was 1 report of grade 2 retinal vein occlusion in a 61-year-old man in the filgotinib, 200 mg, group, which resolved with 3-monthly doses of intraocular bevacizumab; no other venous thrombotic events were reported. Two major cardiovascular serious AEs (as judged by an independent cardiovascular event adjudication committee) were reported: grade 1 myocardial ischemia in a 61-year-old man in the filgotinib, 100 mg, group and grade 2 subarachnoid hemorrhage in a 53-year-old woman in the placebo group. There were no cases of opportunistic infection, active tuberculosis, malignancy, gastrointestinal perforation, or death.

### Laboratory Abnormalities

Table 3 also shows laboratory abnormality treatment-emergent AEs of any grade and grade 3 or higher. The overall frequency of hepatic transaminase elevations ( $>1 \times$  upper limit of normal [ULN]) was higher in the filgotinib groups compared with placebo; however, no grade 3 or 4 increases for alanine aminotransferase and aspartate aminotransferase levels were reported. Most alanine aminotransferase and aspartate aminotransferase elevations were grade 1 or 2 in severity and none coincided with increased bilirubin levels. Three patients in the filgotinib groups (1 [0.7%] in the filgotinib, 200 mg, group and 2 [1.3%] in the filgotinib, 100 mg, group) were reported to have transient increases in alanine aminotransferase and aspartate aminotransferase levels greater than  $3 \times$  ULN; none were greater than  $5 \times$  ULN. No Hy's law cases (aspartate aminotransferase or alanine aminotransferase  $>3 \times$  ULN and total bilirubin  $>2 \times$  ULN) suggestive of drug-induced hepatocellular injury were identified. Transient grade 2 elevations in serum creatinine were reported in 6 patients (4.1%) receiving filgotinib, 200 mg, and 2 patients (1.4%) receiving placebo; no patient had a grade 3 or higher increased creatinine laboratory abnormality. Serum creatine kinase levels were increased in both filgotinib groups with grade 3 or 4 elevation reported for 3 (2.0%) in the filgotinib, 100 mg, group, 1 (0.7%) in the placebo group, and none in the filgotinib, 200 mg, group. Most cases were transient and were not associated with symptoms of muscle toxicity or rhabdomyolysis.

eFigure 5 in Supplement 3 shows mean values for hemoglobin, neutrophils, platelets, and fasting low-density lipoprotein/high-density lipoprotein cholesterol ratio over the course of the study. Mean hemoglobin level changes from baseline were  $+0.2$  g/dL at week 12 with both filgotinib, 200 mg and 100 mg, and  $-0.1$  g/dL at week 12 with placebo. AEs of anemia were reported in 4 patients (1.4% for filgotinib, 200 mg, and 1.3% for filgotinib, 100 mg) receiving filgotinib vs 4 patients (2.7%) receiving placebo. There were no clinically relevant changes in lymphocyte, platelet, and neutrophil counts.

Table 3. Adverse Events and Laboratory Data, Weeks 0 to 12 and Weeks 0 to 24<sup>a</sup>

	No. (%)					
	Weeks 0-12			Weeks 0-24		
	Filgotinib, 200 mg (n = 147)	Filgotinib, 100 mg (n = 153)	Placebo (n = 148)	Filgotinib, 200 mg (n = 147)	Filgotinib, 100 mg (n = 153)	Placebo (n = 148)
<b>Safety Data</b>						
Treatment-emergent adverse events	82 (55.8)	77 (50.3)	80 (54.1)	102 (69.4)	97 (63.4)	100 (67.6)
Most common treatment-emergent adverse events (occurring in >5% of patients)						
Nasopharyngitis	9 (6.1)	5 (3.3)	4 (2.7)	15 (10.2)	9 (5.9)	7 (4.7)
Upper respiratory tract infection	6 (4.1)	3 (2.0)	5 (3.4)	8 (5.4)	9 (5.9)	6 (4.1)
Headache	7 (4.8)	6 (3.9)	2 (1.4)	8 (5.4)	9 (5.9)	2 (1.4)
Bronchitis	5 (3.4)	0	7 (4.7)	8 (5.4)	3 (2.0)	8 (5.4)
Nausea	7 (4.8)	7 (4.6)	4 (2.7)	7 (4.8)	8 (5.2)	6 (4.1)
Serious adverse events <sup>b</sup>	4 (2.7)	6 (3.9)	4 (2.7)	6 (4.1)	8 (5.2)	5 (3.4)
Discontinued study drug because of treatment-emergent adverse event	4 (2.7)	6 (3.9)	3 (2.0)	5 (3.4)	6 (3.9)	3 (2.0)
Death	0	0	0	0	0	0
Treatment-emergent adverse events of interest						
Infection	34 (23.1)	29 (19.0)	27 (18.2)	53 (36.1)	52 (34.0)	38 (25.7)
Herpes zoster (uncomplicated)	1 (0.7)	2 (1.3)	0	2 (1.4)	2 (1.3)	0
<b>Safety data</b>						
Active tuberculosis	0	0	0	0	0	0
Opportunistic infection	0	0	0	0	0	0
Serious infection <sup>c</sup>	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)	3 (2.0)	2 (1.4)
Venous thrombotic events	1 (0.7) <sup>c</sup>	0	0	1 (0.7) <sup>d</sup>	0	0
Malignancy (excluding nonmelanoma skin cancer)	0	0	0	0	0	0
Nonmelanoma skin cancer	0	0	0	0	0	0
Major adverse cardiovascular event (adjudicated) <sup>e</sup>	0	1 (0.7)	1 (0.7)	0	1 (0.7) <sup>f</sup>	1 (0.7) <sup>g</sup>
Gastrointestinal perforation	0	0	0	0	0	0
	Week 0-24 Any Grade			Week 0-24 Grade 3 or 4 <sup>h</sup>		
<b>Laboratory Abnormalities</b>						
<b>Decreased</b>						
Hemoglobin	28 (19.0)	24 (15.7)	43 (29.1)	1 (0.7)	1 (0.7)	2 (1.4)
Neutrophil count	17 (11.6)	8 (5.2)	7 (4.7)	2 (1.4)	0	1 (0.7)
Lymphocyte count	21 (14.3)	11 (7.2)	19 (12.8)	4 (2.7)	1 (0.7) <sup>g</sup>	3 (2.0)
Platelet count	1 (0.7)	1 (0.7)	4 (2.7)	0	0	0
<b>Increased</b>						
Alanine aminotransferase	34 (23.1)	30 (19.6)	21 (14.2)	0	0	0
Aspartate aminotransferase	38 (25.9)	30 (19.6)	18 (12.2)	0	0	0
Creatinine	12 (8.2)	4 (2.6)	3 (2.0)	0	0	0
Creatine kinase	43 (29.3)	22 (14.4)	16 (10.8)	0	3 (2.0) <sup>h</sup>	1 (0.7)

<sup>a</sup> Week 0 to 24 data include events that began on or after the study drug start date up to 30 days after permanent discontinuation of study drug or that led to premature study drug discontinuation.

<sup>b</sup> At week 24, serious adverse events in the filgotinib, 200 mg, group included 1 case each of dehydration, bursitis, cellulitis, concussion, diarrhea, laceration, lactic acidosis, pulmonary edema, rib fracture, uterine hemorrhage, and vertigo; in the filgotinib, 100 mg, group 1 case each of oral abscess, anemia, bronchitis, depression, gallbladder empyema, lumbar spinal stenosis, myocardial ischemia, osteitis, and vulval abscess; and in the placebo group 2 cases of gastroenteritis and 1 case each of dehydration, chest pain, dyspnea, hyponatremia, lumbar vertebral fracture, nausea, rheumatoid arthritis, subarachnoid hemorrhage, systemic inflammatory response syndrome, and vomiting.

<sup>c</sup> Serious infectious adverse events were defined as all patients in the infections and infestations System Organ Class that were serious adverse events.

<sup>d</sup> Retinal vein thrombosis.

<sup>e</sup> Positively adjudicated major adverse cardiovascular events as assessed by an independent cardiovascular safety end point adjudication committee.

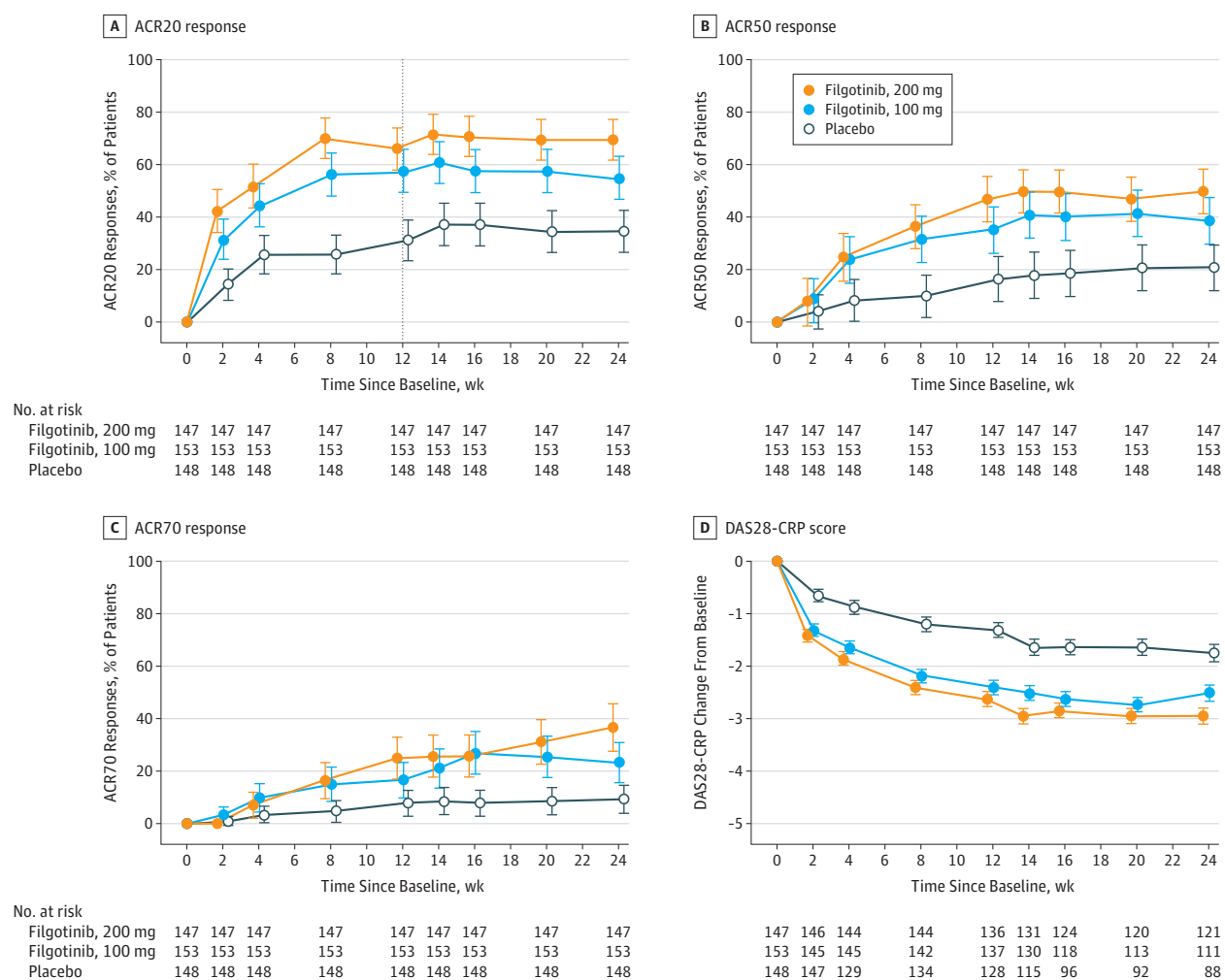
<sup>f</sup> Myocardial ischemia.

<sup>g</sup> Subarachnoid hemorrhage.

<sup>h</sup> All laboratory abnormalities reported were grade 3 except 1 patient (0.7%) experienced a grade 4 decrease in lymphocyte count and 1 (0.7%) experienced a grade 4 increase in creatine kinase.



Figure 2. Primary and Secondary Efficacy End Points



Panels A, B, and C show the percentage of patients who had 20% improvement in American College of Rheumatology criteria (ACR20), 50% improvement (ACR50), and 70% improvement (ACR70), respectively, with nonresponder imputation. The vertical line in panel A at 12 weeks indicates the primary efficacy time point. Panel D shows the least square mean change from baseline in the 28-joint disease activity score based on the level of disease activity score in 28 joints using C-reactive protein (DAS28-CRP). A mixed-effects model with repeated measures was used to evaluate treatment effect on change from baseline with treatment, visit, treatment-by-visit interaction, stratification

factors, and baseline value included in the model as fixed effects and patient as a random effect. No imputation was used for change from baseline data that were missing. In panels A and D, filgotinib, 200 mg, and filgotinib, 100 mg, vs placebo were significant ( $P \leq .001$ ) at all postbaseline time points. In panel B, postbaseline time points were significant ( $P \leq .01$ ), with the exception of filgotinib, 200 mg, and filgotinib, 100 mg, at week 2 ( $P > .05$ ). In panel C, postbaseline time points were significant ( $P \leq .01$ ), with the exception of filgotinib, 200 mg, and filgotinib, 100 mg, at week 2 ( $P > .05$ ); filgotinib, 200 mg, at week 4 ( $P > .05$ ); and filgotinib, 100 mg, at weeks 4 and 12 ( $P \leq .05$ ).

## Discussion

Once-daily filgotinib, 200 mg or 100 mg, in the setting of concurrent csDMARD use met the primary end point of difference vs placebo on ACR 20 at week 12. All hierarchically tested secondary end points (ACR response, DAS28-CRP, Simplified Disease Activity Index, Clinical Disease Activity Index, and individual ACR core set parameters) demonstrated significant improvements vs placebo in patients who had active RA despite prior bDMARD therapy.

Similar treatment-refractory patient populations have previously been evaluated in other phase 3 trials of JAK inhibitors

(upadacitinib,<sup>21</sup> baricitinib,<sup>22</sup> and tofacitinib<sup>23</sup>). The ACR20 response rates at week 12 in these trials were as follows: upadacitinib, 30 mg, 65%; baricitinib, 4 mg, 55%; and tofacitinib, 5 mg, 42%, compared with filgotinib, 200 mg, 66%.<sup>21-23</sup> Improvements in ACR20 with filgotinib were evident at week 2 (earliest assessment), and responses were maintained or improved over 24 weeks, reflecting a time course similar to that seen with other JAK inhibitors.<sup>21-23</sup> The proportions of patients achieving DAS28-CRP of 3.2 or less at week 12 in these studies showed a similar trend: upadacitinib, 30 mg, 42%; baricitinib, 4 mg, 31%; and tofacitinib, 5 mg, 21%, compared with filgotinib, 200 mg, 41%.<sup>21-23</sup> At week 24, 30.6% of patients treated with filgotinib, 200 mg, achieved disease

remission (DAS28-CRP <2.6). Responses with the filgotinib, 200-mg, dose were numerically higher compared with the 100-mg dose, but no statistical analysis for potential dose response was done.

For patients with active RA refractory to bDMARDs, subsequent treatment has generally been observed to be less effective, especially as the number of previous treatments increases.<sup>22,24</sup> In this study, patient randomization was stratified based on the number of previous bDMARDs and the analysis was prespecified to examine the number of prior treatments. ACR20 response rates with filgotinib were independent of the number of prior bDMARDs; the ACR20 response rates to filgotinib, 200 mg and 100 mg, were 70.3% and 58.8%, respectively, in patients previously treated with 3 or more bDMARDs, while that of the overall population was 66% and 57.5%, respectively. These results are similar to the response rates in filgotinib phase 2 studies, which mainly enrolled patients who were naive to bDMARDs.<sup>8,9</sup> The response rates for patients taking placebo (background csDMARDs only) did decrease as expected with the number of prior bDMARDs, suggesting that the consistent efficacy of filgotinib in these patients is not an artifactual finding.

This study was not powered to make statistical comparisons of adverse events among the randomized groups, which limits the interpretation of these findings. There was little difference in the proportion of adverse events between treatment groups, and most were grade 1 or 2 in severity. Few patients in any treatment group discontinued study drugs due to an AE. AEs reported with other JAK inhibitors were rare, including serious infectious AEs ( $\leq 2\%$  in the filgotinib groups), major adverse cardiovascular events (1 each in the filgotinib, 100 mg, and placebo groups), and 1 AE of retinal vein occlusion (which did not result in an interruption of filgotinib treatment and resolved with bevacizumab treatment). Infections occurred in 35% of filgotinib-treated patients (with similar event rates at both filgotinib doses) and 26% of placebo-treated patients. There were no opportunistic infections, active tuberculosis, malignancies, gastrointestinal perforations, or deaths. Laboratory abnormality AEs were reported at similar frequencies across all groups and there

were no clinically relevant changes from baseline in mean values for hematology. Mostly mild increases in creatine kinase and transaminases in the filgotinib groups were observed; however, elevations greater than  $\times 3$  ULN were infrequent. Similar to the other JAK inhibitors, transient and symptomatic increases in creatine kinase values were more common in the filgotinib groups; however, they did not require any intervention.

### Limitations

This study has several limitations. First, the 24-week duration precludes conclusions regarding longer-term safety and duration of benefit. Second, there were no radiographic end points to evaluate structural joint damage. Third, the study population was limited to the more refractory group of patients who continue to have active disease despite prior bDMARD therapy. Fourth, this trial was conducted primarily in patients from North America and Western Europe; thus, the ability to translate these data to additional populations remains a focus for future study. AEs, efficacy, and radiographic end points in other patient populations are being evaluated in multinational phase 3 trials of filgotinib (FINCH 1 [methotrexate-inadequate responders, [NCT02889796](#)] and FINCH 3 [methotrexate-naive patients, [NCT02886728](#)]). Fifth, the trial was limited in duration and not powered to study safety. Therefore, additional analyses will be needed across different RA populations over the longer term to better define the safety profile of filgotinib, and an extension trial (FINCH 4, [NCT03025308](#)) is being conducted to evaluate the long-term outcomes of patients who completed the FINCH studies.

### Conclusions

Among patients with active RA who had an inadequate response or intolerance to 1 or more bDMARDs, filgotinib, 100 mg or 200 mg daily, compared with placebo resulted in a significantly greater proportion achieving a clinical response at week 12. However, further research is needed to assess longer-term efficacy and safety.

#### ARTICLE INFORMATION

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**Correction:** This article was corrected online on February 4, 2020, to fix demographic data reported in Table 1 and disease characteristic data reported in eTable 2 in [Supplement 3](#).

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**Author Contributions:** Dr Genovese had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Supervision:** Genovese, Gottenberg, Mozaffarian, Bartok, Matzkies, Sundry, de Vlam, Takeuchi.

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## REFERENCES

- Singh JA, Saag KG, Bridges SL Jr, et al; American College of Rheumatology. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-25. doi:10.1002/acr.22783
- Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 2014;73(3):492-509. doi:10.1136/annrheumdis-2013-204573
- Kalden JR, Schulze-Koops H. Immunogenicity and loss of response to TNF inhibitors: implications for rheumatoid arthritis treatment. *Nat Rev Rheumatol*. 2017;13(12):707-718. doi:10.1038/nrrheum.2017.187
- Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs*. 2017;77(5):521-546. doi:10.1007/s40265-017-0701-9
- Walker JG, Smith MD. The Jak-STAT pathway in rheumatoid arthritis. *J Rheumatol*. 2005;32(9):1650-1653.
- Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. *J Clin Invest*. 2008;118(11):3537-3545. doi:10.1172/JCI36389
- Van Rompaey L, Galien R, van der Aar EM, et al. Preclinical characterization of GLPG0634, a selective inhibitor of JAK1, for the treatment of inflammatory diseases. *J Immunol*. 2013;191(7):3568-3577. doi:10.4049/jimmunol.1201348
- Kavanaugh A, Kremer J, Ponce L, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). *Ann Rheum Dis*. 2017;76(6):1009-1019. doi:10.1136/annrheumdis-2016-210105
- Westhovens R, Taylor PC, Alten R, et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). *Ann Rheum Dis*. 2017;76(6):998-1008. doi:10.1136/annrheumdis-2016-210104
- Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569-2581. doi:10.1002/art.27584
- Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum*. 1995;38(6):727-735. doi:10.1002/art.1780380602
- Disease Activity Score in rheumatoid arthritis. <https://www.das-score.nl/das28/en/introduction-menu.html>. Accessed January 15, 2019.
- Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum*. 1995;38(1):44-48. doi:10.1002/art.1780380107
- Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum*. 1980;23(2):137-145. doi:10.1002/art.1780230202
- Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol*. 1982;9(5):789-793.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36), I: conceptual framework and item selection. *Med Care*. 1992;30(6):473-483. doi:10.1097/00005650-199206000-00002
- Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. *Health Qual Life Outcomes*. 2003;1:79. doi:10.1186/1477-7525-1-79
- Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther*. 2005;7(4):R796-R806. doi:10.1186/ar1740
- Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol*. 2005;23(5)(suppl 39):S100-S108.
- Smolen JS, Breedveld FC, Schiff MH, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford)*. 2003;42(2):244-257. doi:10.1093/rheumatology/keg072
- Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet*. 2018;391(10139):2513-2524. doi:10.1016/S0140-6736(18)31116-4
- Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374(13):1243-1252. doi:10.1056/NEJMoa1507247
- Burmester GR, Blanco R, Charles-Schoeman C, et al; ORAL Step investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet*. 2013;381(9865):451-460. doi:10.1016/S0140-6736(12)61424-X
- Rendas-Baum R, Wallenstein GV, Koncz T, et al. Evaluating the efficacy of sequential biologic therapies for rheumatoid arthritis patients with an inadequate response to tumor necrosis factor- $\alpha$  inhibitors. *Arthritis Res Ther*. 2011;13(1):R25. doi:10.1186/ar3249