Modern Rheumatology, **33**, 2023, 668–679
DOI: https://doi.org/10.1093/mr/roac084
Advance access publication date: 3 August 2022
Original Article

Safety and efficacy of filgotinib for Japanese patients with RA and inadequate response to MTX: FINCH 1 52-week results and FINCH 4 48-week results

Yoshiya Tanaka[a,*], Tsukasa Matsubara[b], Tatsuya Atsumi[c], Koichi Amano[d], Naoki Ishiguro[e], Eiji Sugiyama[f], Kunihiro Yamaoka[g], Bernard G. Combe[h], Alan J. Kivitz[i], Sang-Cheol Bae[j], Edward C. Keystone[k], Peter Nash[l], Mark Genovese[m], Franziska Matzkies[m], Beatrix Bartok[m], Alena Pechonkina[m], Akira Kondo[n], Lei Ye[m], Qi Gong[m], Chantal Tasset[o] and Tsutomu Takeuchi[p]

[a]First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
[b]Department of Orthopedics, Matsubara Mayflower Hospital, Kato, Hyogo, Japan
[c]Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan
[d]Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Hidaka, Saitama, Japan
[e]Aichi Developmental Disability Center, Kasugai, Aichi, Japan
[f]Department of Clinical Immunology and Rheumatology, Hiroshima University Hospital, Hiroshima, Japan
[g]Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan
[h]Rheumatology Department, CHU Montpellier, Montpellier University, Montpellier, France
[i]Altoona Center for Clinical Research, Duncansville, PA, USA
[j]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Hanyang University Institute for Rheumatology Research and Hanyang University Institute of Bioscience and Biotechnology, Seoul, Korea
[k]Department of Medicine, University of Toronto, Toronto, ON, Canada
[l]Griffith University of Queensland, Brisbane, Queensland, Australia
[m]Gilead Sciences Inc., Foster City, CA, USA
[n]Gilead Sciences K.K., Tokyo, Japan
[o]Galapagos NV, Mechelen, Belgium
[p]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, and Saitama Medical University, Iruma, Saitama, Japan

*Correspondence: Yoshiya Tanaka; tanaka@med.uoeh-u.ac.jp; The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahata-nishi, Kitakyushu 807-8555, Japan.

ABSTRACT

Objectives: To present safety and efficacy of the JAK1 preferential inhibitor filgotinib in Japanese patients with prior inadequate response (IR) to methotrexate (MTX) from a 52-week randomised controlled parent study (PS) and long-term extension (LTE) through June 2020.

Methods: The PS (NCT02889796) randomised MTX-IR patients to filgotinib 200 (FIL200) or 100 mg (FIL100), adalimumab (ADA) 40 mg, or placebo; all took stable background MTX. At week (W) 24, placebo patients were rerandomised to FIL200 or FIL100. The primary endpoint was W12 American College of Rheumatology 20% improvement; safety was assessed by adverse event (AE) reporting. For the LTE (NCT03025308), eligible filgotinib patients continued FIL200/FIL100; ADA patients were rerandomised (blinded) to FIL200 or FIL100; all continued MTX.

Results: In all, 114/147 Japanese patients completed the PS, 115 enrolled in LTE, and 103 remained on study in June 2020. In the PS, AEs were consistent with the overall population, and W24 efficacy was maintained or improved through W52, comparable with the overall population. LTE AE incidences were similar between doses; filgotinib efficacy was consistent from baseline to W48 and similar between PS ADA and filgotinib patients.

Conclusions: Among MTX-IR Japanese patients, filgotinib maintained efficacy over 1 year; LTE safety was consistent with the PS.

KEYWORDS: Filgotinib; long-term follow-up; rheumatoid arthritis; safety

Introduction

Rheumatoid arthritis (RA) is a common inflammatory disorder. In Japan, prevalence of RA has recently been estimated to be 0.65% overall and is particularly high among the country's growing population of older adults (1.63% in patients aged 70–79 years) [1]. Therapeutic approaches have focused on the amelioration of chronic inflammation and relied on conventional synthetic disease-modifying antirheumatic drugs

Received 13 April 2022; Accepted 24 July 2022

(csDMARDs) such as methotrexate (MTX) [2], non-steroidal anti-inflammatory drugs, and glucocorticoids [3]. In standard Japanese medical practice, MTX doses are lower compared with the US or Europe, and the recommended dosing is given at a 12-h interval over 2 days to reduce the risk of gastrointestinal side effects [4]. While MTX remains a first-line therapy, it may achieve only partial clinical benefit, and its use is limited due to safety and tolerability concerns [2, 5].

Filgotinib, an oral Janus kinase 1 preferential inhibitor, has been evaluated in two Phase 2 and three Phase 3 randomised controlled trials (RCTs) [6–11] in adults with moderately to severely active RA. Filgotinib is approved in Japan and Europe as a treatment for RA [12, 13].

Subpopulation analyses showed that filgotinib was safe and efficacious in Japanese patients up to Week 24 in three Phase 3 RCTs including patients with previous inadequate response (IR) to MTX (NCT02889796; FINCH 1), biologic disease-modifying antirheumatic drugs (bDMARD)-IR patients (NCT02873936; FINCH 2), and MTX-naïve patients (NCT02886728; FINCH 3) [14–16]. While 24-week results in the Japanese subpopulation are informative, it is important to evaluate safety and efficacy of new compounds over longer-term use. In this paper, we report results from the Japanese subpopulation of the MTX-IR trial through Week 52 as well as preliminary data from a long-term extension (LTE; NCT03025308; FINCH 4) in eligible Japanese patients.

Methods

Study design and patients

The detailed design of the 52-week parent study (PS) is described in the FINCH 1 global study publication [8]. Patients who completed the PS taking filgotinib or adalimumab (ADA) could enter the LTE if they were willing to do so (including written consent) and if the investigator thought they could benefit from filgotinib treatment. The trials were conducted in accordance with the Declaration of Helsinki and the International Council on Harmonisation Good Clinical Practice guidelines and were approved by each study centre's institutional review board or ethics committee. All patients provided informed written consent. Adult patients, male or female, with moderately to severely active RA 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 [16]. The LTE is planned to continue for a total of 6 years of treatment; we present LTE efficacy data through treatment Week 48 and safety data up to 1 June 2020.

Randomisation and treatment procedures

As previously reported [8, 16], eligible patients who provided written consent for the PS were randomised in a 3:3:2:3 ratio to receive filgotinib 200 mg (FIL200), filgotinib 100 mg (FIL100), ADA, or placebo (as shown in Figure 1); all received stable background MTX. Randomisation was stratified by geographic region (including Japan as its own region), prior exposure to bDMARDs, and presence of rheumatoid factor or anti-cyclic citrullinated peptide antibody at screening. Per protocol, patients with IR (<20% improvement in swollen or in tender joint count) at Week 14 or at two consecutive visits after Week 30 were switched to standard of care through Week 52 but continued study visits and assessments; these patients were not eligible for the LTE. At Week 24, patients taking placebo were rerandomised 1:1 to either FIL200 or FIL100 and continued in the trial through Week 52.

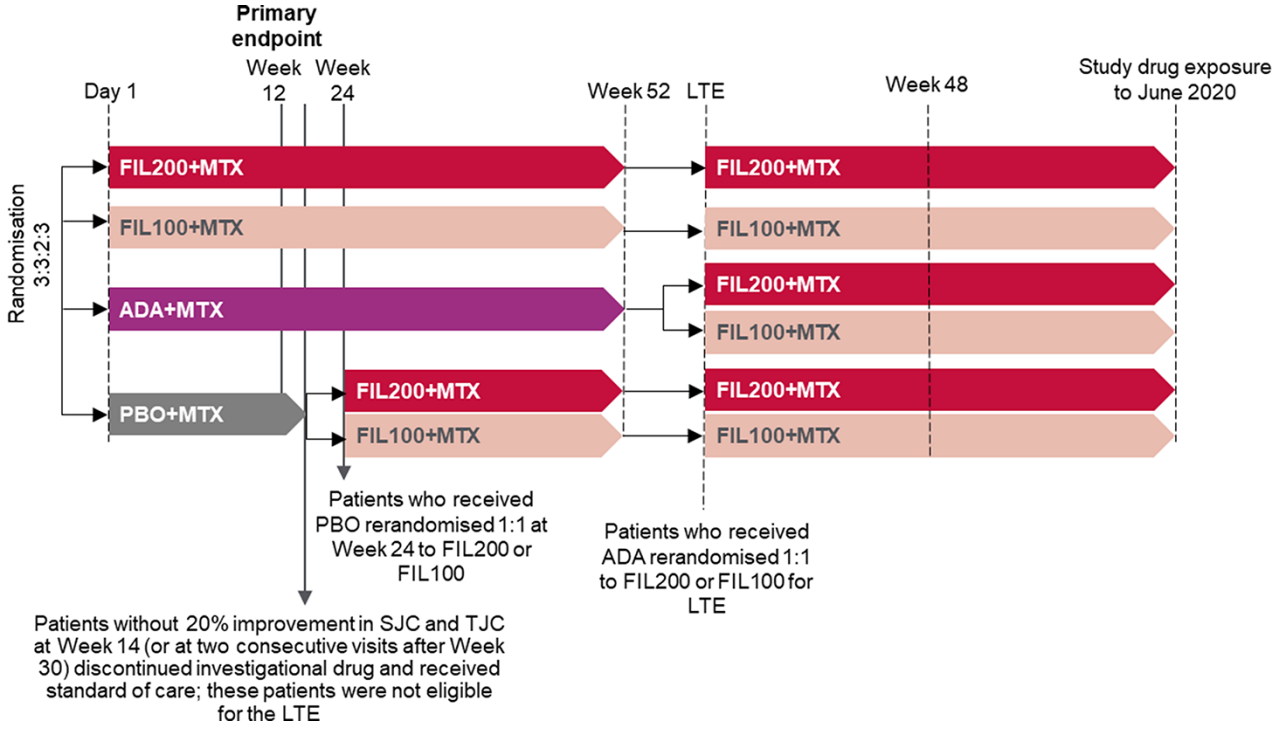

Figure 1. Overall study design for PS (FINCH 1) and those entering the LTE (FINCH 4).

PBO, placebo; SJC, swollen joint count; TJC, tender joint count.

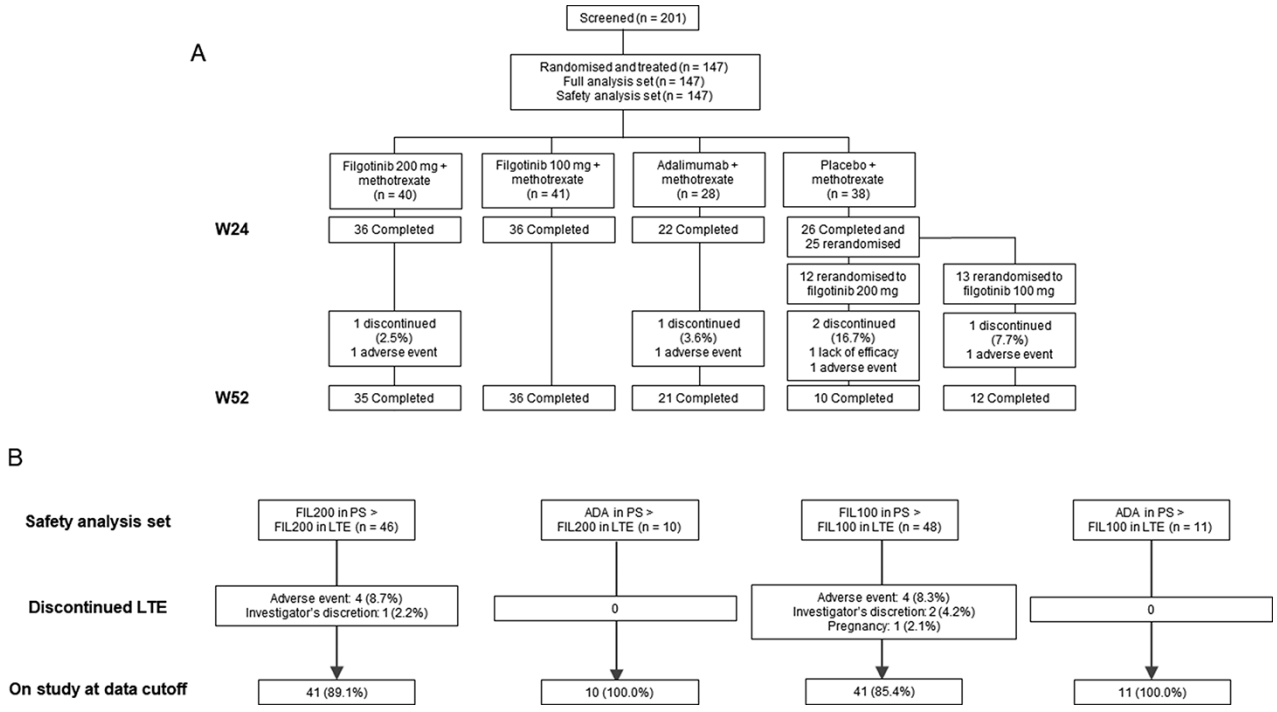

Figure 2. Patient disposition for Japanese patients. (A) PS disposition. (B) LTE disposition.

One patient was included at LTE baseline but not at completion of PS. This patient terminated treatment on Day 365 of the PS due to 'noncompliance with study drug'; thus, at discontinuation, the patient had completed the 52 weeks of treatment despite being recorded as discontinuing. The patient was enrolled into the LTE immediately following PS discontinuation. W, week.

For the LTE, patients who were taking blinded filgotinib at the final visit of the PS continued on their same dosage of filgotinib in a blinded fashion (200 or 100 mg once daily). Patients who were receiving ADA plus MTX at their final visit of the PS were rerandomised on Day –1 of the LTE in a 1:1 ratio to FIL200 or FIL100 once daily in a blinded fashion (randomisation was again stratified by region, with Japan as its own region). In addition to the randomised treatment, all patients continued to be maintained on their PS protocol-approved background therapy (MTX); the background therapy for all patients during the LTE was managed by the primary investigator/clinician and was to be adjusted as needed for safety and disease control. Results of the LTE were stored in a separate database from the PS results. This paper includes efficacy and safety data from previously MTX-IR patients with RA enrolled at sites in Japan ($n = 147$) in the randomised 52-week study and eligible patients who rolled into the LTE from FINCH 1.

Outcome measures

Parent study

Safety outcomes in the PS included adverse events (AEs). The AEs were coded using Medical Dictionary for Regulatory Activities Version 21.0 in the PS and 22.0 in the LTE with severity grades defined by the Common Terminology Criteria for Adverse Events Version 4.03. Treatment-emergent AEs (TEAEs) were defined as events that met one or both of the following criteria: (1) an onset date on or after the start date of study drug and not later than 30 days after permanent discontinuation of study drug and (2) any AE leading to premature discontinuation of study drug. Overall TEAEs, Grade ≥3 TEAEs, serious TEAEs, TEAEs leading to premature discontinuation of study drug, deaths, TEAEs of interest, and laboratory test results were summarised by treatment group.

The primary efficacy endpoint of the PS was the proportion of patients who achieved American College of Rheumatology 20% increase (ACR20) [17] at Week 12. Key secondary efficacy endpoints included the proportions of patients who achieved Disease Activity Score for 28 joint counts using C-reactive protein [DAS28(CRP)] ≤3.2 at Week 12 [18], change from baseline (CFB) in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 12 [19, 20], and proportions achieving DAS28(CRP) <2.6 at Week 24. Additional secondary endpoints included CFB in 36-Item Short-Form Health Survey (SF-36) Physical Component Summary (PCS) score [21], CFB in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score [22], and CFB in modified Total Sharp Score (mTSS). Additional endpoints included 50% and 70% improvement in ACR response rate (ACR50 and ACR70); Boolean remission; CFB in high-sensitivity CRP (hsCRP); additional patient-reported outcomes, such as the Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI); and additional radiographic assessments including erosion score and joint space narrowing. Radiographic methods have been described in detail previously [8]. Briefly, radiographs were scored centrally as Campaign A [radiographs taken at baseline (BL), Week 12, and Week 24 or pretermination visit before Week 24] and Campaign B (radiographs taken at BL, Week 24, and Week 52 or pretermination visit after Week 24). Week 52 results were based on the combination of Campaign B and Campaign A results (Campaign B/A). Radiographs were scored centrally by two independent readers with adjudication by a third if necessary.

Table 1. Demographics and disease characteristics at LTE BL.

	FIL200 + MTX in LTE		FIL100 + MTX in LTE	
	FIL200 + MTX in PS ($n = 46$)	ADA + MTX in PS ($n = 10$)	FIL100 + MTX in PS ($n = 48$)	ADA + MTX in PS ($n = 11$)
Age, mean (SD)	55 (12.6)	54 (9.6)	57 (11.2)	53 (12.6)
Female, *n* (%)	37 (80.4)	9 (90.0)	38 (79.2)	10 (90.9)
Duration of RA, years, mean (SD)	8.3 (9.33)	6.8 (4.12)	7.8 (8.01)	5.0 (5.32)
Prior exposure to bDMARDs, *n* (%)	0	10 (100.0)	0	11 (100.0)
Concurrent oral corticosteroids on first dosing date, *n* (%)	17 (37.0)	2 (20.0)	15 (31.3)	3 (27.3)
Concurrent oral corticosteroid dose on first dosing date, mg/day, mean (SD)	3.6 (2.24)	5.0 (0.00)	3.3 (2.50)	5.0 (2.5)
Concurrent MTX dose on first dosing date, mg/week, mean (SD)	10.2 (3.38)	9.4 (3.66)	9.8 (2.76)	9.6 (2.8)
Concurrent use of 1 csDMARD on first dosing, *n* (%)	45 (97.8)	10 (100.0)	46 (95.8)	11 (100.0)
Swollen joint count based on 66 joints, mean (SD)	2 (2.9)	3 (2.9)	3 (3.6)	3 (3.3)
Tender joint count based on 68 joints, mean (SD)	3 (5.4)	4 (1.9)	4 (5.3)	1 (1.7)
HAQ-DI, mean (SD)	0.42 (0.590)	0.38 (0.445)	0.52 (0.576)	0.26 (0.364)
DAS28(CRP), mean (SD)	2.2 (1.10)	2.5 (0.66)	2.5 (1.01)	2.0 (0.80)
Subject's pain assessment, mm, mean (SD)	18 (23.1)	21 (20.7)	17 (19.7)	18 (20.4)
Subject's global assessment of disease activity, mm, mean (SD)	18 (22.8)	20 (19.6)	17 (18.2)	19 (21.2)
Physician's global assessment of disease activity, mm, mean (SD)	16 (16.5)	19 (10.3)	15 (13.4)	11 (9.9)
SDAI, mean (SD)	7.4 (7.85)	7.8 (3.70)	8.6 (7.74)	6.1 (4.26)
CDAI, mean (SD)	7.1 (7.06)	7.6 (3.57)	8.2 (7.64)	6.0 (4.25)
hsCRP, mg/l, mean (SD)	3.20 (11.812)	1.50 (1.704)	3.80 (7.573)	0.72 (0.879)

Long-term extension

Safety assessments evaluated in the PS were also recorded during the LTE. The primary endpoints of the LTE study were the proportion of patients experiencing AEs and the proportion of patients experiencing clinically significant laboratory abnormalities. Compiled data from the following were summarised (system organ class/patient-level data not included): any TEAE, TEAE Grade ≥3, serious TEAEs, TEAEs leading to discontinuation of study drug, deaths, AEs of special interest [infections, serious infections, herpes zoster, opportunistic infections, tuberculosis, hepatitis B and C, major adverse cardiovascular events (MACE), venous thromboembolism (VTE), nonmelanoma skin cancer (NMSC), non-NMSC malignancy, and gastrointestinal perforations]. Positively adjudicated MACE and VTE were reported. MACE was defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Efficacy endpoints in the LTE were the same as in the Phase 3 trials from which patients were enrolled; here, we report the proportion of patients achieving ACR improvement (relative to PS BL) [23], as well as proportions of responders achieving DAS28(CRP), CDAI, SDAI, and Boolean remission endpoints; and CFB in SF-36 PCS, FACIT-Fatigue, HAQ-DI, patient assessment of pain, and hsCRP.

Statistical analysis

Assessment of patients in FINCH 1 enrolled in Japan was a prespecified analysis for the PS. Safety was analysed using the safety analysis set, which included all patients who received ≥1 dose of study drug. AE data in the PS were summarised by treatment group using descriptive statistics.

The primary analysis set for efficacy analyses was the full analysis set, which included all randomised patients who received ≥1 dose of study drug. All available data were included, including those collected from patients who had discontinued study drug and were receiving standard of care. In the PS, treatment group comparisons for binary efficacy endpoints were conducted using Fisher's exact test with nonresponder imputation for missing data. The 95% confidence intervals (CIs) for response rates and differences in response rates were based on the normal approximation method with continuity correction. CFB in continuous endpoints, including radiographic endpoints, was compared between groups using the mixed-effects model for repeated measures (MMRM), including treatment, visit (as categorical), treatment by visit, and BL value as fixed effects and patients as the random effect ('campaign' was also a fixed effect in the analyses at Week 52 for radiographic endpoints). Least squares mean, 95% CI, and *p* value from MMRM were provided. Missing change scores were not otherwise imputed using the MMRM approach, assuming an unstructured variance–covariance matrix for the repeated measures.

For radiographic data, the comparisons at Week 24 were between each dose of filgotinib and placebo. The comparisons at Week 52 were FIL100 vs placebo switched to FIL100 and FIL200 vs placebo switched to FIL200.

In the LTE analysis, patients originally taking filgotinib or placebo and rerandomised to filgotinib were combined into one group of 'patients with prior filgotinib exposure'. AE data were summarised by treatment group using descriptive statistics. Efficacy endpoints in the LTE were summarised descriptively with 95% CIs using observed cases without imputing

Table 2. Safety in the PS to W52.

	FIL200 + MTX ($n = 40$)	FIL100 + MTX ($n = 41$)	ADA + MTX ($n = 28$)	PBO + MTX group before switching at Week 24 ($n = 38$)	PBO + MTX group after switching to FIL200 + MTX at Week 24 ($n = 12$)	PBO + MTX on FIL100 + MTX period ($n = 13$)
TEAE	40 (100.0)	35 (85.4)	26 (92.9)	28 (73.7)	9 (75.0)	8 (61.5)
TEAE with Grade 3 or higher	6 (15.0)	2 (4.9)	3 (10.7)	3 (7.9)	1 (8.3)	1 (7.7)
Serious TEAE	4 (10.0)	3 (7.3)	3 (10.7)	3 (7.9)	0	0
TEAE leading to premature discontinuation of any study drug	2 (5.0)	0	3 (10.7)	4 (10.5)	0	1 (7.7)
Deaths	0	0	0	0	0	0
TEAE of interest						
Infection	29 (72.5)	16 (39.0)	13 (46.4)	13 (34.2)	4 (33.3)	3 (32.1)
Serious infection	1 (2.5)	1 (2.4)	3 (10.7)	2 (5.3)	0	0
Herpes zoster	1 (2.5)	1 (2.4)	0	0	0	0
Hepatitis B or C	0	0	0	0	0	0
Opportunistic infections	0	0	1 (3.6)	0	0	0
Active tuberculosis	0	0	0	0	0	0
MACE	0	0	0	0	0	0
Malignancy excluding NMSC	0	0	1 (3.6)[a]	0	0	0
NMSC	0	0	0	0	0	0
Deep vein thrombosis and pulmonary embolism	0	0	0	0	0	0
Gastrointestinal perforations	1 (2.5)	0	0	0	0	0
Laboratory abnormalities reported as AEs						
ALT increase	0	3 (7.3)	0	0	0	0
AST increase	0	2 (4.9)	0	0	0	0
CPK increase	4 (10.0)	0	0	0	0	0
Neutrophil decrease	0	0	0	0	0	0
Lymphocyte decrease	2 (5.0)	1 (2.4)	0	0	1 (8.3)	0
Haemoglobin decrease	0	0	0	0	0	0
LDL increased	0	0	0	0	0	0
HDL increased	0	0	0	0	0	0

[a]Lymphocyte morphology abnormal. All data are n (%).
ALT, alanine transaminase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PBO, placebo.

missing data, as the study is ongoing, and many patients have not yet reached later visits.

Results

Patient population

The PS included 147 treated patients from Japan out of 201 randomised/screened, with 114 completing the study to Week 52; 35, 36, and 21 completed 52 weeks taking FIL200, FIL100, and ADA, respectively, while 10 and 12 remained on study to Week 52 taking FIL200 and FIL100, respectively, after 24 weeks of placebo. The safety analysis set in the LTE consisted of 115 patients (56 in the FIL200 group and 59 in the FIL100 group). A total of 103 patients in the LTE (51 taking FIL200 and 52 taking FIL100) were on study drug at the time of the data cut; median duration of exposure in the LTE was approximately 69 weeks. Disposition is shown in Figure 2. Patient demographics and characteristics are shown in Supplementary Table S1 (characteristics at PS BL) and Table 1 (characteristics at LTE BL). Characteristics at PS BL were comparable among treatment groups of Japanese patients. At LTE BL following 52 weeks of treatment, characteristics were generally similar among groups. Mean DAS28(CRP) ranged from 2.0 to 2.5, and mean patient pain assessment ranged from 17 to 21 mm. Differences were not considered sufficient to preclude evaluation of safety and efficacy in the subgroup of Japanese patients.

PS outcomes

Safety outcomes

As shown in Table 2, incidence of AEs in the PS through Week 52 was similar (≥85% of patients) across FIL200, FIL100, and ADA groups, while among patients originally randomised to placebo, comparable proportions had AEs in the 24 weeks before switching and after switching to filgotinib for weeks 24–52. TEAEs led to discontinuation in two (5.0%), zero, and three (10.7%) patients in the FIL200, FIL100, and ADA groups, respectively, by Week 52; four (10.5%) discontinued placebo before Week 24, and one patient (7.7%) discontinued FIL100 after switching from placebo.

Serious AEs occurred in either three or four patients in each of the four treatment groups as randomised. In addition to the previously reported serious infections that occurred before Week 24 [one in the FIL200 group (gastroenteritis), three in the ADA group (pneumonia, cellulitis, and *Pneumocystis*

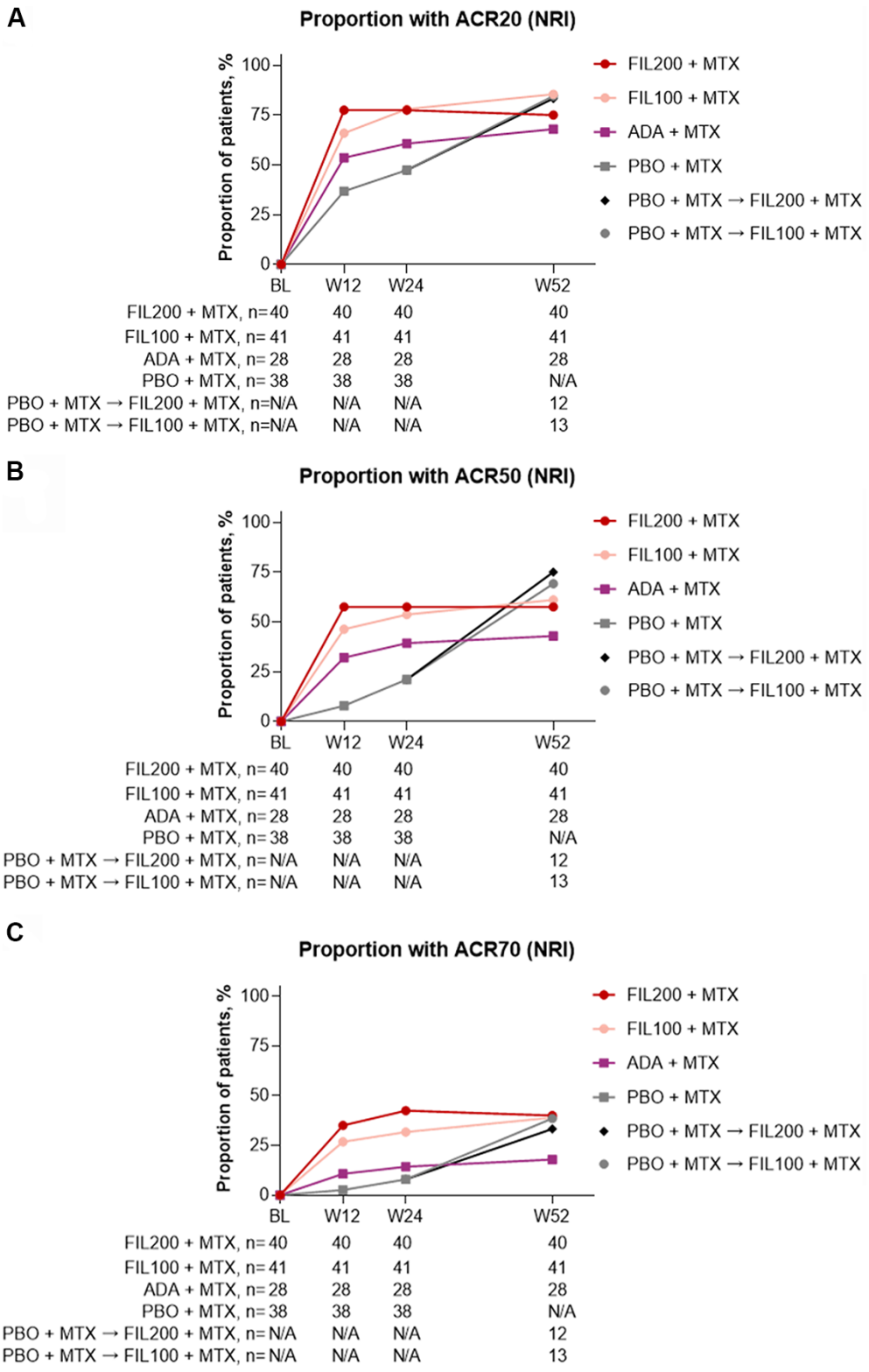

Figure 3. Proportions of ACR20 (A), ACR50 (B), and ACR70 (C) responders in the PS. (A) Patients achieving ACR20 in the PS. (B) Patients achieving ACR50 in the PS. (C) Patients achieving ACR70 in the PS.

N/A, not applicable; NRI, nonresponder imputation; PBO, placebo.

jirovecii pneumonia), and two in the placebo group (pneumonia and pneumonia pneumococcal)] [16], over 52 weeks, there was one serious infection in the FIL100 group. Overall incidences of serious infections were 2.5%, 2.4%, and 10.7% in FIL200, FIL100, and ADA groups, respectively, and 5.3% in the placebo group before Week 24, with no serious infections after switching from placebo to filgotinib. One patient experienced herpes zoster in each filgotinib group (incidence

Table 3. Radiographic progression.

	FIL200 + MTX ($n = 40$)	FIL100 + MTX ($n = 41$)	ADA + MTX ($n = 28$)	PBO + MTX → FIL200 + MTX ($n = 12$)	PBO + MTX → FIL100 + MTX ($n = 13$)
mTSS, BL–Week 52[a]					
mTSS BL, mean (SD)	38.29 (45.822)	23.20 (31.324)	24.04 (34.282)	27.21 (45.427)	45.50 (99.392)
n at W52	40	40	26	12	13
mTSS W52, mean (SD)	38.60 (45.942)	24.71 (31.213)	26.27 (34.873)	29.46 (46.890)	46.54 (99.046)
CFB, BL to W52, LS mean (95% CI)	0.31 (–0.89, 1.52)	1.18 (–0.02, 2.39)		2.25 (0.05, 4.45)	1.04 (–1.07, 3.16)
LS mean difference (95% CI) vs PBO → FIL	–1.93 (–4.44, 0.58); $p = 0.13$	0.14 (–2.31, 2.59); $p = 0.91$			
Erosion score, BL–W52[a]					
Erosion score at BL, mean (SD)	15.90 (22.687)	9.38 (13.561)	11.27 (17.864)	13.54 (25.894)	24.04 (58.534)
n at W52	40	40	26	12	13
Erosion score at W52, mean (SD)	16.15 (22.757)	9.84 (13.350)	12.33 (18.315)	15.17 (25.989)	24.73 (58.316)
LS mean CFB (95% CI) erosion score at W52	0.26 (–0.43, 0.94)	0.46 (–0.23, 1.15)		1.62 (0.37, 2.88)	0.73 (–0.49, 1.94)
LS mean (95% CI) difference vs PBO → FIL	–1.37 (–2.80, 0.06); $p = 0.061$	–0.27 (–1.67, 1.14); $p = 0.71$			
JSN score, BL–W52[a]					
JSN score at BL, mean (SD)	22.39 (24.662)	13.82 (18.884)	12.77 (17.190)	13.67 (20.945)	21.46 (41.841)
n at W52	40	40	26	12	13
JSN score at W52, mean (SD)	22.45 (24.709)	14.88 (18.731)	13.94 (17.408)	14.29 (21.799)	21.81 (41.724)
LS mean (95% CI) CFB at W52	0.06 (–0.57, 0.69)	0.72 (0.09, 1.35)		0.63 (–0.52, 1.78)	0.34 (–0.76, 1.45)
LS mean (95% CI) treatment difference vs PBO → FIL	–0.57 (–1.89, 0.74); $p = 0.39$	0.37 (–0.90, 1.65); $p = 0.56$			

[a]The Campaign B/A set of radiographs represented the analysis for mTSS at Week 52 using MMRM. Full analysis set includes patients who were randomised and received at least one dose of study drug. The MMRM included treatment, visit (as categorical), treatment by visit, campaign, and BL value as fixed effects and patients being the random effect. LS mean, 95% CI, and *p* value were provided from MMRM. Missing change scores were not imputed using the MMRM approach assuming an unstructured variance–covariance matrix for the repeated measures. The comparisons at Week 52 were FIL100 vs PBO switched to FIL100 and FIL200 vs PBO switched to FIL200.
JSN, joint space narrowing; LS, least squares; PBO, placebo; SD, standard deviation.

2.5% and 2.4% for FIL200 and FIL100, respectively) vs none in the ADA or placebo groups. The patient with herpes zoster in the FIL200 group (a 65-year-old unvaccinated female) had one event on Day 162 and another event on Day 302; both events were mild or moderate, addressed by interrupting study drug, and resolved on Days 183 and 323, respectively. After the second event, the patient completed 52 weeks of treatment without any additional herpes zoster event. A Grade 4 serious duodenal ulcer perforation was reported for one patient (0.2%) in the FIL200 group and was judged by the investigator to be related to study drug. Study drug was discontinued as a result. The patient had risk factors for helicobacter infection diagnosed during the event, non-steroidal anti-inflammatory drug use, and alcohol and tobacco use. No deaths, active tuberculosis, hepatitis B or C, VTE, or NMSC occurred in the Japanese population over 52 weeks. The most commonly reported laboratory abnormality AEs were creatine phosphokinase increase, which occurred in four patients (10.0%) in the FIL200 group, and lymphocyte decrease in 2 (5.0%), 1 (2.4%), and 1 (8.3%) in the FIL200, FIL100, and placebo after switching to FIL200 groups, respectively. Patients who experienced creatine phosphokinase increase did not show evidence of muscle toxicity.

Efficacy outcomes

Figure 3 shows changes over time in ACR20/50/70. At Week 52, 75.0%, 85.4%, 67.9%, 83.3%, and 84.6% of patients receiving FIL200, FIL100, ADA, placebo to FIL200, and placebo to FIL100 achieved ACR20, respectively; corresponding proportions for ACR50 were 57.5%, 61.0%, 42.9%, 75.0%, and 69.2%, respectively; corresponding proportions for ACR70 were 40.0%, 39.0%, 17.9%, 33.3%, and 38.5%, respectively. Supplementary Table S2 displays proportions achieving ACR20/50/70, DAS28(CRP) <2.6 and ≤3.2, CDAI ≤2.8, SDAI ≤3.3, and Boolean remission and CFB in HAQ-DI, SF-36 PCS, FACIT-Fatigue, and hsCRP to Week 52. At Week 52, proportions achieving low disease activity (DAS28[CRP] ≤3.2) and remission thresholds, such as DAS28(CRP) <2.6 or CDAI ≤2.8 at Week 52, were numerically larger among patients receiving FIL200 than among those receiving ADA (75.0% vs 67.9%, 65.0% vs 60.7%, and 27.5% vs 7.1%). Changes from BL in continuous variables were similar between filgotinib groups and ADA or trended higher with filgotinib.

Table 3 shows radiographic progression across treatments in the PS. At BL (Campaign B/A), mTSS was 38.29, 23.20, 24.04, 27.21, and 45.50 in the FIL200, FIL100, ADA, placebo to FIL200, and placebo to FIL100 groups, respectively. Least squares mean CFB at Week 52 was 0.31, 1.18, 2.25, and 1.04 in the FIL200, FIL100, placebo to FIL200, and placebo to FIL100 groups, respectively. Similarly, changes from BL erosion score and joint space narrowing score were greater in those who received FIL100 throughout than in those who received FIL200 throughout.

Table 4. Overall safety and AEs of special interest in the LTE.

	FIL200 + MTX in LTE		FIL100 + MTX in LTE	
	FIL200 + MTX in PS ($n = 46$)	ADA + MTX in PS ($n = 10$)	FIL100 + MTX in PS ($n = 48$)	ADA + MTX in PS ($n = 11$)
TEAE	43 (93.5)	10 (100.0)	44 (91.7)	10 (90.9)
TEAE with Grade 3 or higher	8 (17.4)	1 (10.0)	9 (18.8)	0
TE serious AE	6 (13.0)	0	6 (12.5)	0
TEAE leading to premature discontinuation of any study drug	4 (8.7)	0	4 (8.3)	0
Deaths	0	0	0	0
TEAE of interest				
Infections	29 (63.0)	6 (60.0)	24 (50.0)	6 (54.5)
Serious infections	1 (2.2)	0	2 (4.2)	0
Herpes zoster	3 (6.5)	0	3 (6.3)	0
Opportunistic infection	2 (4.3)	0	0	0
Active tuberculosis	0	0	0	0
Hepatitis B or C	0	0	0	0
MACE	0	0	0	0
Deep vein thrombosis and pulmonary embolism	0	0	0	0
Malignancy excluding NMSC	0	0	0	0
NMSC	0	0	0	0
Gastrointestinal perforations	0	0	0	0
Laboratory abnormalities reported as AEs				
ALT increase	0	0	3 (6.3)	0
AST increase	0	0	2 (4.2)	0
CPK increase	1 (2.2)	0	0	0
Neutrophil decrease	0	0	1 (2.1)	0
Lymphocyte decrease	0	1 (10.0)	0	0
Haemoglobin decrease	0	0	0	0
LDL increased	0	0	0	0
HDL increased	0	0	0	0

Results are presented as *n* (%). FIL200 + MTX and FIL100 + MTX groups include patients originally assigned to PBO but were later rerandomised to FIL200 + MTX or FIL100 + MTX.
ALT, alanine transaminase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

LTE outcomes

Safety outcomes

In the LTE, as shown in Table 4, AE incidences were similar between patients receiving FIL200 throughout and those receiving FIL100 throughout. Proportions of patients with AEs and serious AEs in the LTE were similar to those in the PS. There were three patients with herpes zoster each in the group that continued taking FIL200 from the PS and in the group that continued taking FIL100; all cases of herpes zoster occurred in unvaccinated patients. One case (in the 46 patients taking FIL200 in the PS and LTE; 2.2%) was disseminated. This patient, a 69-year-old female, experienced a non-serious incident of herpes zoster on LTE Day 44; on Day 51, the patient experienced serious Grade 3 disseminated herpes zoster, and study drug was withdrawn. The event was resolved on LTE Day 84. Additionally, one patient in the FIL100 group had a serious Grade 3 herpes zoster event requiring hospitalisation and treatment with intravenous acyclovir followed by oral amenamevir; filgotinib was interrupted and restarted following the event. No cases of malignancy, MACE, or VTE occurred.

Efficacy outcomes

Efficacy in the LTE is shown in Table 5 and Supplemental Table S3. In each treatment arm, proportions achieving response thresholds remained generally consistent from LTE BL to Week 12 and Week 48, and mean values of continuous endpoints were similar between LTE BL and Week 48. By Week 48, results were similar between patients who took filgotinib throughout and those who switched from ADA.

Discussion

In a prespecified subgroup analysis of the PS, FIL200 and FIL100 showed a safety profile in Japanese patients with previous MTX-IR that was similar to that shown in the overall population of these trials [8, 24, 25]. FIL200, FIL100, and ADA were generally well tolerated in the Japanese population through Week 52 of the PS; rates of TEAEs (100.0%, 85.4%, and 92.9%, respectively) and serious TEAEs (10.0%, 7.3%, and 10.7%, respectively) were similar between groups, and no deaths were reported. Incidences of herpes zoster and lymphopeania and of other AEs of special interest (infections, serious infections, tuberculosis, hepatitis, MACE, DVT, pulmonary embolism malignancy excluding NMSC, NMSC, and gastrointestinal perforations) were low. The few laboratory abnormalities reported as AEs that occurred were without known sequelae.

In the overall population of the PS, FIL200 and FIL100 showed comparable ACR20/50/70 response to ADA at Week 52, with higher proportions in the FIL200 achieving DAS28(CRP) $\leq$3.2 or <2.6 compared with ADA (based on nominal *p* value) [24], and efficacy during the PS was generally similar between the treatment groups in this subpopulation of patients from Japan. In Japanese patients, switching to

Table 5. Efficacy in LTE up to Week 48.

	FIL200 + MTX in LTE		FIL100 + MTX in LTE	
	FIL200 + MTX in PS ($n = 46$)	ADA + MTX in PS ($n = 10$)	FIL100 + PS ($n = 48$)	ADA + MTX in PS ($n = 11$)
Binary endpoints, *n*/N (%)				
ACR20 at LTE BL	39/46 (84.8)	9/9 (100.0)	45/48 (93.8)	10/11 (90.9)
ACR20 at LTE W12	42/45 (93.3)	8/9 (88.9)	41/45 (91.1)	11/11 (100.0)
ACR20 at LTE W48	39/42 (92.9)	9/9 (100.0)	41/42 (97.6)	9/11 (81.8)
ACR50 at LTE BL	31/45 (68.9)	5/10 (50.0)	33/46 (71.7)	7/11 (63.6)
ACR50 at LTE W12	37/45 (82.2)	7/9 (77.8)	31/44 (70.5)	10/11 (90.9)
ACR50 at LTE W48	30/42 (71.4)	8/9 (88.9)	35/42 (83.3)	8/10 (80.0)
ACR70 at LTE BL	19/45 (42.2)	1/10 (10.0)	20/48 (41.7)	4/10 (40.0)
ACR70 at LTE W12	22/44 (50.0)	6/10 (60.0)	25/45 (55.6)	4/10 (40.0)
ACR70 at LTE W48	22/42 (52.4)	7/9 (77.8)	23/41 (56.1)	7/11 (63.6)
DAS28(CRP) ≤3.2 at LTE BL	40/46 (87.0)	9/10 (90.0)	39/48 (81.3)	10/11 (90.9)
DAS28(CRP) ≤3.2 at LTE W12	40/45 (88.9)	10/10 (100.0)	39/45 (86.7)	11/11 (100.0)
DAS28(CRP) ≤3.2 at LTE W48	39/42 (92.9)	10/10 (100.0)	39/42 (92.9)	10/11 (90.9)
DAS28(CRP) <2.6 at LTE BL	32/46 (69.6)	9/10 (90.0)	27/48 (56.3)	8/11 (72.7)
DAS28(CRP) <2.6 at LTE W12	33/45 (73.3)	9/10 (90.0)	28/45 (62.2)	10/11 (90.9)
DAS28(CRP) <2.6 at LTE W48	33/42 (78.6)	9/10 (90.0)	31/42 (73.8)	8/11 (72.7)
CDAI ≤10 at LTE BL	37/46 (80.4)	9/10 (90.0)	34/48 (70.8)	8/11 (72.7)
CDAI ≤10 at LTE W12	35/45 (77.8)	7/10 (70.0)	36/45 (80.0)	11/11 (100.0)
CDAI ≤10 at LTE W48	33/42 (78.6)	10/10 (100.0)	35/42 (83.3)	9/11 (81.8)
CDAI ≤2.8 at LTE BL	14/46 (30.4)	0	11/48 (22.9)	2/11 (18.2)
CDAI ≤2.8 at LTE W12	18/45 (40.0)	6/10 (60.0)	12/45 (26.7)	6/11 (54.5)
CDAI ≤2.8 at LTE W48	18/42 (42.9)	4/10 (40.0)	15/42 (35.7)	5/11 (45.5)
Continuous endpoints, mean (SD)				
HAQ-DI at LTE BL	0.42 (0.590)	0.38 (0.445)	0.52 (0.576)	0.26 (0.364)
HAQ-DI at LTE W12	0.37 (0.518)	0.26 (0.361)	0.47 (0.570)	0.20 (0.308)
HAQ-DI at LTE W48	0.32 (0.455)	0.28 (0.353)	0.41 (0.542)	0.19 (0.364)

FIL200 + MTX and FIL100 + MTX groups include patients originally assigned to PBO but were later rerandomised to FIL200 + MTX or FIL100 + MTX.
LS, least squares.

filgotinib treatment following 24 weeks of placebo was associated with notable improvements in disease activity during the PS, as indicated by ACR20/50/70; at Week 52, patients who switched from placebo had comparable proportions with treatment response as patients who had received filgotinib throughout.

In the LTE, FIL200 and FIL100 continued to be generally well tolerated in the Japanese population; doses showed similar safety profiles to those demonstrated during the PS. Herpes zoster occurred in 6.5% and 6.3% of those who maintained FIL200 or FIL100, respectively, and exclusively in unvaccinated patients; an inactive recombinant herpes zoster-specific vaccine became commercially available in Japan in 2020 [26, 27]. Incidences of most AEs of special interest were low. Rates of treatment response at LTE BL were maintained at Week 48; percentages with DAS28(CRP) <2.6 status among patients continuing FIL200 and FIL100 were 70% and 56%, respectively, at LTE BL and 79% and 74% at Week 48.

Caution must be taken when interpreting results from a subgroup analysis that lacks statistical power due to small sample size. At BL of the PS, there were some notable differences between the Japanese subpopulation and the overall population. The doses of MTX and corticosteroids were lower in the Japanese subpopulation than in the overall population. Notably, mean CDAI and SDAI in the overall population at PS BL were approximately 40 compared with 28–33 and 29–35 in the Japanese subpopulation, suggesting possibly lower BL disease activity in the Japanese subpopulation within the range of moderate to severe activity required for study entry [24]. However, proportions who achieved treatment responses, such as ACR20/50/70, at Week 52 were similar between Japanese patients and the overall population, suggesting BL disease activity did not notably influence efficacy.

Herpes zoster is an AE of special concern among patients with RA, as its risk is elevated by commonly used therapies, such as corticosteroids and tumour necrosis factor inhibitors [28]. Among patients treated with Janus kinase inhibitors for RA, Japanese patients have shown a higher incidence of herpes zoster vs other patients [29, 30]. During the PS, herpes zoster was not seen over 24 weeks of placebo administration (in 38 patients) or 52 weeks of ADA administration (in 28 patients), indicating that this population may not have been at high risk of herpes zoster (by comparison, in a study of 1987 Japanese patients with RA receiving DMARDs, the crude incidence rate of herpes zoster was 6.7/1000 patient-years) [28]. Any putative increase in risk associated with 52 weeks of filgotinib administration in this population nevertheless led to just two cases of herpes zoster. Some research has identified elevated risks for lymphoma and/or malignancy or cardiovascular disease in Japanese patients with RA compared with the general Japanese population and/or patients with osteoarthritis [31–33]. In the present subpopulation analysis, there were no cases of MACE or malignancy. Additionally, the absence of active tuberculosis and hepatitis B or C in both the PS and LTE do not suggest an increased risk of opportunistic infection associated with filgotinib treatment in the current population and in the timeframe assessed. The small size of the Japanese population examined here does complicate interpretation; the exposure-adjusted incidence rates for infection in the Japanese integrated safety analysis long-term data

set indicate similar risk between filgotinib doses (exposure-adjusted incidence rates of 45.9/100 patient-years of exposure for FIL200 vs 39.5 for FIL100). In the future, longer-term results of the ongoing LTE and the postmarketing surveillance assessing 1000 Japanese patients will be useful in assessing risks of infection and of relatively uncommon AEs.

In the original report from the overall population of this trial, DAS28(CRP) <2.6 response was achieved by higher proportions in the FIL200 and FIL100 arms at 12 weeks compared with placebo; in the analysis of the Japanese subpopulation at Week 24, higher DAS28(CRP) <2.6 response rates were also found for both filgotinib doses vs placebo [8, 16]. The DAS28(CRP) <2.6 rates reported here (65.0% and 51.2% at PS Week 52 for FIL200 and FIL100, respectively; 78.6% and 73.8% at LTE Week 48 for those maintained on FIL200 and FIL100 throughout, respectively) show that filgotinib maintained efficacy over longer-term treatment. Both doses of filgotinib significantly improved mTSS change and erosion score vs placebo at Week 24 in the overall population of this trial [8]. Due to the small sample size and high variability of mTSS, it is challenging to draw clinically meaningful conclusions from the mTSS data in this analysis. However, considering that mTSS and clinical remission by SDAI and CDAI are well-associated [34, 35] and the data from these studies are consistent between the Japanese and overall populations in both clinical and radiographic effects, the results suggest that filgotinib may be able to prevent radiographic progression.

Limitations of this study include the relatively small numbers of patients that made up the Japanese subpopulation for the study and the duration of interim efficacy assessment in the LTE period being limited to 48 weeks. Additional data from the ongoing LTE and post-marketing surveillance will provide further insights.

Conclusions

Among MTX-IR patients from Japan treated in the RCT and LTE trials, safety and efficacy of filgotinib were maintained through Week 52 and beyond, up to the data cutoff point in LTE. Safety profiles remained consistent over time, and incidence of MACE, VTE, malignancy, infection, and other AEs of special interest did not appreciably increase; herpes zoster rates increased but remained low. Efficacy and safety profiles for the Japanese subpopulation in the parent RCT were consistent with the overall global population of the trial [8, 24].

Funding

This study was funded by Gilead Sciences, Inc., Foster City, CA.

Medical writing assistance was provided by Rob Coover, MPH, of AlphaScientia, LLC, San Francisco, CA, and funded by Gilead Sciences, Inc., Foster City, CA.

Supplementary data

Supplementary data are available at *Modern Rheumatology* online.

Conflict of interest

Y.T. has received speaking fees and/or honoraria from Gilead, Abbvie, Boehringer-Ingelheim, Eli Lilly, Mitsubishi-Tanabe, Chugai, Amgen, YL Biologics, Eisai, Astellas, Bristol-Myers, and Astra-Zeneca; research grants from Asahi-Kasei, Abbvie, Chugai, Mitsubishi-Tanabe, Eisai, Takeda, Daiichi-Sankyo, Kowa, and Boehringer-Ingelheim; and consultant fee from Eli Lilly, Daiichi-Sankyo, Taisho, Ayumi, Sanofi, GSK, and Abbvie. T.M. has received research support and/or speaker honoraria from Astellas Pharma Inc.; Bristol-Myers Squibb; AbbVie GK; Eli Lilly Japan K.K.; Pfizer Japan Inc.; Gilead Sciences K.K.; Chugai Pharmaceutical Co., Ltd.; Eisai; and Ayumi Pharmaceutical Corporation. T.A. has accepted research grants and/or honoraria for meetings from Gilead Sciences, Inc.; Mitsubishi Tanabe; Chugai Pharmaceutical Co., Ltd.; Astellas Pharma Inc.; Takeda; Pfizer; AbbVie; Eisai; Daiichi Sankyo; Bristol-Myers Squibb; UCB Japan; Eli Lilly Japan K.K.; Otsuka Pharmaceutical Co., Ltd.; and Alexion Inc. K.A. received a research grant from Asahi Kasei Pharma and speaking fees from AbbVie GK; Chugai Pharmaceutical Co., Ltd.; Eisai; Eli Lilly; Gilead Sciences Inc.; GlaxoSmithKline K.K.; and Pfizer Japan. N.I. has received research grants and/or speakers' fees from Mitsubishi Tanabe; Pfizer; Eisai; Chugai Pharmaceutical Co., Ltd.; Asahi Kasei Pharma.; Ono Pharma.; AbbVie; Takeda Industrial Pharma; Astellas Pharma Inc.; Bristol-Myers Squibb; Eli Lilly; Janssen; Gilead GK; and Taisho Pharma. E.S. has received research grants or speakers' fee from Astellas Pharma Inc.; Asahi Kasei Pharma; Ayumi Pharmaceutical Corporation; Bristol-Myers Squibb; Chugai Pharmaceutical Co., Ltd.; Daiichi Sankyo; Eisai; Eli Lilly; Mitsubishi Tanabe; Pfizer; Sanofi; Takeda; and UCB Japan. K.Y. has received research support and/or honoraria from Mitsubishi Tanabe; GlaxoSmithKline; Pfizer; Eisai; Chugai Pharmaceutical Co., Ltd.; Asahi Kasei Pharma Corp.; Ono Pharma; AbbVie; Takeda Industrial Pharma; Astellas Pharma Inc.; Bristol-Myers Squibb; Eli Lilly; Janssen Pharma; and Gilead GK. B.G.C. receives grant/research support from Pfizer and Roche-Chugai and has received consulting and/or speaker fees from AbbVie, Bristol-Myers Squibb, Celltrion, Eli Lilly, Gilead-Galapagos, Janssen, Merck Sharp & Dohme, Novartis, Pfizer, and Roche-Chugai. A.J.K. is a shareholder of Amgen; Gilead Sciences, Inc.; GlaxoSmithKline; Pfizer; and Sanofi; served as a consultant for AbbVie; Boehringer-Ingelheim; Flexion; Genzyme; Gilead Sciences, Inc.; Janssen; Novartis; Pfizer; Regeneron; Sanofi; and Sun Pharmaceuticals; SUN Pharma Advanced Research; is serving as a paid instructor for Celgene, Genzyme, Horizon, Merck, Novartis, Pfizer, Regeneron, and Sanofi; and served on a speakers' bureau for AbbVie, Celgene, Flexion, Genzyme, Horizon, Merck, Novartis, Pfizer, Regeneron, and Sanofi. S.-C.B. has nothing to disclose. E.C.K. reports research support, consulting, and speaker fees from AbbVie; Amgen; AstraZeneca; Bristol-Myers Squibb; Celltrion; F. Hoffman-La Roche Ltd.; Genentech, Inc; Gilead Sciences, Inc.; Janssen; Lilly Pharmaceuticals; Merck; Myriad Autoimmune; Pfizer; PuraPharm; Sandoz; Sanofi-Genzyme; Samsung Bioepsis; and UCB. P.N. reports research support, consulting, and speaker and personal fees from AbbVie; Bristol-Myers Squibb; Celgene; Eli Lilly & Co.; Gilead Sciences, Inc; Janssen; Merck Sharp & Dohme; Novartis; Pfizer; Roche; Sanofi; and UCB. M.G., B.B., A.P., and L.Y. are employees and shareholders of Gilead Sciences, Inc. F.M. and Q.G.

are former employees and/or shareholders of Gilead Sciences, Inc. A.K. is an employee of Gilead Sciences K.K. C.T. is an employee of Galapagos NV. T.T. has received grants from Astellas Pharma, Inc.; Chugai Pharmaceutical Co. Ltd.; Daiichi Sankyo; Takeda; AbbVie GK; Asahi Kasei Pharma; Mitsubishi Tanabe; Eisai; Nippon Kayaku Co.; and JCR Pharma Co. Ltd and has received speaking fees and/or consultancy fees from AbbVie GK; Chugai Pharmaceutical Co. Ltd.; Bristol-Myers K.K.; Eli Lilly Japan K.K.; SRL, Inc.; Astellas Pharma Inc.; Ayumi Pharmaceutical Corporation; Eisai; Ono Pharmaceutical Co. Ltd.; Kissei Pharmaceutical Co. Ltd.; Gilead Sciences, Inc.; Mitsubishi Tanabe; Novartis Pharma K.K.; Pfizer Japan Inc.; Taiho Pharmaceutical Co. Ltd.; Daiichi Sankyo; Taisho Pharmaceutical Co., Ltd.; Nippon Kayaku Co.; Boehringer-Ingelheim; A2 Healthcare Corporation; and The Uehara Memorial Foundation.

Data availability

Anonymised individual patient data will be shared upon request for research purposes dependent upon the nature of the request, the merit of the proposed research, the availability of the data, and its intended use.

References

[1] Nakajima A, Sakai R, Inoue E *et al.* Prevalence of patients with rheumatoid arthritis and age-stratified trends in clinical characteristics and treatment, based on the National Database of Health Insurance Claims and Specific Health Checkups of Japan. *Int J Rheum Dis* 2020;**23**:1676–84. 10.1111/1756-185X.13974.

[2] Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. *JAMA* 2018;**320**:1360–72. 10.1001/jama.2018.13103.

[3] Yamanaka H, Sugiyama N, Inoue E *et al.* Estimates of the prevalence of and current treatment practices for rheumatoid arthritis in Japan using reimbursement data from health insurance societies and the IORRA cohort (I). *Mod Rheumatol* 2014;**24**:33–40. 10.3109/14397595.2013.854059.

[4] Kameda H, Fujii T, Nakajima A *et al.* Japan College of Rheumatology guideline for the use of methotrexate in patients with rheumatoid arthritis. *Mod Rheumatol* 2019;**29**:31–40. 10.1080/14397595.2018.1472358.

[5] Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet* 2016;**388**:2023–38. 10.1016/S0140-6736(16)30173-8.

[6] 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**:998–1008. 10.1136/annrheumdis-2016-210104.

[7] 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**:1009–19. 10.1136/annrheumdis-2016-210105.

[8] Combe B, Kivitz A, Tanaka Y *et al.* Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. *Ann Rheum Dis* 2021;**80**:848–58. 10.1136/annrheumdis-2020-219214.

[9] Genovese MC, Kalunian K, Gottenberg JE *et al.* 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. *JAMA* 2019;**322**:315–25. 10.1001/jama.2019.9055.

[10] Westhovens R, Rigby WFC, van der Heijde D *et al.* Filgotinib in combination with methotrexate or as monotherapy versus methotrexate monotherapy in patients with active rheumatoid arthritis and limited or no prior exposure to methotrexate: the phase 3, randomised controlled FINCH 3 trial. *Ann Rheum Dis* 2021;**80**:727–38. 10.1136/annrheumdis-2020-219213.

[11] Tanaka Y, Kavanaugh A, Wicklund J *et al.* Filgotinib, a novel JAK1-preferential inhibitor for the treatment of rheumatoid arthritis: an overview from clinical trials. *Mod Rheumatol* 2022;**32**:1–11. 10.1080/14397595.2020.1812201.

[12] Jyseleca® (filgotinib) 100 mg film-coated tablets. Summary of product characteristics. London, UK: Gilead Sciences Ltd, 2020.

[13] Jyseleca® (filgotinib maleate tablets). Japanese package insert. Tokyo, Japan: Gilead Sciences K.K., 2020.

[14] Atsumi T, Tanaka Y, Matsubara T *et al.* Efficacy and safety of filgotinib alone and in combination with methotrexate in Japanese patients with active rheumatoid arthritis and limited or no prior exposure to methotrexate: subpopulation analyses of 24-week data of a global phase 3 study (FINCH 3). *Mod Rheumatol* 2022;**32**:273–83. 10.1093/mr/roab021.

[15] Takeuchi T, Matsubara T, Atsumi T *et al.* Efficacy and safety of filgotinib in Japanese patients with refractory rheumatoid arthritis: subgroup analyses of a global phase 3 study (FINCH 2). *Mod Rheumatol* 2022;**32**:59–67. 10.1080/14397595.2020.1859675.

[16] Tanaka YMT, Atsumi T, Amano K *et al.* 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). *Mod Rheumatol* 2022;**32**:263–72. 10.1093/mr/roab030.

[17] Felson DT, Anderson JJ, Boers M *et al.* American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:727–35. 10.1002/art.1780380602.

[18] Prevoo ML, van 't Hof MA, Kuper HH *et al.* 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**:44–8. 10.1002/art.1780380107.

[19] Fries JF, Spitz P, Kraines RG *et al.* Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;**23**:137–45. 10.1002/art.1780230202.

[20] Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the Health Assessment Questionnaire, disability and pain scales. *J Rheumatol* 1982;**9**:789–93.

[21] 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**:473–83. 10.1097/00005650-199206000-00002.

[22] 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. 10.1186/1477-7525-1-79.

[23] United States Library of Medicine. *Long Term Extension Study to Assess the Safety and Efficacy of Filgotinib in Adults with Rheumatoid Arthritis (FINCH 4)*. 2021 https://clinicaltrials.gov/ct2/show/NCT03025308 (28 June 2022, date last accessed).

[24] Combe B, Kivitz A, Tanaka Y *et al.* Efficacy and safety of filgotinib for patients with rheumatoid arthritis with inadequate response to methotrexate: FINCH 1 52-week results. EULAR2020.

[25] Combe B, Tanaka Y, Emery P *et al.* Clinical outcomes up to week 48 of filgotinib treatment in an ongoing long-term extension trial of RA patients with inadequate response to MTX initially treated with filgotinib or adalimumab during the phase 3 parent trial. ACR2021.

[26] Hatsushika Y, Nii I, Taniguchi T. Varicella caused by airborne transmission of a localised herpes zoster infection in a family. *BMJ Case Rep* 2021;**14**:e243217. 10.1136/bcr-2021-243217.

[27] Stadtmauer EA, Sullivan KM, El Idrissi M *et al.* Adjuvanted recombinant zoster vaccine in adult autologous stem cell transplant recipients: polyfunctional immune responses and lessons for clinical practice. *Hum Vaccin Immunother* 2021;**17**:4144–54. 10.1080/21645515.2021.1953346.

[28] Harada S, Sakai R, Hirano F *et al.* Association between medications and herpes zoster in Japanese patients with rheumatoid arthritis: a 5-year prospective cohort study. *J Rheumatol* 2017;**44**:988–95. 10.3899/jrheum.161196.

[29] Harigai M, Honda S. Selectivity of Janus kinase inhibitors in rheumatoid arthritis and other immune-mediated inflammatory diseases: is expectation the root of all headache? *Drugs* 2020;**80**:1183–201. 10.1007/s40265-020-01349-1.

[30] Winthrop KL, Curtis JR, Lindsey S *et al.* Herpes zoster and tofacitinib: clinical outcomes and the risk of concomitant therapy. *Arthritis Rheumatol* 2017;**69**:1960–8. 10.1002/art.40189.

[31] Yamada T, Nakajima A, Inoue E *et al.* Incidence of malignancy in Japanese patients with rheumatoid arthritis. *Rheumatol Int* 2011;**31**:1487–92. 10.1007/s00296-010-1524-0.

[32] Hashimoto A, Chiba N, Tsuno H *et al.* Incidence of malignancy and the risk of lymphoma in Japanese patients with rheumatoid arthritis compared to the general population. *J Rheumatol* 2015;**42**:564–71. 10.3899/jrheum.140533.

[33] Tanaka K, Hamada K, Nakayama T *et al.* Risk for cardiovascular disease in Japanese patients with rheumatoid arthritis: a large-scale epidemiological study using a healthcare database. *Springerplus* 2016;**5**:1111. 10.1186/s40064-016-2800-6.

[34] Strand V, Kavanaugh A, Kivitz AJ *et al.* Long-term radiographic and patient-reported outcomes in patients with rheumatoid arthritis treated with tofacitinib: ORAL start and ORAL scan post-hoc analyses. *Rheumatol Ther* 2018;**5**:341–53. 10.1007/s40744-018-0113-7.

[35] van der Heijde D, Durez P, Schett G *et al.* Structural damage progression in patients with early rheumatoid arthritis treated with methotrexate, baricitinib, or baricitinib plus methotrexate based on clinical response in the phase 3 RA-BEGIN study. *Clin Rheumatol* 2018;**37**:2381–90. 10.1007/s10067-018-4221-0.