Efficacy and safety of filgotinib in combination with methotrexate in Japanese patients with active rheumatoid arthritis who have an inadequate response to methotrexate: Subpopulation analyses of 24-week data of a global phase 3 study (FINCH 1)

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ABSTRACT

Objectives: Evaluate the efficacy and safety of the Janus kinase-1 inhibitor filgotinib in Japanese patients with rheumatoid arthritis (RA) and inadequate response to methotrexate (MTX).

Methods: Data from 147 Japanese patients in FINCH 1, a 52-week global Phase 3 study, were analysed up to 24 weeks. Patients received once-daily filgotinib 200 or 100 mg, biweekly adalimumab, or placebo, all with stable background MTX.

Results: In the Japanese population, American College of Rheumatology 20% response rates at Week 12 (primary endpoint) were 77.5%, 65.9%, 53.6%, and 36.8% for filgotinib 200 mg, filgotinib 100 mg, adalimumab, and placebo. Proportions of patients achieving Disease Activity Score with 28 joints <2.6 at Week 24: filgotinib 200 mg, 65.0%; filgotinib 100 mg, 51.2%; adalimumab, 42.9%; and placebo, 5.3%. Incidence rates of serious infections: filgotinib 200 mg, 2.5%; filgotinib 100 mg, 0%; adalimumab, 10.7%; and placebo, 5.3%. Treatment-emergent laboratory abnormalities Grade ≥3 occurred in five (12.5%) filgotinib 200 mg, three (7.3%) filgotinib 100 mg, one (3.6%) adalimumab, and no placebo patients. No deaths were reported among Japanese patients.

Conclusions: Filgotinib once daily combined with MTX was effective and generally safe and well tolerated up to Week 24 in Japanese patients with RA and inadequate response to MTX.

KEYWORDS: Filgotinib; Janus kinase; Japanese; Phase 3 clinical trials; rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a multifactorial, chronic inflammatory disease that primarily damages peripheral joints, which may lead to marked destruction and deformity of joints, considerable disability, and adverse impact on quality of life (QoL); RA thus imposes substantial burden on both individuals and society [1–4]. Treatment guidelines from the European League Against Rheumatism, American College of Rheumatology (ACR), and Japanese College of Rheumatology recommend first-line treatment with a conventional synthetic disease-modifying antirheumatic drug (csDMARD), most commonly, methotrexate (MTX) [5–7]. If patients fail to achieve clinical remission or low disease activity with MTX, other csDMARDs, biologic DMARDs (bDMARDs), and Janus kinase (JAK) inhibitors, usually in combination with MTX, are recommended as second-line options [5–7]. Despite great improvement in patient outcomes with recent RA treatments, multiple therapeutic challenges remain, including inadequate efficacy, intolerance to currently available therapy, and the potential for bDMARD immunogenicity. Patient needs regarding pain, physical function, mental function, and fatigue also remain challenges to address [8–10].

JAKs are intracellular cytoplasmic tyrosine kinases that transduce cytokine signalling from membrane receptors. Four different types of JAKs are known (JAK1, JAK2, JAK3, and TYK2), which interact in different combinations with distinct sets of membrane receptors [11, 12]. Inhibition of JAKs is a promising therapeutic option for a range of inflammatory conditions, including RA and ulcerative colitis [11–13]. Several small-molecule, orally administered JAK inhibitors have been developed for the treatment of refractory RA [14, 15].

Filgotinib is an oral, small-molecule inhibitor that preferentially inhibits JAK1-dependent signalling in cellular and whole-blood assays and demonstrates robust efficacy in disease models for RA in both mouse and rat [16]. Clinical efficacy of filgotinib both as a monotherapy and in combination with MTX was demonstrated in Phase 2 and 3 studies in patients with moderately to severely active RA [17–20]. A Phase 1 study of filgotinib showed that the pharmacokinetic profile of filgotinib in Japanese and Caucasian healthy participants was similar, suggesting that the inclusion of Japanese patients in global studies is justified. A global Phase 3 study of filgotinib (FINCH 1) in patients with active RA and inadequate response to MTX demonstrated the superiority of filgotinib 200 and 100 mg vs placebo for 20% improvement in ACR criteria (ACR20) response rate at Week 12 [21].

The aim of the present study is to evaluate the efficacy and safety of filgotinib up to Week 24 for Japanese patients with RA and inadequate response to MTX from the FINCH 1 study and to assess whether results in this subpopulation are consistent with the overall study population.

Materials and methods

Study design and patients

This randomised, double-blind, placebo- and active-controlled, multicentre, Phase 3 study (NCT02889796) assessed the efficacy and safety of filgotinib in combination with MTX in adult patients with active RA who had inadequate response to MTX. The detailed study design was previously described in the FINCH 1 global study publication [21].

The Phase 3 study was conducted up to Week 52; however, the present analysis includes interim data up to Week 24. The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines and was approved by each study centre's institutional review board or ethics committee. Male or female patients with moderately to severely active RA [22] who were ≥18 years of age (≥20 years of age in Japan) on the day of consent were screened to determine eligibility per the inclusion and exclusion criteria (**Supplemental Methods**).

Randomisation

Patients who provided written consent and met all eligibility criteria were randomised in a 3:3:2:3 ratio to receive filgotinib 200 mg, filgotinib 100 mg, adalimumab, or placebo. Randomisation was stratified by geographic region, prior exposure to bDMARDs, and presence of rheumatoid factor or anti-cyclic citrullinated peptide antibody at screening.

Treatment procedures

Patients received once-daily oral filgotinib 200 or 100 mg, biweekly subcutaneous adalimumab 40 mg, or matching placebos and stable weekly background MTX. At Week 14, patients who did not achieve at least a 20% improvement from Day 1 in both swollen joint count (SJC) and tender joint count (TJC) discontinued investigational therapy but continued with study visits and assessments per protocol. Clinical assessments, patient questionnaires, collection of adverse events (AEs), and laboratory tests were performed on Day 1 and at Weeks 2, 4, 8, 12, 14, 16, 20, 24, 26, 30, 36, 44, and 52 (or early termination) to evaluate the efficacy and safety. For the interim analysis, data assessed up to Week 24 (or early termination) were used.

Outcome measures

The primary endpoint was the proportion of patients who achieved ACR20 [23] at Week 12. The key secondary efficacy endpoints included the proportions of patients who achieved Disease Activity Score for 28 joint count using C-reactive protein (DAS28-CRP) ≤3.2 at Week 12 and DAS28-CRP <2.6 at Week 24 [24]. Change from baseline at Week 12 in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score was also a key secondary endpoint [25, 26].

Other secondary endpoints included change from baseline in 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) score [27] and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score [28]; 50% and 70% improvement in ACR response rate (ACR50 and ACR70, respectively); and change from baseline in DAS28-CRP and the seven components of the ACR core set (SJC, TJC, patient's pain assessment and Patient's and Physician's Global Assessment of Disease, HAQ-DI, and high-sensitivity C-reactive protein [hsCRP]) [23].

Safety outcomes were evaluated by AEs and laboratory abnormalities, physical examinations, vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiration rate, and body temperature) and 12-lead electrocardiograms (ECG). The AEs were coded using Medical Dictionary for Regulatory Activities Version 21.0 with severity grades defined by the Common Terminology Criteria for Adverse Events Version 4.03.

Statistical analysis

This was a predefined analysis of patients in FINCH 1 enrolled in Japan. The primary analysis set for efficacy analyses is the full analysis set, which included all randomised patients who received at least one dose of study drug. Safety was analysed in the safety analysis set, which included all patients who received at least one dose of study drug. Treatment group comparisons for binary efficacy endpoints were analysed using a Fisher's exact test using nonresponder imputation for missing data. Change from baseline in continuous efficacy endpoints was analysed using a mixed-effects model for repeated measures with baseline value, treatment, visit, and treatment-by-visit interaction included as fixed effects and patients as the random effect. A noninferiority test was performed to compare the proportion of patients who achieved DAS28(CRP) $\leq$3.2 in each filgotinib dose group with the adalimumab group at Week 12 using the same methods as the global analysis [21]. All p-values from treatment comparisons in this subpopulation are exploratory and are not adjusted for multiplicity.

Results

Patient population

In FINCH 1, 1759 patients were randomised and, of these, 147 Japanese patients were randomised and dosed with the assigned study treatment (Figure 1); 40, 41, 28, and 38 Japanese patients received filgotinib 200 mg, filgotinib 100 mg, adalimumab, and placebo, respectively. The majority of patients were female (79.6%). The mean age was 55 [standard deviation (SD), 11.3] years, and 21.8% of patients were 65 years or older. Mean body mass index (BMI) was 22.4 (SD, 4.03) kg/m^2. Baseline characteristics in the Japanese patients were similar among treatment groups (Table 1). Of the Japanese patients, 17 prematurely discontinued study drug due to lack of efficacy prior to Week 24 (three, four, four, and six patients receiving filgotinib 200 mg, filgotinib

100 mg, adalimumab, and placebo, respectively); six patients prematurely discontinued study drug due to AEs (one, two, and three patients receiving filgotinib 200 mg, adalimumab, and placebo, respectively). The AEs leading to discontinuation in patients receiving placebo were progression of RA, pneumonia, and organising pneumonia.

Primary and key secondary outcomes

At Week 12 in the Japanese population, ACR20 response rates were higher with filgotinib 200 [77.5% (31/40)] or 100 mg [65.9% (27/41)] vs placebo [36.8% (14/38)]. The difference vs placebo (95% confidence interval) was 40.7% (18.0% to 63.3%; exploratory p <.001) for filgotinib 200 mg and 29.0% (5.4% to 52.7%; exploratory p =.013) for filgotinib 100 mg. ACR20 response rates at Week 12 for filgotinib 200 and 100 mg (77.5% and 65.9%, respectively) were numerically higher compared with adalimumab (53.6% [15/28]). ACR20 response rates over time are shown in Figure 2(a). The onset of ACR20 response occurred as early as Week 2 in both filgotinib treatment groups, and response rates were maintained or improved over 24 weeks. Adalimumab ACR20 response rate showed separation from placebo at Week 2 but was numerically lower than filgotinib 200 and 100 mg response rates from Week 4 through Week 24.

The proportion of patients who achieved DAS28-CRP <2.6 and $\leq$3.2, respectively, in the Japanese population at 12 and 24 weeks is shown in Table 2. At Week 12, the proportions of patients receiving filgotinib 200 or 100 mg who achieved DAS28-CRP $\leq$3.2 were 70.0% and 56.1%, respectively, which was greater than the proportion of patients treated with placebo (18.4%; exploratory p <.001 and p =.001, respectively). At Week 12, the proportion of patients receiving filgotinib 200 mg who achieved DAS28-CRP $\leq$3.2 was noninferior to adalimumab (60.7%). At Week 24, the proportions of patients receiving filgotinib 200 or 100 mg who achieved DAS28-CRP <2.6 were 65.0% and 51.2%, respectively,
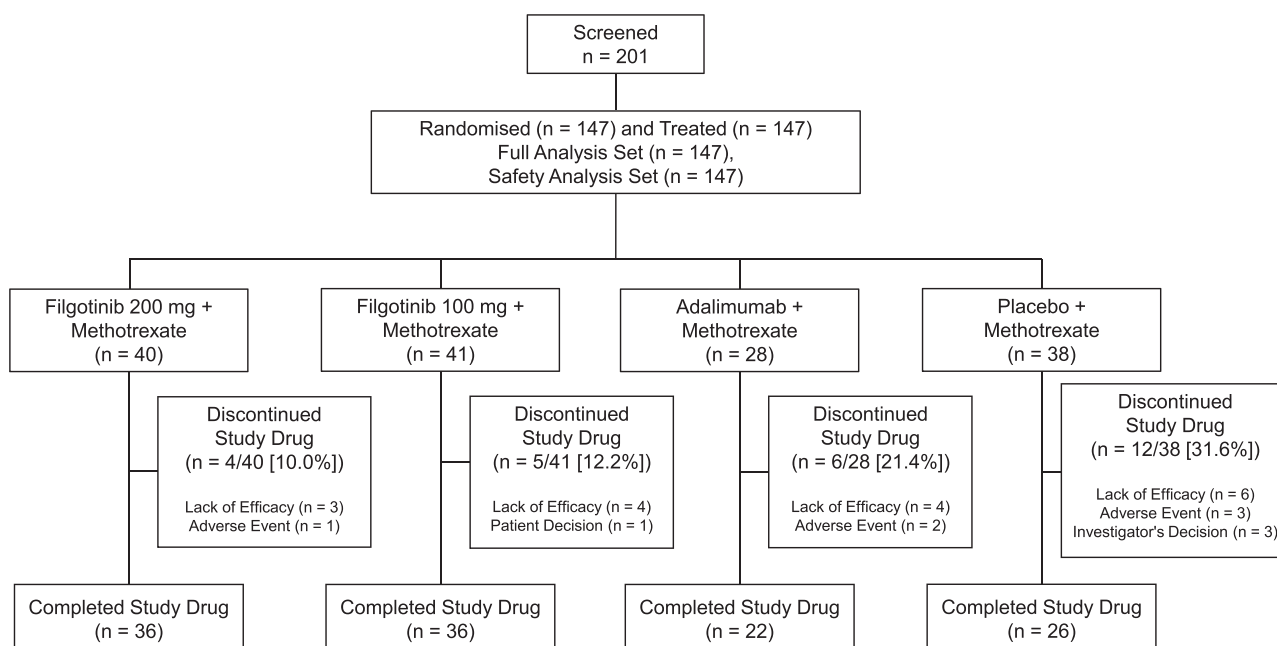

Figure 1. Study flow and patient disposition (up to Week 24). A total of 147 Japanese patients were randomised and treated in the FINCH 1 study.

Table 1. Patient demographics and baseline characteristics.

	FIL 200 mg + MTX ($n = 40$)	FIL 100 mg + MTX ($n = 41$)	ADA + MTX ($n = 28$)	PBO + MTX ($n = 38$)
Age, mean (SD), y	56 (11.7)	54 (11.6)	54 (10.5)	55 (11.6)
<65	28 (70.0%)	33 (80.5%)	24 (85.7%)	30 (78.9%)
≥65	12 (30.0%)	8 (19.5%)	4 (14.3%)	8 (21.1%)
Sex				
Male	8 (20.0%)	7 (17.1%)	6 (21.4%)	9 (23.7%)
Female	32 (80.0%)	34 (82.9%)	22 (78.6%)	29 (76.3%)
Body weight, mean (SD), kg	57.2 (11.76)	54.6 (10.66)	56.8 (9.26)	56.5 (11.54)
Body mass index, mean (SD), kg/m^2	22.7 (3.84)	21.7 (4.09)	22.6 (3.64)	22.7 (4.48)
Duration of RA from diagnosis, mean (SD), y	8.2 (9.88)	6.3 (6.51)	5.4 (6.83)	6.9 (8.57)
Concurrent oral corticosteroid# use on first dosing date				
No. (%)	16 (40.0%)	14 (34.1%)	8 (28.6%)	14 (36.8%)
Mean (SD) dose, mg/day	4.4 (2.10)	4.0 (2.94)	4.2 (1.85)	2.6 (1.84)
Mean (SD) dose of concurrent MTX on first dosing date, mg/week	10.1 (3.39)	11.0 (2.61)	9.8 (3.00)	10.3 (2.50)
hsCRP mean (SD), mg/L	19.40 (18.872)	10.28 (12.554)	12.87 (18.122)	10.07 (12.790)
Presence of RF	32 (80.0%)	33 (80.5%)	15 (53.6%)	28 (73.7%)
Presence of anti-CCP Ab	37 (92.5%)	37 (90.2%)	25 (89.3%)	35 (92.1%)
Presence of both RF and anti-CCP Ab	32 (80.0%)	32 (78.0%)	14 (50.0%)	26 (68.4%)
HAQ-DI, mean (SD)	1.10 (0.650)	1.06 (0.682)	0.88 (0.618)	0.92 (0.559)
DAS28-CRP, mean (SD)	5.3 (1.00)	5.1 (0.89)	4.7 (0.95)	5.0 (0.91)
SF-36 PCS, mean (SD)	40.3 (6.87)	40.3 (8.68)	40.9 (7.40)	39.9 (7.61)
SJC66, mean (SD)	15 (7.5)	15 (8.3)	12 (6.1)	13 (5.6)
TJC68, mean (SD)	17 (11.1)	20 (10.0)	12 (5.7)	17 (9.8)
SJC28, mean (SD)	11 (5.5)	10 (4.4)	9 (3.8)	10 (5.2)
TJC28, mean (SD)	11 (5.9)	11 (4.3)	8 (4.1)	10 (5.0)
FACIT-Fatigue, mean (SD)	32.7 (11.60)	34.9 (10.57)	35.5 (6.76)	34.6 (7.75)
Patient's pain assessment, mean (SD), mm	59 (22.1)	55 (23.9)	51 (21.7)	50 (23.4)
Global assessment of disease activity, mean (SD), mm				
Patient's	58 (22.7)	54 (23.5)	51 (22.4)	51 (22.3)
Physician's	59 (20.7)	56 (21.6)	60 (18.8)	56 (20.3)

Data shown as *n* (%) unless otherwise indicated.
Ab: antibody; ADA: adalimumab; CCP: cyclic citrullinated peptide; DAS28-CRP: Disease Activity Score for 28 joint count using C-reactive protein; FACIT: functional assessment of chronic illness therapy; FIL: filgotinib; HAQ-DI: Health Assessment Questionnaire-Disability Index; hsCRP: high sensitivity C-reactive protein; MTX: methotrexate; No.: number; PBO: placebo; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation; SF-36 PCS: 36-Item Short Form Health Survey Physical Component Summary; SJC: swollen joint count; TJC: tender joint count; y: year; # prednisolone equivalent.

which was higher relative to patients treated with placebo (5.3%; exploratory *p* <.001 for both). In contrast, 42.9% of patients receiving adalimumab achieved DAS28-CRP <2.6.

The mean (SD) changes in HAQ-DI score from baseline at Week 12 in the Japanese population were –0.67 (0.57) and –0.48 (0.49) for patients receiving filgotinib 200 and 100 mg, respectively (Table 2). Improvements in HAQ-DI were greater for patients treated with filgotinib 200 and 100 mg compared with placebo (–0.17; exploratory *p* <.001 and *p* =.002, respectively). Change in HAQ-DI from baseline for patients receiving adalimumab was –0.34.

Other secondary efficacy outcomes

The proportion of patients in the Japanese population achieving ACR50 and ACR70 over time are shown in Figure 2(b) and (c). After Week 2, ACR50 response rates with filgotinib 200 mg were numerically higher compared with placebo. At Week 12, 57.5% and 46.3% of patients receiving filgotinib 200 and 100 mg, respectively, achieved ACR50 vs 7.9% receiving placebo (exploratory *p* <.001 for both) and 32.1% receiving adalimumab. Similarly, after Week 4, ACR70 response rates with filgotinib 200 mg were numerically higher than with placebo. At Week 12, 35.0% and 26.8% of patients

receiving filgotinib 200 and 100 mg, respectively, achieved ACR70 vs 2.6% receiving placebo (exploratory *p* <.001 and .004, respectively) and 10.7% receiving adalimumab. Patients had greater mean decreases from baseline in DAS28-CRP following either filgotinib 200 or 100 mg treatment compared with placebo at all observed time points (Figure 2(d)).

For patients receiving filgotinib, all components of the ACR core criteria, including patient-reported pain, were decreased numerically from baseline at Week 2 and continued to improve up to Week 24 (Figure 3). For all components, patients treated with filgotinib 200 mg had numerically greater improvements relative to those treated with adalimumab at any time point.

Mean (SD) changes from baseline to Week 12 in SF-36 PCS score were 7.6 (5.4) and 7.2 (6.5) with filgotinib 200 and 100 mg, respectively (Table 2), which represented greater improvement from baseline than was achieved with placebo [3.6 (5.6); exploratory *p* <.001 and *p* =.003, respectively]. For patients receiving adalimumab, mean (SD) change from baseline in SF-36 PCS at Week 12 was 5.3 (6.5). The mean (SD) changes from baseline to Week 12 in FACIT-Fatigue score were 5.9 (7.0) and 6.5 (8.7) with filgotinib 200 and 100 mg, respectively, compared with 3.8 (6.6) with placebo and 6.1 (6.6) with adalimumab (Table 2).
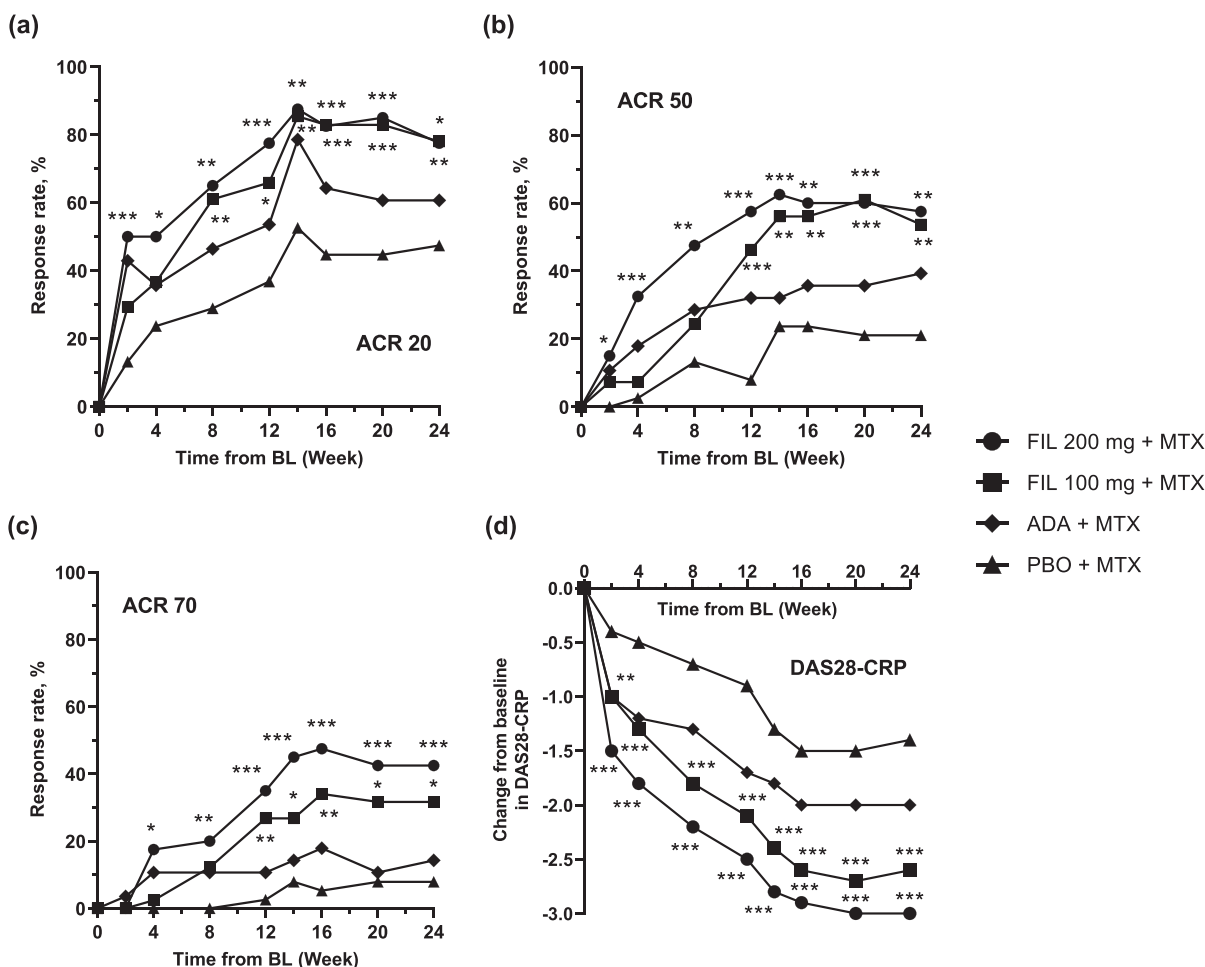
Figure 2. Rates over time of ACR20, ACR50, and ACR70, and mean changes in DAS28-CRP from baseline (BL). Panels (a), (b), (c), and (d) show the percentage of patients who achieved 20% improvement in American College of Rheumatology criteria (ACR20), 50% improvement (ACR50), 70% improvement (ACR70), and the mean changes in Disease Activity Score for 28 joint count using C-reactive protein (DAS28-CRP) from BL, respectively. Solid circles, solid squares, solid diamonds, and solid triangles show the values of filgotinib (FIL) 200 mg + methotrexate (MTX), FIL 100 mg + MTX, adalimumab (ADA) + MTX and placebo (PBO) + MTX, respectively. *Exploratory $p <.05$; **Exploratory $p <.01$; ***Exploratory $p <.001$ for FIL groups vs PBO + MTX.

Safety outcomes

Adverse events

The summary of treatment-emergent AEs (TEAEs) up to Week 24 in the Japanese population is shown in Table 3. Serious TEAEs were reported in three patients (7.5%) receiving filgotinib 200 mg, two patients (4.9%) receiving filgotinib 100 mg, three patients (10.7%) receiving adalimumab, and three patients (7.9%) receiving placebo. No deaths were reported. Most TEAEs of infection were mild or moderate and were reported in 50.0%, 26.8%, 28.6%, and 34.2% of patients receiving filgotinib 200 mg, filgotinib 100 mg, adalimumab, and placebo, respectively. Among patients receiving filgotinib 200 mg, there was one TEAE of serious infection: a patient reported gastroenteritis on Day 29, was hospitalised to receive antibiotic treatment, and study drug was interrupted until recovery at Day 39. No patients receiving filgotinib 100 mg reported a TEAE of serious infection. TEAEs of serious infections were reported by three (10.7%) and two patients (5.3%) receiving adalimumab (pneumonia, cellulitis, and *Pneumocystis jirovecii* pneumonia) and

placebo (pneumonia and pneumonia pneumococcal), respectively. One case of nonserious herpes zoster was reported in each filgotinib group. A Grade 1 AE of herpes zoster occurred on Day 162 in a 65-year-old female patient receiving filgotinib 200 mg and was considered by the investigator to be related to study drug. Study drug was withheld, and the patient was treated with gentamicin sulphate and valacyclovir; the event resolved on Day 183. A Grade 2 AE of herpes zoster occurred on Day 102 in a 78-year-old female patient receiving filgotinib 100 mg and was considered by the investigator to be related to the study drug. The patient discontinued study medication and was treated with valacyclovir and vidarabine, and the event resolved on Day 127. No opportunistic infection (OI) was reported with filgotinib treatment, but an OI of *P. jirovecii* pneumonia was reported in one patient receiving adalimumab. No adjudicated major adverse cardiovascular events (MACE), adjudicated venous thromboembolisms (VTE), or gastrointestinal perforations were reported in the Japanese population. No malignancies were reported in patients receiving filgotinib.

Table 2. Primary and secondary outcomes.

	Week 12				Week 24			
	FIL 200 mg + MTX	FIL 100 mg + MTX	ADA + MTX	PBO + MTX	FIL 200 mg + MTX	FIL 100 mg + MTX	ADA + MTX	PBO + MTX
Number of full analysis set	40	41	28	38	40	41	28	38
ACR20 response								
No. (%)	31 (77.5***)	27 (65.9*)	15 (53.6)	14 (36.8)	31 (77.5***)	32 (78.0**)	17 (60.7)	18 (47.4)
% diff. vs PBO + MTX (95% CI)	40.7 (18.0 to 63.3)	29.0 (5.4 to 52.7)	—	—	30.1 (7.1 to 53.2)	30.7 (7.8 to 53.5)	—	—
ACR50 response								
No. (%)	23 (57.5***)	19 (46.3***)	9 (32.1)	3 (7.9)	23 (57.5*)	22 (53.7*)	11 (39.3)	8 (21.1)
% diff. vs PBO + MTX (95% CI)	49.6 (29.5 to 69.7)	38.4 (18.4 to 58.5)	—	—	36.4 (13.8 to 59.1)	32.6 (10.0 to 55.2)	—	—
ACR70 response								
No. (%)	14 (35.0***)	11 (26.8*)	3 (10.7)	1 (2.6)	17 (42.5*)	13 (31.7*)	4 (14.3)	3 (7.9)
% diff. vs PBO + MTX (95% CI)	32.4 (14.2 to 50.6)	24.2 (7.2 to 41.2)	—	—	34.6 (14.5 to 54.7)	23.8 (4.7 to 43.0)	—	—
DAS28-CRP <2.6								
No. (%)	21 (52.5***)	16 (39.0***)	12 (42.9)	2 (5.3)	26 (65.0***)	21 (51.2***)	12 (42.9)	2 (5.3)
% diff. vs PBO + MTX (95% CI)	47.2 (27.6 to 66.8)	33.8 (14.7 to 52.8)	—	—	59.7 (40.8 to 78.7)	46.0 (26.6 to 65.4)	—	—
DAS28-CRP ≤3.2								
No. (%)	28 (70.0***)	23 (56.1**)	17 (60.7)	7 (18.4)	28 (70.0***)	28 (68.3***)	16 (57.1)	10 (26.3)
% diff. vs PBO + MTX (95% CI)	51.6 (30.2 to 72.9)	37.7 (15.6 to 59.8)	—	—	43.7 (21.2 to 66.2)	42.0 (19.5 to 64.5)	—	—
HAQ-DI								
No. of patients measured	39	40	27	34	36	35	22	25
Mean change from baseline (SD)	-0.67*** (0.571)	-0.48** (0.491)	-0.34 (0.466)	-0.17 (0.270)	-0.71*** (0.620)	-0.62** (0.522)	-0.38 (0.484)	-0.25 (0.406)
LS-mean of diff. vs PBO + MTX (95% CI)	-0.47 (-0.64 to -0.29)	-0.28 (-0.46 to -0.11)	—	—	-0.45 (-0.66 to -0.25)	-0.32 (-0.53 to -0.12)	—	—
SF-36 PCS								
No. of patients measured	39	40	27	34	36	36	22	25
Mean change from baseline (SD)	7.6*** (5.39)	7.2** (6.53)	5.3 (6.46)	3.6 (5.55)	7.4* (6.93)	8.3** (7.95)	5.3 (6.25)	3.7 (6.96)
LS-mean of diff. vs PBO + MTX (95% CI)	3.9 (1.7 to 6.2)	3.4 (1.2 to 5.7)	—	—	4.1 (1.1 to 7.2)	4.2 (1.1 to 7.2)	—	—
FACIT-Fatigue								
No. of patients measured	37	39	27	33	36	36	22	24
Mean change from baseline (SD)	5.9 (6.98)	6.5* (8.74)	6.1 (6.56)	3.8 (6.61)	7.6 (9.64)	6.1 (10.26)	3.1 (9.56)	3.9 (8.02)
LS-mean of diff. vs PBO + MTX (95% CI)	1.9 (-0.9 to 4.7)	3.2 (0.4 to 5.9)	—	—	2.5 (-1.4 to 6.4)	2.4 (-1.5 to 6.4)	—	—

ACR20/50/70 response: 20%/50%/70% improvement in American College of Rheumatology criteria; ADA: adalimumab; CI: confidence interval; DAS28-CRP: Disease Activity Score for 28 joint count using C-reactive protein; Diff.: difference; FACIT: Functional Assessment of Chronic Illness Therapy; FIL: filgotinib; HAQ-DI: Health Assessment Questionnaire-Disability Index; LS mean: least-squares mean; MTX: methotrexate; No.: number; PBO: placebo; SD: standard deviation; SF-36 PCS: 36-Item Short Form Health Survey Physical Component Summary.

*Exploratory *p* <.05.

**Exploratory *p* <.01.

***Exploratory *p* <.001 *vs* PBO + MTX.

Table 3. Treatment-emergent adverse events up to Week 24.

	No. of patients (%)			
	FIL 200 mg + MTX (n = 40)	FIL 100 mg + MTX (n = 41)	ADA + MTX (n = 28)	PBO + MTX (n = 38)
Any TEAEs	33 (82.5%)	30 (73.2%)	20 (71.4%)	28 (73.7%)
TEAEs occurring in >10% of patients				
Nausea	4 (10.0%)	3 (7.3%)	0	0
Nasopharyngitis	7 (17.5%)	3 (7.3%)	3 (10.7%)	4 (10.5%)
Bronchitis	4 (10.0%)	1 (2.4%)	0	1 (2.6%)
TEAEs with Grade 3 or higher	5 (12.5%)	1 (2.4%)	3 (10.7%)	3 (7.9%)
Serious TEAEs	3 (7.5%)	2 (4.9%)	3 (10.7%)	3 (7.9%)
Death	0	0	0	0
TEAEs leading to discontinuation of study drug	1 (2.5%)	0	2 (7.1%)	4 (10.5%)
Infectious TEAE (all)	20 (50.0%)	11 (26.8%)	8 (28.6%)	13 (34.2%)
Serious infection	1 (2.5%)	0	3 (10.7%)	2 (5.3%)
Herpes zoster	1 (2.5%)	1 (2.4%)	0	0
Opportunistic infection	0	0	1 (3.6%)	0
Malignancy	0	0	1 (3.6%)	0
MACE	0	0	0	0
VTE	0	0	0	0
Gastrointestinal perforations	0	0	0	0

All data shown as n (%).
MACE and VTE were adjudicated by an independent committee.
ADA: adalimumab; FIL: filgotinib; MACE: major adverse cardiovascular events; MTX: methotrexate; No.: number; PBO: placebo; TEAE: treatment-emergent adverse event; VTE: venous thromboembolism.
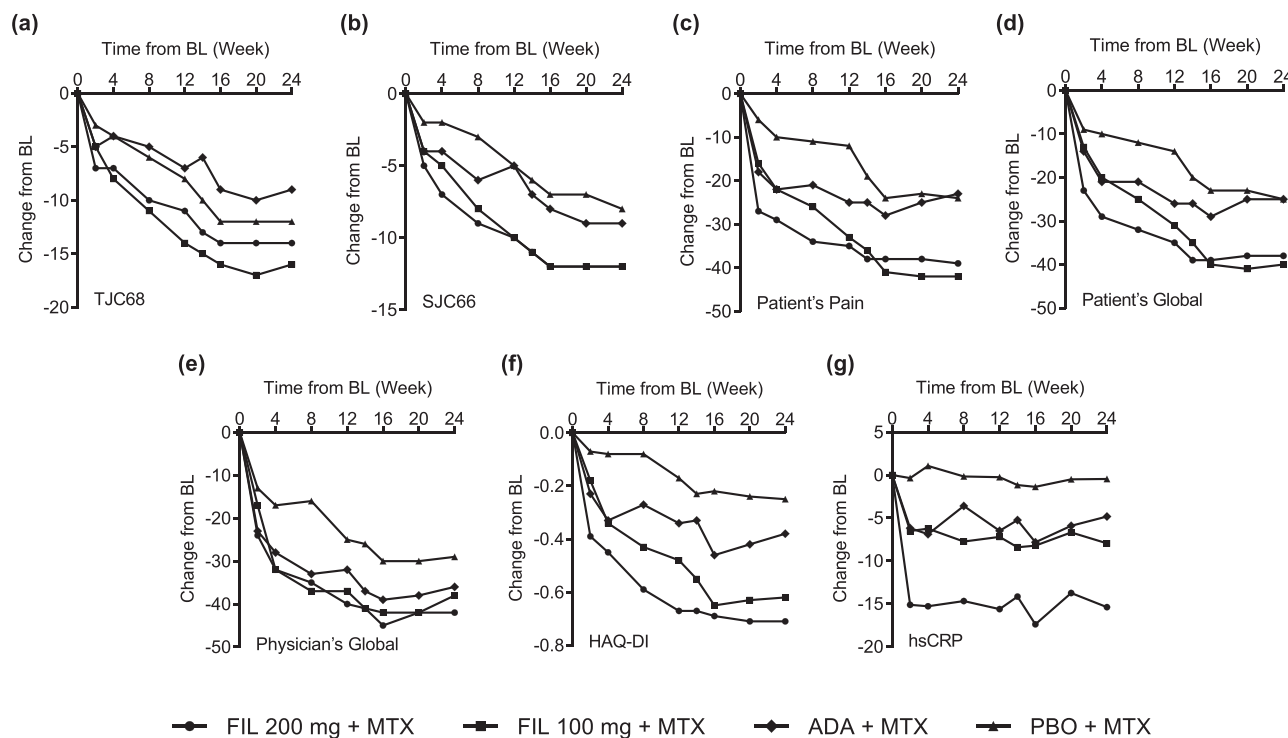
Figure 3. Rates over time of seven components of the American College of Rheumatology core criteria. Panels (a), (b), (c), (d), (e), (f), and (g) show the mean values of changes from baseline (BL) in tender joint count in 68 joints (TJC68), swollen joint count in 66 joints (SJC66), patient's pain assessment, patient's global assessment, physician's global assessment, Health Assessment Questionnaire-Disability Index (HAQ-DI), and high sensitivity C-reactive protein (hsCRP), respectively. Solid circles, solid squares, solid diamonds, and solid triangles show the values of filgotinib (FIL) 200 mg + methotrexate (MTX), FIL 100 mg + MTX, adalimumab (ADA) + MTX, and placebo (PBO) + MTX, respectively.

Laboratory abnormalities

In the Japanese population, treatment-emergent laboratory abnormalities of Grade 3 or higher were reported in five patients (12.5%) receiving filgotinib 200 mg (Grade 3 lymphopenia, two patients; Grade 3 hypophosphatemia, two patients; Grade 3 amylase increase, one patient; Grade 3 creatine kinase increase, one patient; hypophosphatemia and creatine kinase increase occurred together in a single patient), three patients (7.3%) receiving filgotinib 100 mg (Grade 3 serum glucose increase, one patient; Grade 3 triacylglycerol

lipase increase, one patient; and Grade 3 hypophosphatemia, one patient), one patient (3.6%) receiving adalimumab (Grade 3 neutropenia), and no patients receiving placebo. The two patients receiving filgotinib 200 mg with Grade 3 hypophosphatemia were a 63-year-old man with phosphate levels of 1.8 and 1.9 mg/dl on Days 113 and 141, respectively, and a 60-year-old man with a phosphate level of 1.9 mg/dl on Day 113. The latter also reported asymptomatic Grade 3 creatine kinase elevations of 2712 and 1641 U/l on Days 29 and 113, respectively. At Week 24, this patient's creatine kinase level was 1349 IU/l. Grade 3 hypophosphatemia of 1.9 mg/dl was reported in a 55-year-old female patient at the 4-week follow-up visit following early discontinuation from filgotinib 100 mg.

Other safety

In the overall population, there were no clinically relevant changes from baseline within any treatment group or differences among the treatment groups in results from general physical examinations and vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiration rate, or body temperature). No analyses of vital signs in the Japanese subpopulation were conducted. No Japanese patient showed clinically significant shifts in 12-lead ECG.

Discussion

FINCH 1 was a randomised, double-blind, placebo- and active-controlled, multicentre, Phase 3 study assessing the efficacy and safety of filgotinib in combination with MTX in adult patients with active RA who had inadequate response to MTX. In this subpopulation analysis of Japanese patients, improvements in the signs and symptoms of RA as measured by ACR20 response were observed as early as Week 2 in patients receiving both filgotinib doses compared with placebo. Compared with adalimumab, patients receiving filgotinib 200 and 100 mg generally showed similar ACR20 response rates and numerically higher ACR50/70 response rates at Weeks 12 and 24. In addition, more patients achieved DAS28-CRP <2.6 while receiving filgotinib 200 or 100 mg at Week 24 compared to those receiving placebo or adalimumab. Thus, filgotinib treatment may help Japanese patients with RA with inadequate response to MTX reach treatment targets. Furthermore, filgotinib treatment could improve physical function and health-related QoL, as suggested by the favourable outcomes for patients receiving filgotinib 200 and 100 mg vs placebo and measured by changes from baseline in HAQ-DI, SF-36 PCS, and FACIT-Fatigue (Table 2). Patient pain assessments, evaluated as part of the ACR core criteria, also rapidly decreased over time with filgotinib treatment and were maintained at low levels (Figure 3).

No differences expected to impact results were observed in baseline characteristics between the Japanese population and the overall population [21]. Body weight, BMI, MTX dose, corticosteroids dose, and disease severity were slightly lower in the Japanese population than in the overall population (Table 1) [21].

The primary endpoint, ACR20 response rate at Week 12, was higher with both filgotinib doses than with placebo in the Japanese population; these findings are consistent with the FINCH 1 global study [21]. Response rates for other efficacy endpoints were also higher with both filgotinib doses and placebo, with a rapid reduction of hsCRP in patients receiving filgotinib 200 mg (Figure 3). A lower placebo response was observed in the Japanese population compared to the overall global population [21], but the change in HAQ-DI observed here for patients receiving placebo confirms good prestudy compliance, even if Japanese MTX doses are mandated to be lower.

When compared with adalimumab, ACR20 response rates at Week 12 in filgotinib 200 and 100 mg were numerically higher in this analysis of Japanese patients; in the overall population, ACR20 response rates were comparable between filgotinib and adalimumab [21]; the same trend was observed for ACR50 and ACR70 response rates. Numerically higher response rates with filgotinib treatment compared with adalimumab were observed in every ACR component, including SJC66. There were no differences in baseline characteristics that accounted for the differences of ACR20/50/70 response rates between patients receiving filgotinib and adalimumab. Adherence to study drug in patients receiving adalimumab was almost equivalent between the Japanese population and the overall population (data not shown). In the proportion of patients who achieved DAS28-CRP ≤3.2 at Week 12, filgotinib 200 mg was comparable to adalimumab, consistent with the outcome in the overall population [21]. Given the small sample size of the Japanese population, it is challenging to draw conclusions regarding the difference in efficacy between filgotinib and adalimumab.

The safety results of the present study show that filgotinib 200 and 100 mg are generally well tolerated in combination with MTX for 24 weeks. No clear dose-dependent difference in safety profiles was observed between filgotinib 200 and filgotinib 100 mg, except infection rates (Table 3). The incidence rate of TEAEs of infection with filgotinib 200 mg (50.0%) was numerically higher relative to filgotinib 100 mg (26.8%), while the incidence rate of TEAEs of infection was comparable between the filgotinib doses in the overall study population [21]. Most TEAEs of infection were mild or moderate; only one serious infection (gastroenteritis) was reported in a patient receiving filgotinib 200 mg. The safety profile of filgotinib in the Japanese population was generally consistent with the overall population (Table 3) [21].

Patients with RA in the Japanese population are at increased risk of herpes zoster due to the disease and immunosuppressive therapies, including JAK inhibitors [29, 30]. Two cases of herpes zoster were reported with filgotinib treatment in the Japanese population (Table 3). However, it is difficult to assess the elevated risk of herpes zoster caused by filgotinib in this subpopulation analysis, mainly due to small sample size. In the overall population of FINCH 1 (*n* = 1755), herpes zoster (excluding primary varicella) occurred at comparable rates during the placebo-controlled period in patients receiving filgotinib 200 mg (0.4%), 100 mg (0.4%), adalimumab (0.6%), or placebo (0.4%) [21]. No OI, malignancy, MACE, VTE, or gastrointestinal perforation was reported by patients receiving filgotinib in the Japanese population, but further evaluation of the risk of these relatively rare and serious AEs with filgotinib treatment is still needed.

The efficacy and safety of the JAK inhibitor baricitinib in Japanese patients with RA who had inadequate response to MTX was evaluated in a placebo-controlled, double-blind setting through the subpopulation analysis of the RA-BEAM

study, which included 249 Japanese patients, 93 of whom were treated with 4 mg baricitinib [31]. Efficacy and safety, including rates of herpes zoster, of filgotinib 200 mg plus MTX in the present analysis are similar to those of baricitinib plus MTX in the Japanese population analysis from RA-BEAM [31].

There were no AEs related to male reproductive potential among Japanese patients in our analysis. The ongoing clinical studies NCT03201445 (MANTA) and NCT03926195 (MANTA Ray) are designed to evaluate the potential effects of filgotinib on semen parameters in humans. Before starting treatment, male patients of reproductive potential should be advised of potential reduction in fertility with impaired spermatogenesis following treatment with filgotinib.

Treatment-emergent laboratory abnormalities of Grade 3 or higher were observed more commonly among patients receiving filgotinib 200 or 100 mg compared with adalimumab and placebo. The risk of hypophosphatemia is being followed in pharmacovigilance activities in Japan as an important potential risk of filgotinib treatment. There were four cases of hypophosphatemia among the Japanese subpopulation; all were asymptomatic, none required phosphate replacement therapy, and no trend was observed in their onset or duration.

In this subpopulation analysis, filgotinib 200 mg once daily provided consistent reduction in disease activity and added benefit over the 100 mg dose, while both doses were generally well tolerated. Filgotinib 200 mg once daily was thus chosen as the optimal dose for the treatment of RA in the label approved in Japan and the EU [32, 33].

Limitations of the present analysis include the small sample size of Japanese patients and the exploratory nature of the efficacy treatment comparisons, which limit drawing conclusions on the efficacy and safety of filgotinib in the studied patient population. A larger study would confirm the important outcomes shown here. This study is also an interim analysis of a 52-week study, and the 24-week duration precludes drawing conclusions regarding longer-term safety and duration of benefit. Analysis of data in Japanese patients from the long-term extension study (NCT03025308) will be performed.

To summarise these results, filgotinib once daily combined with MTX is effective in reducing the signs and symptoms of RA and improving physical function. Filgotinib is generally safe and well tolerated in Japanese patients with RA who had inadequate response to MTX.

Acknowledgements

Supplementary data

Supplementary data is available at *Modern Rheumatology* online.

Conflict of interest

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