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Original Article

Long-term safety and efficacy of filgotinib treatment for rheumatoid arthritis in Japanese patients naïve to MTX treatment (FINCH 3)

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ABSTRACT

Objectives: To evaluate the long-term safety and efficacy of filgotinib (FIL) for Japanese patients with rheumatoid arthritis (RA) and limited/no prior methotrexate (MTX) exposure. We present a Japanese population subanalysis of a global randomised-controlled trial at Week 52 and interim long-term extension (LTE) to Week 48 through June 2020.

Methods: Patients were randomised to FIL 200 mg plus MTX, FIL 100 mg plus MTX, FIL 200 mg, or MTX for 52 weeks. At completion, eligible patients could enrol in the LTE. Those receiving FIL continued; those receiving MTX were rerandomised (blinded) to FIL 200 or 100 mg upon discontinuation of MTX. After a 4-week washout period, MTX could be re-added.

Results: Adverse event rates at Week 52 and in the LTE to Week 48 were comparable across treatment groups. Week 52 American College of Rheumatology 20% improvement (ACR20) rates were 83% (19/23), 82% (9/11), 75% (9/12), and 76% (19/25) for FIL 200 mg plus MTX, FIL 100 mg plus MTX, FIL 200 mg, and MTX, respectively. Through LTE Week 48, ACR20 rates were maintained.

Conclusions: In the 56 Japanese patients treated with FIL, efficacy was maintained through Week 52 and beyond, with no increases in the incidence of adverse events.

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

Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disorder that causes joint pain, disability, and joint damage. The estimated global prevalence of RA is 0.46% [1]; in Japan, the estimated prevalence is 1.0% of the population—about 1.24 million patients (not including suspected cases) [2]. RA treatment approaches include conventional synthetic disease-modifying antirheumatic drugs [csDMARDs; mainly methotrexate (MTX)], nonsteroidal anti-inflammatory drugs, and steroids [2]. However, not all patients respond to these therapies, and their use can be limited by safety concerns [3]. In Japan, MTX is approved as a treatment for RA with a

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maximum dosage of 16 mg/week; however, many Japanese patients cannot tolerate this dosage, and serious adverse events, such as pneumocystis pneumonia, are more frequent in the Japanese population with MTX use than without MTX [4].

Filgotinib (FIL), an oral Janus kinase 1 (JAK1) preferential inhibitor, has been evaluated in two Phase 2 and three Phase 3 clinical studies [5–9] in adults with moderately to severely active RA, and FIL is approved in Japan and Europe as a treatment for RA [10, 11]. Subpopulation analyses showed that FIL was safe and effective in Japanese patients up to Week 24 in Phase 3 trials for MTX-IR (inadequate-response) patients (NCT02889796; FINCH 1), biologic DMARD-IR patients (NCT02873936; FINCH 2), and MTX-naïve patients (NCT02886728; FINCH 3) [12–14]. Here, we report data from the Japanese subpopulation for patients from the FINCH 3 study [i.e. the parent study (PS)] to Week 52 and to Week 48 for efficacy and all data for safety (data cut-off 1 June 2020) in the long-term extension [LTE; NCT03025308 (FINCH 4)].

Materials and methods

Study design and patients

FINCH 3 was a Phase 3, multicentre, randomised, active-controlled trial designed to assess the safety and efficacy of FIL alone and in combination with MTX in adult patients with active RA who had limited or no prior MTX exposure [8]. FINCH 4 is an ongoing, Phase 3, multicentre, double-blind, LTE study designed to evaluate the long-term safety and efficacy of FIL in patients who completed one of the parent studies of FIL in RA [7–9]. Studies were conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines and approved by each study centre's institutional review board or ethics committee.

The study design and methodological details for FINCH 3 are published elsewhere [8, 12]. Men or women with moderately to severely active RA who were aged ≥18 years (≥20 years in Japan) on the day of consent were screened to determine eligibility as per inclusion and exclusion criteria. The trial was conducted for up to 52 weeks; eligible patients who completed the PS could then enter the LTE if they were willing to do so and if the investigator thought they could benefit from FIL.

Randomisation

In the PS, patients were randomised 2:1:1:2 to FIL 200 mg plus MTX, FIL 100 mg plus MTX, FIL 200 mg alone, or MTX alone (Figure 1). Randomisation was stratified by geographic region (including Japan exclusively) and the presence of rheumatoid factor or anti-cyclic citrullinated peptide antibody at screening.

Patients who completed the 52-week PS and were not rescued with standard of care could enter the LTE study. All patients were required to wash out MTX for 4 weeks. Patients could (re)start MTX and/or other protocol-approved background medications for RA (e.g. csDMARDs) ≥4 weeks after their first dose of study drug in the absence of MTX. Patients who were randomised to PS FIL treatment continued on the same dose for the LTE in a blinded fashion. Patients who were randomised to PS MTX were rerandomised (blinded) 1:1 to FIL 200 or 100 mg for LTE. Blinding of PS treatment was maintained, so investigator-initiated treatment changes (e.g. adding MTX) were done in a blinded fashion.

Treatment procedures

As previously reported, patients received double-blind treatment for up to 52 weeks in the PS. MTX dose was titrated to a maximum of 15 mg/week for Japanese patients by Week 8. At Week 24, patients who did not achieve ≥20% improvement from Day 1 in both swollen joint count (SJC) and tender joint count (TJC) discontinued investigational therapy and instead

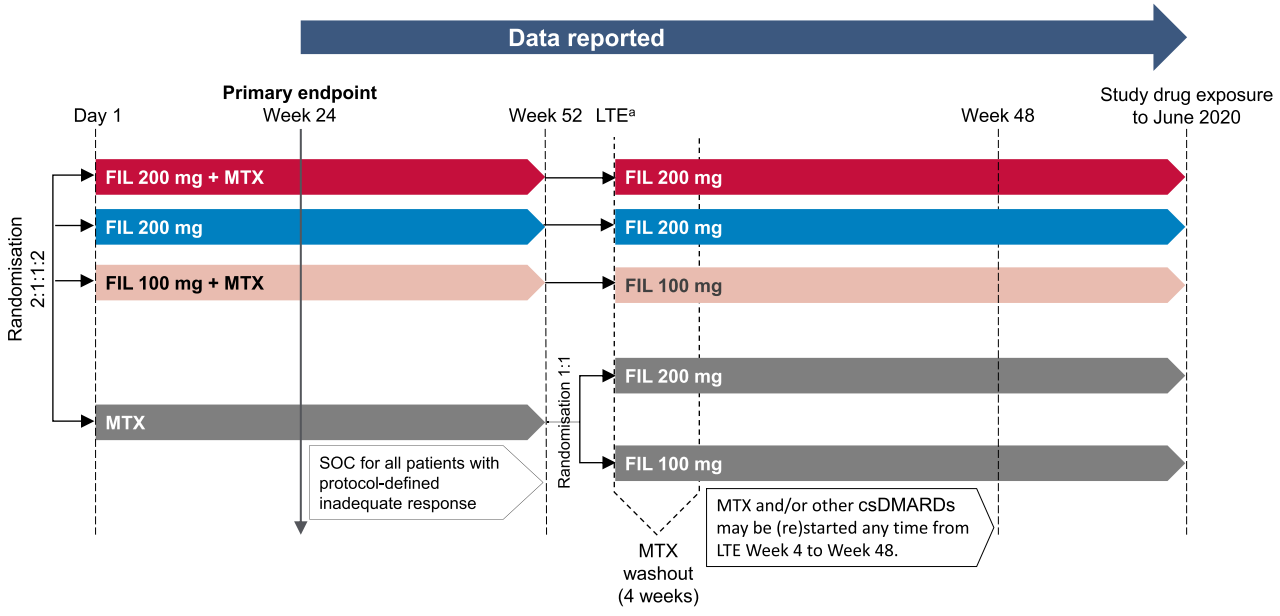

Figure 1. Overall study design for PS (FINCH 3) and those entering the LTE (FINCH 4); [a]FIL groups in the LTE include patients who did and did not receive MTX during the parent trial; SOC, standard of care.

received standard of care consistent with local practice. Although these patients continued with study visits and assessments per protocol, they were not eligible to enrol in the LTE. Clinical assessments, patient questionnaires, collection of adverse events (AEs), and laboratory tests were performed on Day 1 and Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 44, and 52 (or early termination) to evaluate the efficacy and safety of FIL.

Outcome measures

Safety outcomes were evaluated by AEs and laboratory abnormalities, physical examinations, vital signs, and 12-lead electrocardiograms. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0. Severity grades were defined by the Common Terminology Criteria for Adverse Events Version 4.03. Compiled data from the following were summarised (system organ class): any treatment-emergent adverse event (TEAE), TEAEs Grade $\geq$3, serious TEAEs, TEAEs leading to discontinuation of study drug, deaths, and AEs of special interest [AESIs; defined as infections, serious infections, herpes zoster, opportunistic infections, active tuberculosis, adjudicated major adverse cardiovascular events (MACE), venous thromboembolism (VTE), nonmelanoma skin cancer (NMSC), non-NMSC malignancy, and gastrointestinal perforations]. TEAEs were defined as having an onset date on or after the start of the study drug and no later than 30 days after permanent discontinuation of study drug or as any AE leading to premature discontinuation of study drug.

The primary endpoint in the PS was the proportion of patients who achieved 20% improvement in ACR criteria (ACR20) at Week 24. Additional binary efficacy outcomes included proportions of patients achieving ACR50 and ACR70 over time and proportions of patients achieving Disease Activity Score with 28-joint count using C-reactive protein [DAS28(CRP)] $\leq$3.2 and <2.6. Changes from baseline (CFBs) over time were assessed for DAS28(CRP), the seven components of the ACR core criteria [SJC, TJC, patient's pain assessment, Patient's and Physician's Global Assessments of disease, Health Assessment Questionnaire-Disability Index (HAQ-DI), and high-sensitivity (hs)CRP], HAQ-DI score, 36-Item Short Form Health Survey (SF-36) Physical Component Summary (PCS) score, and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score. Inhibition of structural joint damage was assessed radiographically with modified Total Sharp Score (mTSS) and its components, erosion scores and joint space narrowing (JSN) scores, assessed at Weeks 24 and 52. Radiographic methods have been described in detail previously [7]. Radiographs were scored centrally as Campaign A (radiographs taken at baseline and Week 24) and Campaign B (radiographs taken at baseline, Week 24, and Week 52 for patients who had images after Week 24) by two independent readers, with adjudication by a third reader if needed.

Efficacy endpoints in the LTE included proportions of responders achieving ACR20/50/70 response, DAS28(CRP) $\leq$3.2 and <2.6, Clinical Disease Activity Index (CDAI) $\leq$10 and $\leq$2.8, Simple Disease Activity Index (SDAI) $\leq$11 and $\leq$3.3, and Boolean remission; as well as CFB in HAQ-DI, SF-36 PCS, FACIT-Fatigue, hsCRP, and patient's assessment of pain.

Statistical analysis

A subanalysis of patients in the PS who were enrolled in Japan was prespecified as per protocol. The primary analysis set for safety was the safety analysis set, which included all patients who received at least one dose of study drug. Adverse event data in the PS were summarised by treatment group using descriptive statistics. The primary analysis set for efficacy was the full analysis set, which included all randomised patients who received at least one dose of study drug. Missing data for the PS binary endpoints were analysed using a Fisher's exact test with nonresponse imputation (NRI). CFB in continuous endpoints was analysed using a mixed-effects model for repeated measures (MMRM) with baseline value, treatment, visit, and treatment by visit interaction included as fixed effects and patient as a random effect. The least-squares (LS) mean and 95% confidence interval (CI) from the MMRM are presented. All *p*-values for treatment comparisons in this subpopulation are exploratory and were not adjusted for multiplicity.

For radiographic endpoints in the PS, the MMRM included treatment, visit (as categorical), treatment by visit, and baseline value as fixed effects, with patients being the random effect (campaign was also a fixed effect in the analyses at Week 52). LS mean, 95% CI, and *p*-value were provided from MMRM. Missing change scores were not otherwise imputed using the MMRM approach, assuming an unstructured variance–covariance matrix for the repeated measures. Campaign B/A represents the analysis for mTSS at Week 52 using either MMRM or linear extrapolation. For this Week 52 analysis, data from Campaign B were combined with Campaign A for patients with images that were not reread for Campaign B. Therefore, Campaign B analyses alone at Weeks 24 and 52 were considered exploratory.

For the LTE, exposure-adjusted incidence rates (EAIRs) per 100 patient-years of exposure (PYE) were calculated; EAIR, EAIR difference, and 95% CI were estimated using a Poisson regression model including treatment group with an offset of natural log of exposure time. If any treatment had zero events, exact Poisson method was applied.

Efficacy endpoints in the LTE were summarised descriptively and with 95% CIs. The LTE data are presented as observed cases. No radiographic data were collected in the LTE.

For treatment comparisons, binary endpoints were analysed using a Fisher's exact test. The 95% CI for response rates and differences in response rates were based on normal approximation method with continuity correction.

Results

PS outcomes

Patient population

Of 1249 patients in the PS safety analysis set, 71 were from Japan. Figure 2(a) shows the disposition for the Japanese patients. Sixty-five Japanese patients completed Week 24; eight patients subsequently discontinued, while 57 completed the study at Week 52. A summary of baseline demographics for the Japanese patients in the PS is presented in Supplementary Table S1; full baseline demographics and disease characteristics for the PS have been previously published [12].

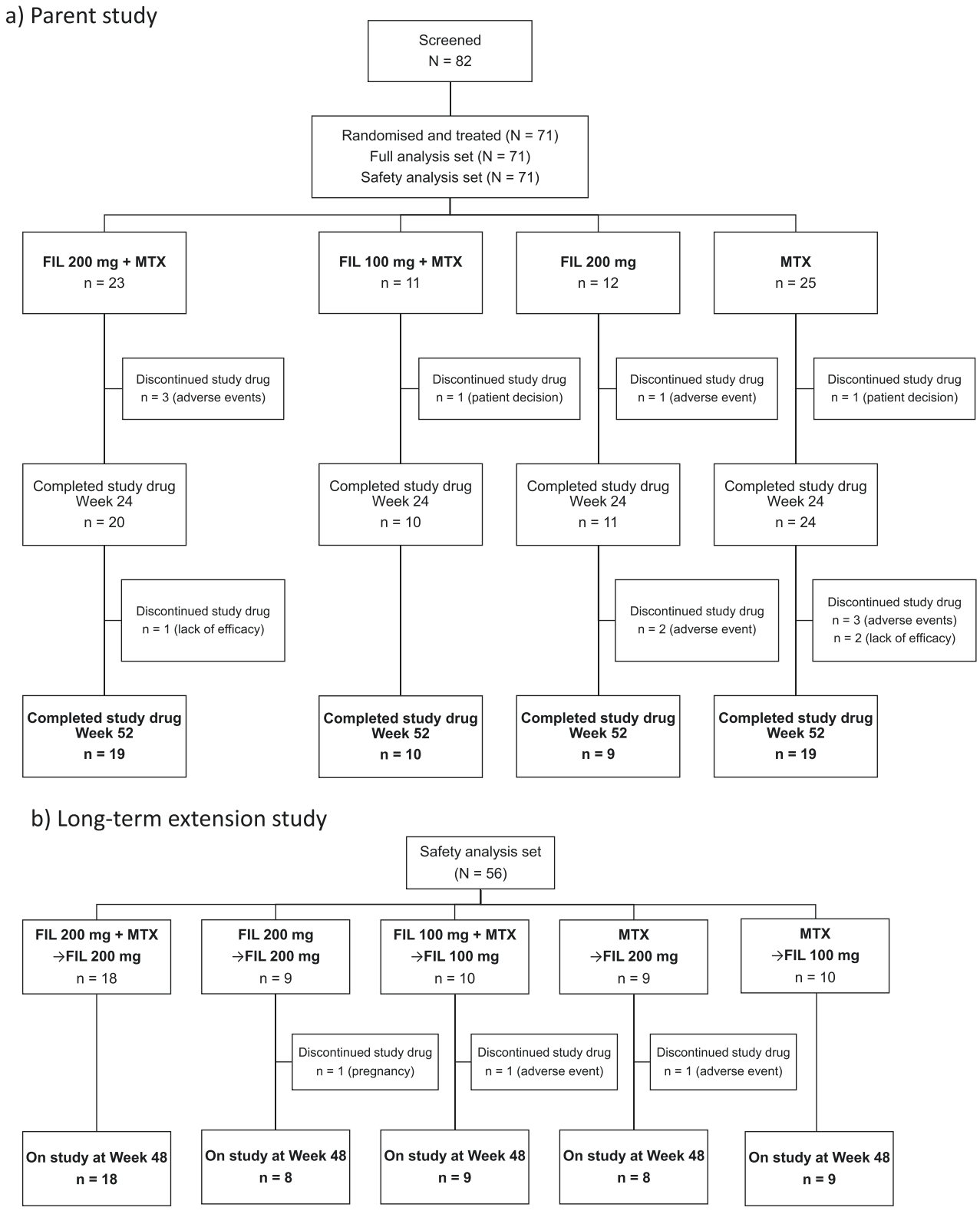

Figure 2. Patient disposition for Japanese patients.

Safety outcomes

In the Japanese population up to Week 52, TEAEs were reported in 23/23 patients (100%) receiving FIL 200 mg plus MTX, 10/11 patients (90.9%) receiving FIL 100 mg plus MTX, 11/12 patients (91.7%) receiving FIL 200 mg alone, and 20/25 patients (80.0%) receiving MTX alone. An overall safety summary and rates of AESIs at Week 52 are shown in Table 1. No deaths were reported in any treatment arm. Overall, rates of infection were generally similar across treatment arms at Week 52. There were reports of serious infections

Table 1. Safety to PS Week 52.

PS	FIL 200 mg + MTX $n = 23$	FIL 100 mg + MTX $n = 11$	FIL 200 mg alone $n = 12$	MTX alone $n = 25$
TEAE summary				
Any TEAE	23 (100)	10 (90.9)	11 (91.7)	20 (80.8)
TEAEs Grade 3 or higher	6 (26.1)	3 (27.3)	3 (25.0)	3 (12.0)
Serious TEAEs	2 (8.7)	2 (18.2)	3 (25.0)	3 (12.0)
TEAEs leading to discontinuation of study drug	3 (13.0)	0	2 (16.7)	3 (12.0)
Deaths	0	0	0	0
TEAEs occurring in >10% of patients				
Nausea	3 (13.0)	1 (9.1)	1 (8.3)	5 (20.0)
Nasopharyngitis	6 (26.1)	2 (18.2)	5 (41.7)	10 (40.0)
Headache	1 (4.3)	0	2 (16.7)	2 (8.0)
Bronchitis	0	0	0	5 (20.0)
Gastro-oesophageal reflex disease	0	1 (9.1)	2 (16.7)	1 (4.0)
Abdominal discomfort	3 (13.0)	1 (9.1)	1 (8.3)	4 (16.0)
Pharyngitis	0	0	2 (16.7)	0
Hepatic enzyme increased	4 (17.4)	0	1 (8.3)	0
Hypercholesterolaemia	0	0	0	5 (20.0)
Hyperlipidaemia	1 (4.3)	0	2 (16.7)	0
Hepatic function abnormal	2 (8.7)	0	0	3 (12.0)
Cystitis	1 (4.3)	0	2 (16.7)	0
Dental caries	0	1 (9.1)	2 (16.7)	0
Blood creatinine increased	0	2 (18.2)	0	0
Renal impairment	0	1 (9.1)	2 (16.7)	0
Periodontal disease	0	2 (18.2)	0	0
AESI				
Infections	12 (52.2)	5 (45.5)	7 (58.3)	14 (56.0)
Serious infections	1 (4.3)	0	1(8.3)	1 (4.0)
Opportunistic infections	0	0	0	1 (4.0)
Herpes zoster	1 (4.3)	1 (9.1)	1 (8.3)	0
MACE	0	0	1 (8.3)	0
VTE	0	0	0	1 (4.0)
Non-NMSC malignancy	0	0	0	1 (4.0)
NMSC	0	0	0	0
GI perforations	0	0	0	0
Lab abnormalities				
ALT increase	12 (52.2)	3 (27.3)	1 (8.3)	10 (40.0)
AST increase	11 (47.8)	2 (18.2)	3 (25.0)	7 (28.0)
CK increase	4 (17.4)	1 (9.1)	5 (41.7)	2 (8.0)
Neutrophil count decrease	8 (34.8)	5 (45.5)	2 (16.7)	2 (8.0)
Lymphocyte count decrease	9 (39.1)	1 (9.1)	2 (16.7)	9 (36.0)
Anaemia	5 (21.7)	2 (18.2)	3 (25.0)	9 (36.0)

Safety analysis set includes patients who received at least one dose of study drug. AEs were coded according to MedDRA Version 22.0. Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug or led to premature study drug discontinuation. Severity grades were defined by the CTCAE Version 4.03. Death includes any death that occurred during the study. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CTCAE, Common Terminology Criteria for AEs; GI, gastrointestinal.

in both FIL 200 mg arms and the MTX arm (one patient each). Herpes zoster was reported in the FIL arms (one patient each). One patient was a 54-year-old male receiving FIL 200 mg who experienced herpes zoster (Grade 3) that resolved with medication, hospitalisation, and study drug interruption. The second patient (a 50-year-old female receiving FIL 100 mg + MTX) experienced Grade 2 herpes zoster that resolved with study drug interruption and medication. The third patient (a 56-year-old female receiving FIL 200 mg + MTX) also experienced Grade 2 herpes zoster that resolved without the need for medication or study drug interruption. Opportunistic infections, non-NMSC malignancy, and VTE were reported only in the MTX arm (one patient each). The reported VTE was a pulmonary embolism that led to study drug discontinuation.

Efficacy outcomes

The primary endpoint, proportion of patients achieving ACR20 at Week 24, has been previously reported [12] and showed 82.6% (19/23), 90.9% (10/11), 83.3% (10/12), and 80.0% (20/25) of patients achieved ACR20 for FIL 200 mg plus MTX, FIL 100 mg plus MTX, FIL 200 mg, and MTX, respectively. A summary of outcomes for the Japanese population at Week 52 of the PS is shown in Table 2. Week 52 ACR20 rates in Japanese patients were 82.6% (19/23), 81.8% (9/11), 75% (9/12), and 76% (19/25) for FIL 200 mg + MTX, FIL 100 mg + MTX, FIL 200 mg, and MTX, respectively. Over time, ACR20 and ACR50 rates in all treatment arms showed improvements in the PS. For ACR70, there was a decrease in response rates from Week 24 to Week 52 among patients in the FIL 200 mg alone and MTX-alone treatment arms. In the

Table 2. Efficacy outcomes at PS Week 52 (full analysis set).

	FIL 200 mg + MTX $n = 23$	FIL 100 mg + MTX $n = 11$	FIL 200 mg alone $n = 12$	MTX alone $n = 25$
ACR20, *n* (%)	19 (82.6)	9 (81.8)	9 (75.0)	19 (76.0)
% Difference vs MTX alone (95% CI)	6.6 (–20.4, 33.6)	5.8 (–29.0, 40.6)	–1.0 (–36.8, 34.8)	NA
ACR50, *n* (%)	19 (82.6)	8 (72.7)	7 (58.3)	17 (68.0)
% Difference vs MTX alone (95% CI)	14.6 (–13.5, 42.7)	4.7 (–33.9, 43.3)	–9.7 (–49.2, 29.9)	NA
ACR70, *n* (%)	16 (69.6)	7 (63.6)	3 (25.0)	8 (32.0)
% Difference vs MTX alone (95% CI)	37.6 (7.2, 68.0)	31.6 (–8.7, 72.0)	–7.0 (–43.7, 29.7)	NA
DAS28(CRP) <2.6, *n* (%)	17 (73.9)	9 (81.8)	6 (50.0)	12 (48.0)
% Difference vs MTX alone (95% CI)	25.9 (–4.8, 56.6)	33.8 (–2.8, 70.4)	2.0 (–38.6, 42.6)	NA
DAS28(CRP) ≤3.2, *n* (%)	19 (82.6)	10 (90.9)	9 (75.0)	15 (60.0)
% Difference vs MTX alone (95% CI)	22.6 (–6.2, 51.5)	30.9 (–1.3, 63.1)	15.0 (–22.3, 52.3)	NA
CDAI ≤2.8, *n* (%)	14 (60.9)	7 (63.6)	3 (25.0)	4 (16.0)
% Difference vs MTX alone (95% CI)	44.9 (16.1, 73.6)**	47.6 (9.2, 86.0)**	9.0 (–25.6, 43.6)	NA
SDAI ≤3.3, *n* (%)	14 (60.9)	7 (63.6)	3 (25.0)	6 (24.0)
% Difference vs MTX alone (95% CI)	36.9 (6.7, 67.1)*	39.6 (0.1, 79.2)	1.0 (–34.8, 36.8)	NA
Boolean remission, *n* (%)	13 (56.5)	5 (45.5)	2 (16.7)	4 (16.0)
% Difference vs MTX alone (95% CI)	40.5 (11.5, 69.5)**	29.5 (–9.8, 68.7)	0.7 (–31.0, 32.4)	NA
HAQ-DI, *n*	19	10	9	19
Mean change from baseline (SD)	–1.04 (0.94)	–0.94 (0.69)	–1.06 (0.81)	–1.09 (0.85)
LS mean of treatment difference vs MTX alone (95% CI)	0.05 (–0.36, 0.46)	–0.03 (–0.53, 0.47)	–0.11 (–0.62, 0.39)	NA
SF-36 PCS, *n*	19	10	9	19
Mean change from baseline (SD)	10.5 (9.22)	13.1 (9.31)	12.6 (8.14)	11.9 (9.84)
LS mean of treatment difference vs MTX alone (95% CI)	–0.1 (–4.7, 4.5)	1.6 (–4.0, 7.2)	–0.5 (–6.2, 5.2)	NA
FACIT-Fatigue, *n*	19	10	9	19
Mean change from baseline (SD)	8.6 (11.41)	8.9 (10.73)	11.8 (11.83)	14.3 (8.44)
LS mean of treatment difference vs MTX alone (95% CI)	–1.5 (–6.0, 3.1)	–1.7 (–7.3, 3.9)	–0.3 (–5.9, 5.3)	NA

*Exploratory $p < .05$ for FIL groups vs MTX alone.
**Exploratory $p < .01$ for FIL groups vs MTX alone. All *p*-values from treatment comparisons are exploratory and without adjustment for multiplicity.
NA, not applicable.

PS, the proportion of patients achieving DAS28(CRP) ≤3.2 and <2.6, CDAI ≤10 and SDAI ≤11, and CDAI ≤2.8 and SDAI ≤3.3 increased from baseline through Week 52 in all treatment arms (Table 2); between Weeks 24 and 52, proportions of responders were either maintained or increased. Compared with the MTX-alone treatment arm, significantly more patients achieved CDAI ≤2.8 with FIL 200 mg + MTX and FIL 100 mg + MTX in an exploratory analysis. Significantly more patients achieved SDAI ≤3.3 and Boolean remission with FIL 200 mg + MTX compared with the MTX-only arm. Across all treatment groups, HAQ-DI, SF-36 PCS, and FACIT-Fatigue showed similar CFB.

Radiographic progression presenting mTSS, erosion scores, and JSN scores in the PS is described in Table 3. Proportions of patients with no radiographic progression from baseline at Week 52 are presented in Supplementary Figure S1. Nonprogression rates for the change in mTSS ≤0.5 for FIL groups vs MTX were not different ($p = .41$, 1.00, and 1.00 for FIL 200 + MTX, FIL 200 mg, and FIL 100 mg + MTX, respectively). Similarly, there were no differences in nonprogression rates for the change in mTSS ≤0 between FIL groups and MTX ($p = .49$, 1.00, and .68 for FIL 200 + MTX, FIL 200 mg, and FIL 100 mg + MTX, respectively) nor in nonprogression rates for the change in mTSS ≤ smallest detectable change (1.77) between FIL groups and MTX ($p = .34$, 1.00, and 1.00 for FIL 200 + MTX, FIL 200 mg, and FIL 100 mg + MTX, respectively). Cumulative percentile of mTSS change from baseline at Week 52 is presented in Supplementary Figure S2.

LTE outcomes

Patient population

Figure 2(b) shows the disposition for the Japanese patients. Of the 56 Japanese patients from the PS who enrolled in the LTE, three prematurely discontinued study drug (two due to AEs and one due to pregnancy). Overall, 41/56 (73%) patients did not add MTX in LTE. For each dose, 28/36 (77%) and 13/20 (65%) did not add MTX in LTE among the FIL 200 and 100 mg groups, respectively (Supplementary Table S2). The mean duration of exposure to any study drug was 76.9 weeks for those receiving FIL 200 mg (PS FIL 200 mg + MTX), 67.4 weeks for those receiving FIL 200 mg (PS FIL 200 mg), 76.4 weeks for those receiving FIL 100 mg (PS FIL 100 mg + MTX), and 70.4 and 71.9 weeks for those receiving FIL 200 mg and 100 mg (PS MTX), respectively. At LTE baseline, patient demographics were similar to those in the PS, while patients in the LTE had lower disease activity compared with the PS baseline (Table 4).

Safety outcomes

Within the Japanese population during the LTE, TEAEs were reported in 15/18 patients (83.3%) receiving FIL 200 mg (PS 200 mg + MTX), 9/9 (100%) receiving 200 mg (PS 200 mg only), 10/10 (100%) receiving FIL 100 mg (PS 100 mg + MTX), 8/9 (88.9%) receiving FIL 200 mg (PS MTX), and 6/10 (60.0%) receiving FIL 100 mg (PS MTX). An overall summary of the safety data and rates of AESI through the whole LTE by the cut-off date is shown in Table 5.

Table 3. Radiographic progression in PS.

	FIL 200 mg + MTX $n = 23$	FIL 100 mg + MTX $n = 11$	FIL 200 mg alone $n = 12$	MTX alone $n = 25$
Campaign A				
mTSS, mean (SD)				
Baseline	4.57 (6.605)	9.32 (13.350)	4.04 (5.483)	6.72 (8.435)
Week 24	4.60 (7.447)	10.16 (13.343)	5.09 (9.013)	6.44 (8.029)
Erosion score, mean (SD)				
Baseline	3.35 (4.007)	6.36 (6.929)	2.42 (1.222)	4.70 (5.920)
Week 24	3.08 (4.206)	6.71 (6.437)	2.41 (1.241)	4.94 (6.104)
JSN score, mean (SD)				
Baseline	1.22 (2.950)	2.95 (6.532)	1.63 (5.474)	2.02 (4.663)
Week 24	1.53 (3.618)	3.45 (7.053)	2.68 (8.730)	1.50 (2.610)
Campaign B/A				
mTSS, mean (SD)				
Baseline	5.17 (6.770)	8.91 (12.680)	3.83 (4.793)	5.60 (7.763)
Week 24	5.29 (6.795)	10.23 (13.404)	5.18 (8.433)	5.96 (7.958)
Week 52	5.31 (7.076)	10.36 (13.438)	5.45 (7.960)	6.50 (8.422)
Erosion score, mean (SD)				
Baseline	3.86 (3.700)	5.95 (6.093)	2.50 (1.279)	4.46 (5.445)
Week 24	3.94 (3.879)	6.58 (5.964)	2.77 (1.849)	4.70 (5.547)
Week 52	3.80 (3.851)	6.76 (5.897)	2.85 (2.028)	4.95 (5.705)
JSN score, mean (SD)				
Baseline	1.31 (3.447)	2.95 (6.843)	1.33 (4.619)	1.14 (2.748)
Week 24	1.35 (3.231)	3.65 (7.768)	2.41 (7.990)	1.26 (2.927)
Week 52	1.51 (3.505)	3.60 (7.680)	2.60 (7.709)	1.55 (3.258)

Campaign A represents radiographs taken at baseline and Week 24, and Campaign B radiographs taken at baseline, Week 24, and Week 52 for patients who had images after Week 24.

Table 4. Demographics and disease characteristics at LTE baseline.

Parent study→LTE	FIL 200 mg + MTX→FIL 200 mg $n = 18$	FIL 200 mg →FIL 200 mg $n = 9$	FIL 100 mg + MTX→FIL 100 mg $n = 10$	MTX→FIL 200 mg $n = 9$	MTX→ FIL 100 mg $n = 10$
Age, mean (SD), years	52 (11.3)	52 (13.2)	62 (8.4)	58 (14.7)	54 (12.1)
Sex, *n* (%)					
Male	5 (27.8)	4 (44.4)	5 (50.0)	5 (55.6)	5 (50.0)
Female	13 (72.2)	5 (55.6)	5 (50.0)	4 (44.4)	5 (50.0)
bDMARD-naïve	100	100	100	100	100
Concurrent oral corticosteroid use, *n* (%)	2 (11.1)	2 (22.2)	0	2 (22.2)	3 (30.0)
Dosage, mean (SD), mg/day	6.5 (4.95)	2.5 (2.12)	–	5.5 (6.36)	5.2 (2.25)
RA duration, mean (SD), years	1.8 (2.56)	1.8 (1.24)	2.9 (5.03)	1.8 (1.46)	1.1 (0.09)
SJC66, mean (SD)	0 (0.7)	3 (3.6)	1 (1.3)	4 (5.6)	1 (1.7)
TJC68, mean (SD)	2 (4.9)	2 (2.2)	1 (3.8)	3 (4.7)	3 (3.9)
DAS28(CRP), mean (SD)	1.5 (0.65)	2.3 (0.61)	1.5 (0.62)	2.6 (1.37)	2.5 (0.98)
CDAI, mean (SD)	2.3 (2.98)	6.3 (5.26)	3.0 (4.17)	7.8 (9.00)	7.3 (5.49)
HAQ-DI, mean (SD)	0.39 (0.671)	0.35 (0.526)	0.26 (0.560)	0.29 (0.385)	0.39 (0.320)

Safety analysis set includes enrolled patients who received at least one dose of study drug.
Imputation rule for incomplete initial diagnosis date: the first day of the month is used for missing day; January is used for missing month.
A patient was counted for exposure for each prior medication.
Concurrent medication use was defined as medications taken while a patient took the study drug.
Concurrent oral corticosteroid use at as-needed frequency was not counted towards the mean oral corticosteroid daily dose.
bDMARD, biologic disease-modifying anti-rheumatic drug SJC66, swollen joint count based on 66 joints; TJC68, tender joint count based on 68 joints.

Similar to the PS, no deaths were reported in any treatment arm. Overall rates of infections were generally comparable across arms: 10/18 (55.6%) in the FIL 200 mg (PS FIL 200 mg + MTX) group, 6/9 (66.7%) in the FIL 200 mg (PS FIL 200 mg alone) group, 4/10 (40.0%) in the FIL 100 mg (PS FIL 100 mg + MTX) group, 5/9 (55.6%) in the FIL 200 mg (PS MTX) group, and 4/10 (40.0%) in the FIL 100 mg (PS MTX) group. Serious infections were reported in one patient (11.1%) who experienced colon diverticulitis and infective gastroenteritis while receiving FIL 200 mg (PS FIL 200 mg alone) and two patients (22.2%) receiving FIL 200 mg (PS MTX) (one with pyothorax and one with acute tonsilitis) in the LTE. No patients reported other AESIs in the LTE.

Table 5. Safety and AESIs in the LTE.

Parent study→LTE	FIL 200 mg + MTX →FIL 200 mg *n* = 18 PYE = 26.5	FIL 200 mg →FIL 200 mg *n* = 9 PYE = 11.6	FIL 100 mg + MTX→FIL 100 mg *n* = 10 PYE = 14.6	MTX→ FIL 200 mg *n* = 9 PYE = 12.2	MTX→ FIL 100 mg *n* = 10 PYE = 13.8
TEAE summary					
Any TEAE	15 (83.3)	9 (100)	10 (100)	8 (88.9)	6 (60.0)
	56.5 (34.1, 93.8)	77.4 (40.3, 148.8)	68.3 (36.7, 126.9)	65.8 (32.9, 131.7)	43.5 (19.6, 96.9)
TEAEs Grade 3 or higher	1 (5.6)	1 (11.1)	1 (10.0)	3 (33.3)	0
	3.8 (0.5, 26.8)	8.6 (1.2, 61.1)	6.8 (0.2, 38.1)	24.7 (8.0, 76.6)	0 (0.0, 26.8)
Serious TEAEs	0	1 (11.1)	1 (10.0)	3 (33.3)	0
	0 (0.0, 13.9)	8.6 (1.2, 61.1)	6.8 (0.2, 38.1)	24.7 (8.0, 76.6)	0 (0.0, 26.8)
TEAES leading to discontinuation of study drug	0	0	1 (10.0)	1 (11.1)	0
	0 (0.0, 13.9)	0 (0.0, 31.7)	6.8 (0.2, 38.1)	8.2 (0.2, 45.9)	0 (0.0, 26.8)
Deaths	0	0	0	0	0
	0 (0.0, 13.9)	0 (0.0, 31.7)	0 (0.0, 25.2)	0 (0.0, 30.4)	0 (0.0, 26.8)
AESI					
Infections	10 (55.6)	6 (66.7)	4 (40.0)	5 (55.6)	4 (40.0)
	37.7 (20.3, 70.0)	51.6 (23.2, 114.9)	27.3 (10.3, 72.8)	41.2 (17.1, 98.9)	29.0 (10.9, 77.3)
Serious infections	0	1 (11.1)	0	2 (22.2)	0
	0 (0.0, 13.9)	8.6 (1.2, 61.1)	0 (0.0, 25.2)	16.5 (4.1, 65.8)	0 (0.0, 26.8)
Opportunistic infections	0	0	0	0	0
	0 (0.0, 13.9)	0 (0.0, 31.7)	0 (0.0, 25.2)	0 (0.0, 30.4)	0 (0.0, 26.8)
Herpes zoster	0	0	0	0	0
	0 (0.0, 13.9)	0 (0.0, 31.7)	0 (0.0, 25.2)	0 (0.0, 30.4)	0 (0.0, 26.8)
MACE	0	0	0	0	0
	0 (0.0, 13.9)	0 (0.0, 31.7)	0 (0.0, 25.2)	0 (0.0, 30.4)	0 (0.0, 26.8)
VTE	0	0	0	0	0
	0 (0.0, 13.9)	0 (0.0, 31.7)	0 (0.0, 25.2)	0 (0.0, 30.4)	0 (0.0, 26.8)
Non-NMSC malignancy	0	0	0	0	0
	0 (0.0, 13.9)	0 (0.0, 31.7)	0 (0.0, 25.2)	0 (0.0, 30.4)	0 (0.0, 26.8)
NMSC	0	0	0	0	0
	0 (0.0, 13.9)	0 (0.0, 31.7)	0 (0.0, 25.2)	0 (0.0, 30.4)	0 (0.0, 26.8)
GI perforations	0	0	0	0	0
	0 (0.0, 13.9)	0 (0.0, 31.7)	0 (0.0, 25.2)	0 (0.0, 30.4)	0 (0.0, 26.8)
Lab abnormalities					
LDL increase (fasted)	5 (27.8)	1 (11.1)	1 (10.0)	4 (44.4)	5 (50.0)
	18.8 (7.8, 45.3)	8.6 (1.2, 61.1)	6.8 (1.0, 48.5)	32.9 (12.4, 87.7)	36.3 (15.1, 87.1)
HDL decrease (fasted)	0	2 (22.2)	0	0	0
	0.0 (0.0, 13.9)	17.2 (2.1, 62.2)	0.0 (0.0, 25.2)	0.0 (0.0, 30.4)	0 (0.0, 26.8)
LDL:HDL increase (fasted)	4 (22.2)	0	2 (20.0)	0	0
	15.1 (4.1, 38.6)	0 (0.0, 31.7)	13.7 (1.7, 49.3)	0.0 (0.0, 30.4)	0 (0.0, 26.8)
ALT increase	1 (5.6)	2 (22.2)	0	3 (33.3)	3 (30.0)
	3.8 (0.5, 26.8)	17.2 (4.3, 68.6)	0.0 (0.0, 25.2)	24.7 (8.0, 76.6)	21.8 (4.5, 63.6)
AST increase	0	3 (33.3)	0	1 (11.1)	1 (10.0)
	0 (0.0, 13.9)	25.8 (8.3, 80.0)	0 (0.0, 25.2)	8.2 (1.2, 58.4)	7.3 (0.2, 40.4)
CK increase	5 (27.8)	3 (33.3)	3 (30.0)	2 (22.2)	1 (10.0)
	18.8 (7.8, 45.3)	25.8 (8.3, 80.0)	20.5 (6.6, 63.5)	16.5 (4.1, 65.8)	7.3 (1.0, 51.5)
Neutrophil count decrease	8 (44.4)	0	3 (30.0)	1 (11.1)	0
	30.2 (15.1, 60.3)	0 (0.0, 31.7)	20.5 (4.29, 59.9)	8.2 (1.2, 58.4)	0 (0.0, 26.8)
Lymphocyte count decrease	3 (16.7)	2 (22.2)	0	1 (11.1)	3 (30.0)
	11.3 (3.6, 35.1)	17.2 (4.3, 68.8)	0.0 (0.0, 25.2)	8.2 (1.2, 58.4)	21.8 (4.5, 63.6)
Anaemia	1 (5.6)	1 (11.1)	1 (10.0)	0	1 (10.0)
	3.8 (0.1, 21.0)	8.6 (0.2, 47.9)	6.8 (1.0, 48.5)	0.0 (0.0, 30.4)	7.3 (1.0, 51.5)

Safety analysis set includes enrolled patients who received at least one dose of study drug. A treatment-emergent laboratory abnormality was defined as at least one level of change from baseline at any time postbaseline up to and including the date of last study drug dose plus 30 days.
EAIR, EAIR Diff, and 95% CI were estimated using Poisson regression model including treatment group with an offset of natural log of exposure time. If any treatment had zero events, exact Poisson method was applied.

Efficacy outcomes

Outcomes at LTE baseline and Week 48 in Japanese patients are displayed in Table 6; treatment effects were largely maintained throughout this time period. Efficacy measure response rates over time in the LTE are presented in Figure 3. During the LTE, assessing ACR20 and ACR50 rates over time shows that in all treatment arms, response rates were generally maintained. Over time, the ACR70 rates in the LTE were maintained for patients receiving either FIL 200 or 100 mg (PS 200 or 100 mg + MTX) and were improved in patients receiving FIL 200 mg (PS FIL alone) or FIL 200 or 100 mg (PS MTX). Response rates for CDAI ≤2.8 and SDAI ≤3.3

Table 6. Primary and secondary outcomes at baseline and Week 48 of the LTE study (observed cases, safety analysis set).

	FIL 200 mg + MTX→FIL 200 mg *n* = 18	FIL 200 mg →FIL 200 mg *n* = 9	FIL 100 mg + MTX→FIL 100 mg *n* = 10	MTX→ FIL 200 mg *n* = 9	MTX→ FIL 100 mg *n* = 10
LTE BASELINE					
ACR20, *n* (%)	18 (100)	9 (100)	9 (90.0)	9 (100)	10 (100)
ACR50, *n* (%)	18 (100)	7 (77.8)	8 (80.0)	8 (88.9)	9 (90.0)
ACR70, *n* (%)	15 (83.3)	3 (37.5)	7 (70.0)	3 (33.3)	5 (50.0)
DAS28(CRP) <2.6, *n* (%)	16 (88.9)	6 (66.7)	9 (90.0)	6 (66.7)	6 (60.0)
DAS28(CRP) ≤3.2, *n* (%)	18 (100)	9 (100)	10 (100)	7 (77.8)	8 (80.0)
CDAI ≤2.8, *n* (%)	13 (72.2)	3 (33.3)	7 (70.0)	3 (33.3)	1 (10.0)
SDAI ≤3.3, *n* (%)	13 (72.2)	3 (33.3)	7 (70.0)	3 (33.3)	3 (30.0)
Boolean remission, *n* (%)	13 (72.2)	2 (22.2)	5 (50.0)	2 (22.2)	2 (20.0)
HAQ-DI, mean (SD)	0.39 (0.671)	0.35 (0.526)	0.26 (0.560)	0.29 (0.385)	0.39 (0.320)
SF-36 PCS, mean (SD)	48.6 (7.78)	47.6 (6.93)	50.5 (10.03)	49.1 (5.51)	48.7 (5.82)
FACIT-Fatigue, mean (SD)	41.8 (8.78)	43.7 (7.62)	41.4 (9.77)	43.9 (4.40)	40.2 (5.85)
LTE WEEK 48					
ACR20 response, *n* (%)	17 (94.4)	8 (100)	8 (80.0)	9 (100)	10 (100)
ACR50 response, *n* (%)	15 (83.3)	7 (87.5)	8 (80.0)	9 (100)	10 (100)
ACR70 response, *n* (%)	14 (77.8)	6 (75.0)	7 (70.0)	8 (88.9)	10 (100)
DAS28(CRP) <2.6, *n* (%)	15 (83.3)	6 (75.0)	9 (90.0)	8 (88.9)	8 (80.0)
DAS28(CRP) ≤3.2, *n* (%)	17 (94.4)	7 (87.5)	9 (90.0)	9 (100)	9 (90.0)
CDAI ≤2.8, *n* (%)	12 (66.7)	3 (37.5)	7 (70.0)	7 (77.8)	3 (30.0)
SDAI ≤3.3, *n* (%)	13 (72.2)	3 (37.5)	7 (70.0)	6 (66.7)	5 (50.0)
Boolean remission, *n* (%)	11 (61.1)	2 (25.0)	6 (60.0)	6 (66.7)	5 (50.0)
HAQ-DI, mean (SD)	0.35 (0.410)	0.38 (0.522)	0.11 (0.239)	0.08 (0.125)	0.18 (0.307)
SF-36 PCS, mean (SD)	50.1 (6.99)	52.4 (7.58)	53.2 (4.65)	52.1 (4.83)	52.6 (5.51)
FACIT-Fatigue, mean (SD)	40.8 (10.92)	39.8 (10.24)	44.0 (7.42)	43.0 (5.32)	41.2 (6.01)

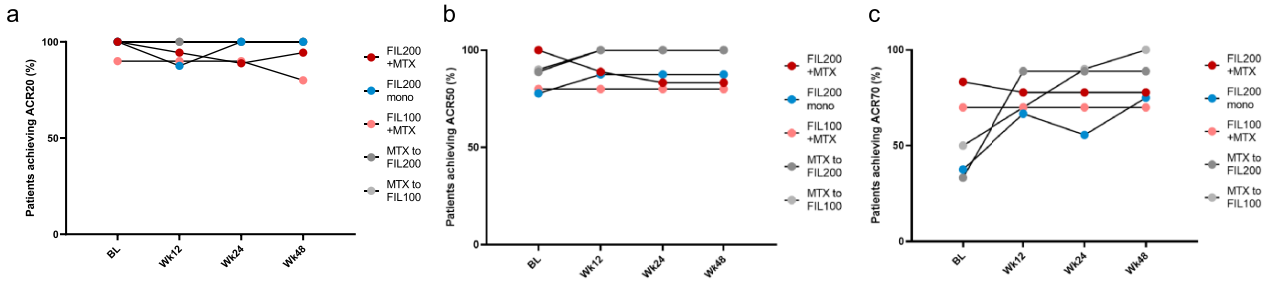

Figure 3. Proportions of ACR20 (a), ACR50 (b), ACR70 (c), responders in the LTE ACR20/50/70, 20%/50%/70% improvement in ACR criteria; BL, baseline; Wk, week.

remained higher in the PS FIL 200 mg + MTX and the FIL 100 mg + MTX groups through LTE Week 48. In the LTE, the proportion of patients achieving CDAI ≤2.8 was maintained among PS FIL 200 or 100 mg + MTX, whereas those who had received PS MTX monotherapy showed an increase over time [3/9 (33.3%) at baseline to 7/9 (77.8%) at Week 48 for FIL 200 mg (PS MTX) group and 1/10 (10%) to 3/10 (30%) for FIL 100 mg (PS MTX)].

Discussion

In this prespecified subpopulation analysis of patients with RA (who had limited or no prior MTX exposure) enrolled in Japan, the safety profile was similar to that previously seen in both the global study and the Japanese subanalysis at Week 24 [8, 12].

Rates of infections were similar across groups at Week 52 in the PS and were generally similar in the LTE. Herpes zoster is of special concern among Japanese patients with RA, because the background rate of herpes zoster is higher in RA patients independent of treatment [15] and commonly used therapies, including glucocorticoids and tumour necrosis factor inhibitors, appear to elevate the risk of herpes zoster [16]. There were three cases of herpes zoster in the PS and none in the LTE observed in this analysis, and there were no cases of active tuberculosis or hepatitis B or C in either the PS or

LTE. The long-term results of the ongoing LTE study complemented with real-world evidence will provide additional information that will be useful in assessing risks of infection and of relatively uncommon AEs in a larger study population.

Japanese patients receiving FIL 200 or 100 mg + MTX or FIL 200 mg alone had similar ACR20 responses to patients receiving MTX alone at Week 52, while greater proportions of patients who received FIL 200 or 100 mg + MTX achieved CDAI ≤2.8 than did those treated with MTX alone. Patients who then enrolled in the LTE and received FIL 200 or 100 mg showed maintained ACR20 responses. A similar trend was shown for ACR50, whereas a greater proportion of patients receiving FIL compared with MTX achieved ACR70. Among patients who had been on PS MTX only, response rates tended to increase after switching to FIL for the LTE. Most patients did not restart MTX after washout during LTE, but their disease activity remained well controlled, demonstrating the efficacy of FIL monotherapy in maintaining low disease activity over the longer term. At LTE baseline, the proportions of patients who were ACR 20/50/70 responders were substantially greater than the proportions of responders at Week 52 of the PS. This is because not all PS patients enrolled in the LTE, and the baseline visit for LTE was later than the Week-52 PS visit. Also, efficacy measures were analysed using NRI for the PS, while observed cases were used for the LTE.

Due to the small sample size and high variability of mTSS, it is challenging to draw conclusions from the mTSS data. Change in mTSS and proportions with clinical remission by CDAI and SDAI were consistent between the Japanese and the overall populations, suggesting that FIL can delay or prevent radiographic progression. This is supported by similar findings in an MTX-IR population treated with FIL [14].

Limitations of this prespecified subanalysis include the small sample size of Japanese patients and the exploratory nature of the analyses. Caution must be taken when interpreting results from a subgroup analysis that lacks statistical power, and the results reported here should be considered exploratory. Additionally, while a proportion of patients had controlled disease activity with FIL monotherapy, further research is required to identify what population of patients can reasonably withdraw from MTX. Postmarketing surveillance and ongoing clinical study will provide further safety data.

Conclusions

Among patients enrolled in Japan who were treated in the PS and the LTE, the efficacy of FIL was maintained through Week 48 of the LTE. The safety profile in this population remained stable over time. Safety and efficacy profiles for the Japanese subpopulation were consistent with the overall, global population of both the PS and LTE.

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Supplementary data

Supplementary data are available at *Modern Rheumatology* online.

Conflict of interest

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. Y.T. has received speaking fees and/or honoraria from Daiichi Sankyo, Eli Lilly, Novartis, YL Biologics, Bristol-Myers Squibb, Eisai, Chugai, AbbVie, Astellas Pharma Inc., Pfizer, Sanofi, Asahi Kasei Pharma, GlaxoSmithKline, Mitsubishi Tanabe, Gilead Sciences, Inc., and Janssen and has received research grants from Mitsubishi Tanabe, Chugai, AbbVie, Takeda, UCB, Daiichi Sankyo, and Eisai. 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. 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. 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. R.W. reports grant/research support from and serving as a consultant for Celltrion and Galapagos/Gilead Sciences, Inc. D.W.T.C. reports serving as a consultant for AbbVie. O.D.M. reports nothing to disclose. G.R.B. reports serving as a consultant and on a speakers' bureau for AbbVie, Eli Lilly, Pfizer, and Gilead Sciences, Inc. M.G., B.B., A.P., Z.Y., and Q.G. are employees and 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.

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