SUPPLEMENTAL METHODS

Inclusion criteria

1. Age ≥18 years at signing of informed consent
2. Diagnosis of rheumatoid arthritis (RA) according to 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) and are ACR functional class I–III[1]
3. At screening and day 1, ≥6 swollen joints from a count of 66 (SJC66) and ≥6 tender joints from a count of 68 (TJC68)
4. At least one of the following at screening:
    a. ≥1 documented joint erosion on radiographs of hands, wrists, or feet by central reading
    b. Positive for rheumatoid factor or anti-cyclic citrullinated peptide antibodies by central laboratory analysis
    c. Serum C-reactive protein (CRP) ≥4 mg/L by central laboratory analysis
5. No more than 3 doses of methotrexate (MTX) ≤25 mg each for the treatment of RA in the patient's lifetime, with the last dose ≥28 days prior to day 1, and the patient is an appropriate candidate for MTX treatment by the investigator's judgement
6. Female patients of childbearing potential must have a negative pregnancy test at screening and day 1
7. Male and female patients of childbearing potential who engage in heterosexual intercourse must agree to use appropriate contraception during study participation
8. Female patients who are lactating must agree to discontinue nursing during study participation
9. Meet one of the following tuberculosis (TB) screening criteria:

a. No evidence of active or latent TB: a negative QuantiFERON TB-Gold test at screening, a chest radiograph taken at screening or within 3 months prior to screening without evidence of active or latent TB infection, or no history of untreated or inadequately treated latent or active TB infection
b. Previously received adequate treatment for TB per local standard of care for either latent TB or active TB. In these cases, a chest radiograph must be obtained within 3 months prior to screening and be made available for investigator review
c. Newly identified latent TB at screening in which active TB has been ruled out and appropriate ongoing prophylactic treatment for immunocompromised individuals has been initiated prior to the first administration of study drug

10. Able and willing to sign the informed consent form after reading and understanding it
11. Patients receiving nonprohibited medication for any reason should be on a stable dose within 7 days or 5 half-lives (whichever is longer) prior to day 1

Exclusion criteria

1. Prior treatment for RA with any of the following:
   a. Alkylating agents at any time
   b. Any Janus kinase (JAK) inhibitor
   c. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) other than MTX or hydroxychloroquine, unless exposure was limited to ≤3 months total with an appropriate washout period
   d. Any biologic DMARDs

2. Known hypersensitivity or allergy to study drug
3. Known hypersensitivity or allergy to MTX
4. Oral steroids at a dose >10 mg/day of prednisone or equivalent or a prescription for oral steroids that has changed within 4 weeks of day 1
5. Receipt of intra-articular or injectable corticosteroids within 4 weeks prior to day 1
6. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) that have not been at a stable dose for ≥2 weeks prior to day 1, with the exception of acetylsalicylic acid ≤325 mg daily for cardiac prophylaxis or occasional NSAIDs for non-RA indications
7. Administration of a live/attenuated vaccine within 30 days of day 1, or planned during the study
8. Participation in any clinical study of an investigational drug/device within 4 weeks or 5 half-lives prior to screening
9. Have undergone surgical treatment for RA in >4 joints
10. Any chronic uncontrolled medical condition that would put the patient at increased risk during study participation per judgement of the investigator (eg, diabetes, hypertension, morbid obesity, psychiatric disease)
11. A history of major surgery requiring regional block or general anaesthesia within 3 months prior to screening or planned major surgery during the study
12. Moderate to severe active generalised musculoskeletal disorder that would interfere with assessment of study parameters or increase risk to the patient by participating in the study (eg, ankylosing spondylitis, psoriatic arthritis, gout). Patients with any history of Felty's syndrome or juvenile idiopathic arthritis are excluded regardless of disease activity level at screening. Patients with Sjogren's syndrome or limited cutaneous vasculitis associated with RA may be enrolled per investigator judgement

13. Active autoimmune disease that would interfere with assessment of study parameters or increase risk to the patient by participating (eg, inflammatory bowel disease, uncontrolled thyroiditis)
14. Any known condition or contraindication in the local labelling or clinical practice for MTX
15. History or current moderate to severe congestive heart failure or, within the last 6 months, a cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia, new or significant electrocardiogram finding at screen, or any other cardiovascular condition that would put the patient at risk by participation in the study per investigator judgement
16. History of malignancy within 5 years prior to screening, except for adequately treated basal cell carcinoma or nonmetastatic squamous cell carcinoma of the skin or cervical carcinoma in situ with no evidence of recurrence
17. History or current lymphoproliferative disease
18. History of gastrointestinal perforation
19. History of organ or bone marrow transplant
20. Positive serology for human immunodeficiency virus 1 or 2
21. Evidence of active hepatitis C virus (HCV) infection, indicated with positive HCV ribonucleic acid viral load
22. Evidence of active hepatitis B virus (HBV) infection, indicated with positive HBV surface antigen or deoxyribonucleic acid
23. History of opportunistic infection or immunodeficiency syndrome that would put the patient at risk per investigator judgement

24. Active infection that is clinically significant per investigator judgement, or any infection requiring hospitalisation or treatment with intravenous anti-infectives within 60 days of screening, or any infection requiring oral anti-infectives within 30 days of screening
25. Currently on therapy for any chronic infection (eg, pneumocystis, cytomegalovirus), and history of disseminated Staphylococcus aureus or disseminated herpes simplex infection
26. History of symptomatic herpes zoster within 12 weeks prior to screening or history of disseminated/complicated herpes zoster infection
27. History of an infected joint prosthesis or other implanted device with the retention of the prothesis or device in situ
28. Current drug, tobacco, or alcohol abuse per investigator judgement
29. Any condition that would make it difficult to appropriately assess RA activity for the purpose of this study, including active fibromyalgia
30. Any condition or circumstances that may make a subject unlikely or unable to complete the study or comply with study procedures in the opinion of the investigator or sponsor
31. Use of prohibited medication
32. Blood loss >450 mL or transfusion of blood product within 12 weeks prior to day 1
33. Central laboratory test results performed at screening that meet any of the following criteria:
    a. Haemoglobin <8.0 g/dL
    b. White blood cells <3.0 x 103 cells/mm^3
    c. Neutrophils <1.5 x 103 cells/mm^3

d. Lymphocytes <0.5 x 103 cells/mm^3
e. Platelets <100 x 103 cells/mm^3
f. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥1.5x upper limit of normal (ULN)
g. Total bilirubin ≥2x ULN, unless the subject has been diagnosed with Gilbert's disease and this is clearly documented
h. Estimated creatinine clearance <40 mL/min based on the Cockroft-Gault formula

Masking and randomisation

Patients were randomised 2:1:1:2 to receive filgotinib 200 mg with MTX, filgotinib 100 with MTX, filgotinib 200 mg, or MTX. Randomisation was stratified by geographic region per standard of care and RF or anti-CCP antibody presence at screening. An independent statistician prepared a prespecified randomisation scheme that was implemented via interactive web response system.

Patients, investigators, study staff, and sponsor were blinded to treatment allocation. Placebo tablets and capsules identical in appearance to filgotinib 100- or 200-mg tablets or methotrexate 2.5-mg capsules were administered to maintain blinding; all patients received 2 tablets of blinded filgotinib or matched placebo and 1 capsule of blinded methotrexate or matched placebo, as appropriate.

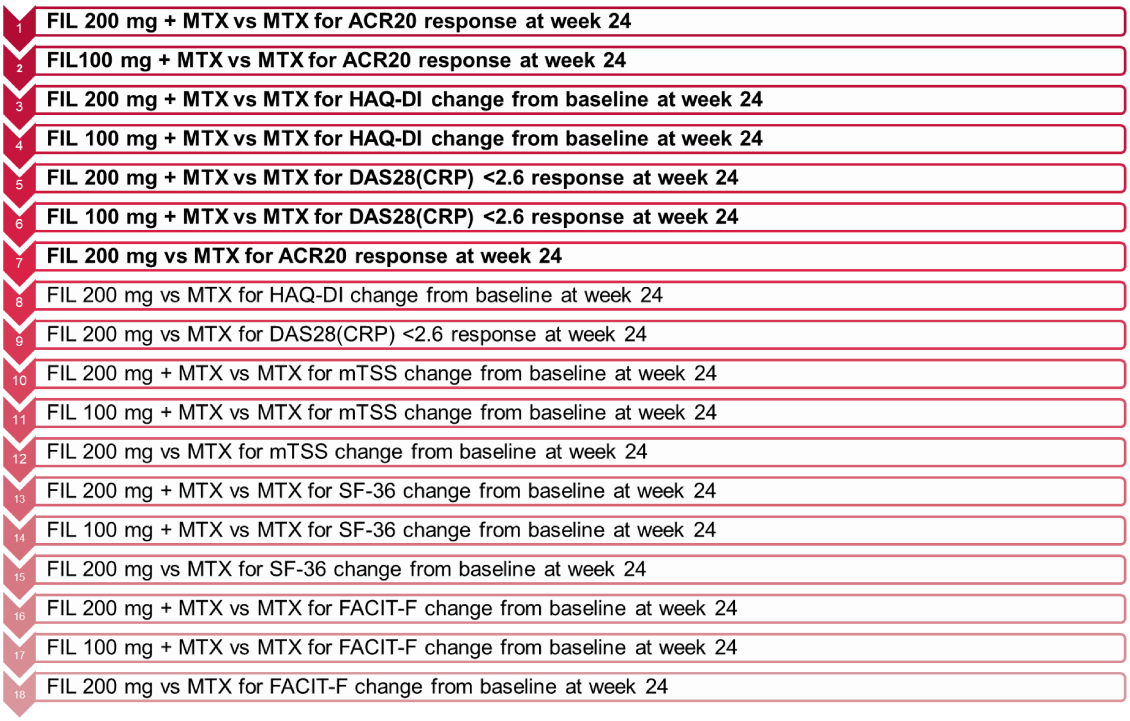
Secondary outcome definitions

The SF-36 is a health-related quality-of-life questionnaire of 36 items that measures 8 domains grouped into a mental and a physical component, with higher scores indicating greater health.[2, 3] The FACIT-F is a 13-question measure that evaluates fatigue in chronic illness on a

0-to-52-point scale, with higher scores indicating less fatigue.[4, 5] The SDAI and CDAI are also composite measures of disease activity compiled from TJC, SJC, and patient and physician global assessment of disease; the SDAI also includes CRP levels.[6, 7] CDAI ≤2.8 and SDAI ≤3.3 are accepted thresholds for remission.[8] The HAQ-DI assesses 8 functional categories with scores ranging from 0 to 3 (completely disabled).[9, 10] The DAS28(CRP) is a composite disease activity index using TJC and SJC of 28 joints, CRP, and patient global assessment of disease to generate a score from 0 to 10, with scores of ≤3.2 and <2.6 indicating low disease activity and remission, respectively.[11, 12] Radiographs of the hands and feet were evaluated centrally by 2 independent assessors blinded for time order, patient characteristics and treatment allocation and an adjudicator if needed to calculate modified total van der Heidje/Sharp Score (mTSS), a measure of disease progression including erosion and joint space narrowing.[13]

SUPPLEMENTAL FIGURES

Figure S1. Sequence for formal hypothesis testing



All tests were for superiority with a two-sided α=0.05. The hypothesis tests in bolded rows were carried out formally and adjusted for multiplicity. All other hypothesis tests were exploratory and not adjusted for multiplicity.

ACR20, 20% improvement in American College of Rheumatology criteria; DAS28(CRP), Disease Activity Score with C-reactive protein; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FIL, filgotinib; HAQ-DI, Health Assessment Questionnaire-Disability Index; mTSS, modified total van der Heijde/Sharp Score; MTX, methotrexate; SF-36, Short Form 36.

Table S1. MTX dosing at weeks 8 and 24

	FIL 200 mg + MTX n=416	FIL 100 mg + MTX n=207	MTX n=416
Week 8			
n	388	190	384
Mean (SD)	17.0 (3.1)	17.0 (3.1)	16.9 (3.1)
Median (Q1, Q3)	15.0 (15.0, 20.0)	15.0 (15.0, 20.0)	15.0 (15.0, 20.0)
Week 24			
n	360	187	366
Mean (SD)	18.3 (3.2)	18.1 (3.5)	18.4 (3.2)
Median (Q1, Q3)	20.0 (20.0, 20.0)	20.0 (15.0, 20.0)	20.0 (20.0, 20.0)

FIL, filgotinib; MTX, methotrexate; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Table S2. Patients with no radiographic progression at week 24

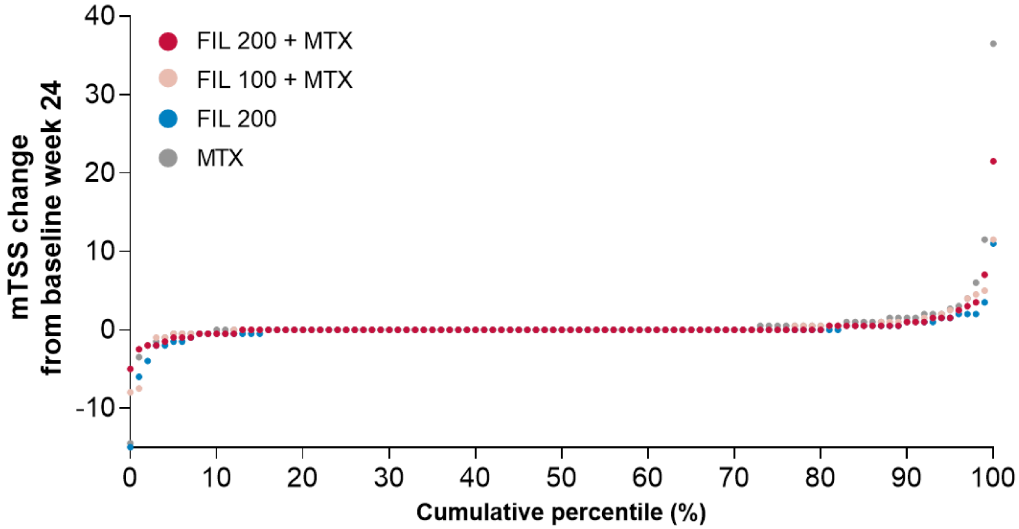
%, (95% CI)	FIL 200 mg + MTX n=355	FIL 100 mg + MTX n=184	FIL 200 mg n=173	MTX n=356
ΔmTSS ≤0.5	90% (86.3, 92.9)	87% (81.8, 92.1)	90% (84.8, 94.4)	82% (77.9, 86.2)
Exploratory *P* vs MTX	0.006	0.16	0.029	
ΔmTSS ≤0	81% (76.3, 84.8)	77% (70.2, 83.0)	83% (76.7, 88.6)	73% (67.7, 77.3)
Exploratory *P* vs MTX	0.015	0.33	0.013	
ΔmTSS ≤SDC (1.53)	95% (92.8, 97.6)	94% (89.6, 97.3)	96% (92.7, 99.2)	92% (88.5, 94.6)
Exploratory *P* vs MTX	0.074	0.49	0.075	

All *P* values are exploratory, without adjustment for multiplicity. Data are from campaign A.

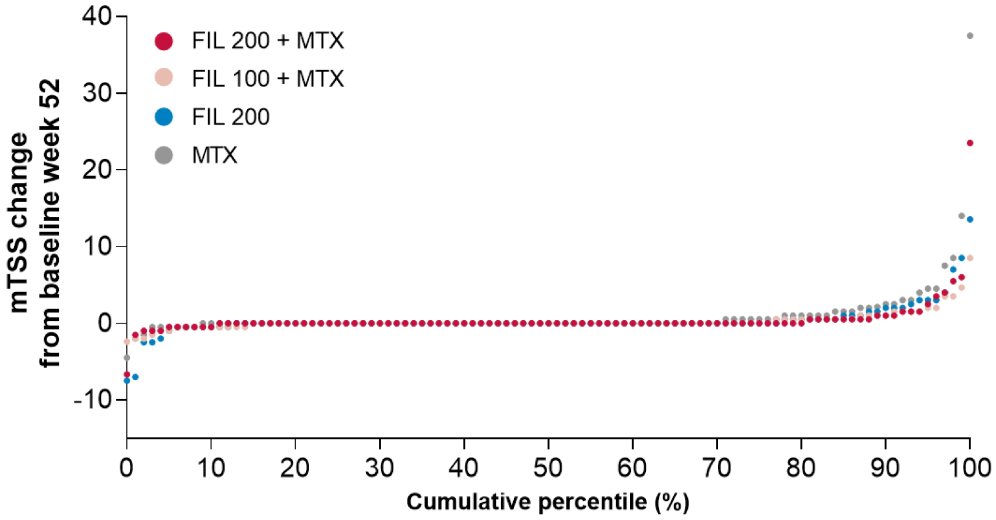
Δ, change from baseline; CI, confidence interval; FIL, filgotinib; mTSS, modified total Sharp/van der Heijde score; MTX, methotrexate; SDC, smallest detectable change.

Figure S2. Cumulative percentile of mTSS change from baseline at weeks **A)** 24, and **B)** 52

A) Cumulative percentile of mTSS change from baseline at week 24



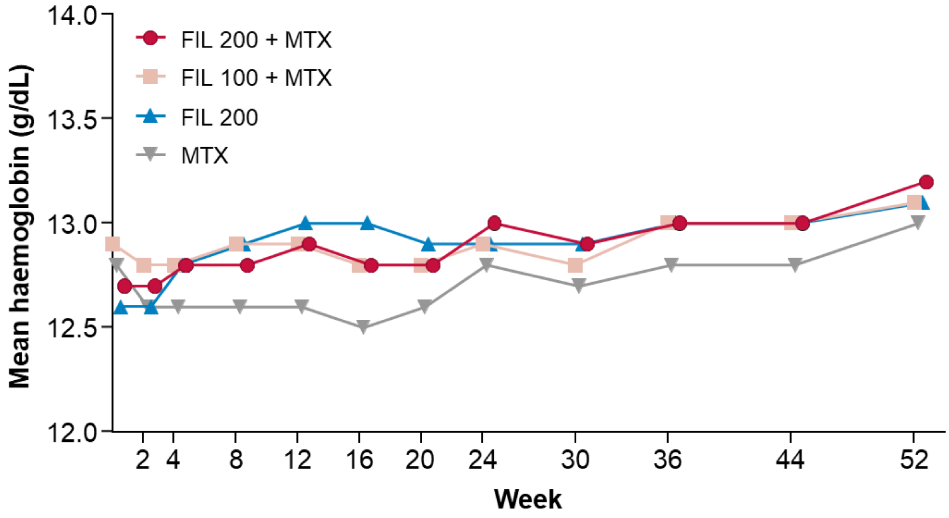
B) Cumulative percentile of mTSS change from baseline at week 52



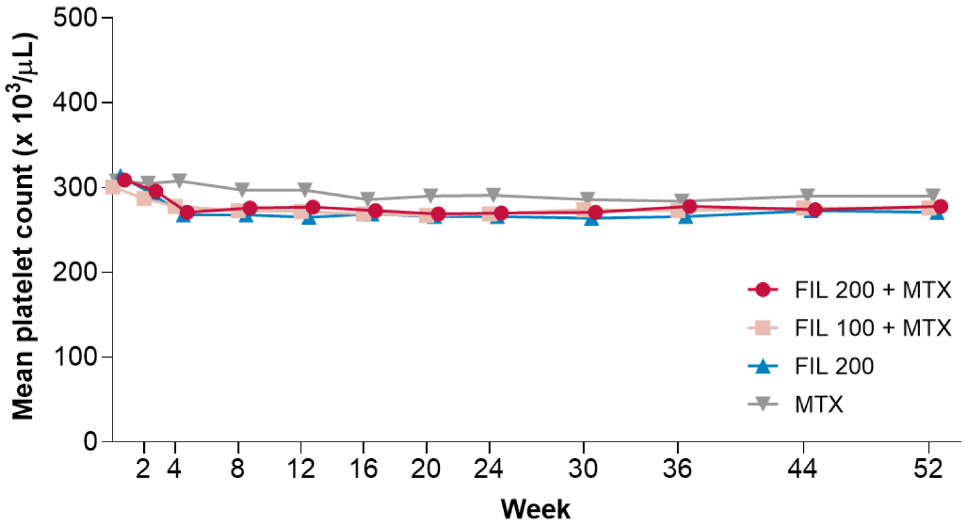
Week 24 includes only data from campaign A and week 52 includes data from campaign A and B. FIL, filgotinib; mTSS, modified total van der Heijde/Sharp score; MTX, methotrexate.

Figure S3. Mean laboratory results over 52 weeks: **A)** haemoglobin; **B)** platelets; **C)** neutrophils; **D)** lymphocytes

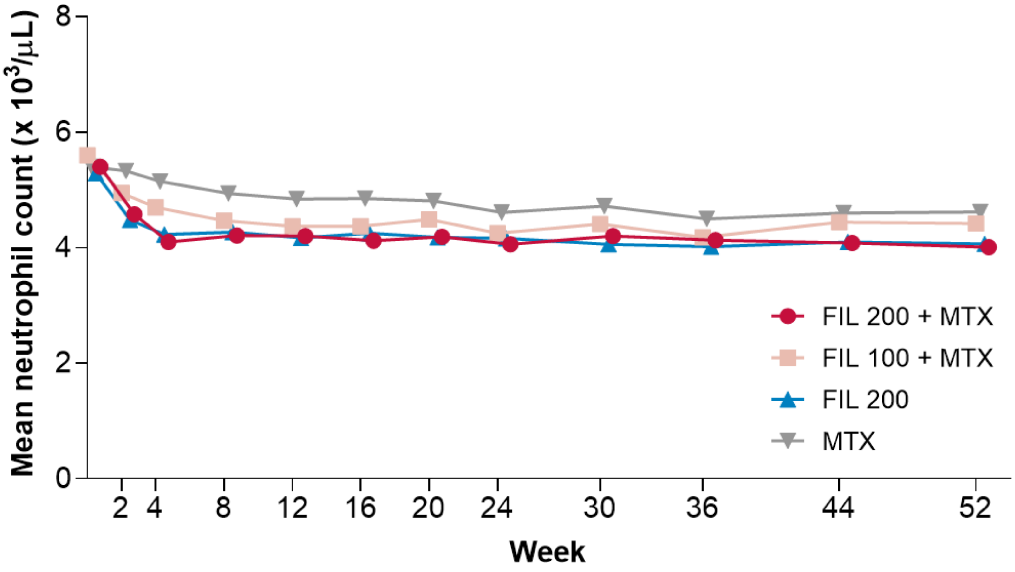
A) Haemoglobin



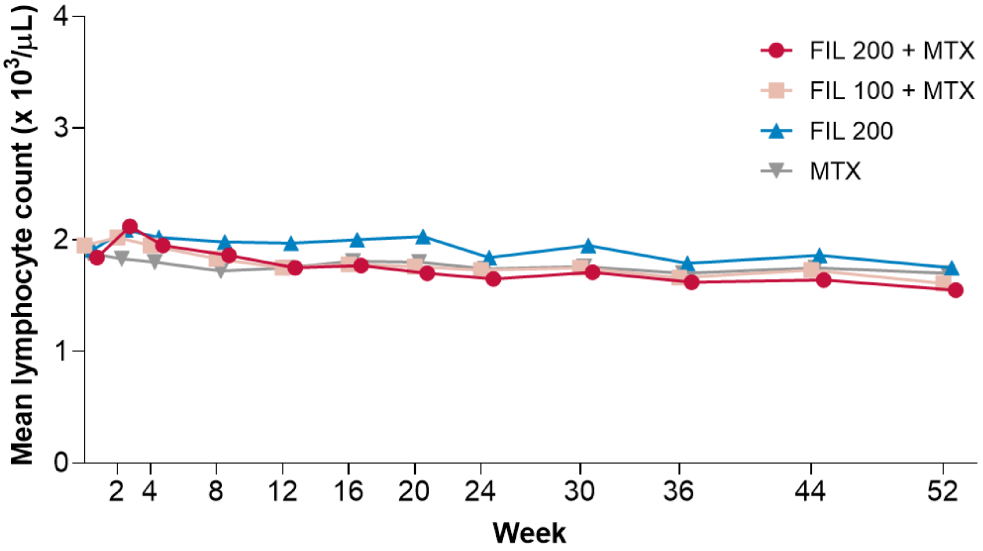
B) Platelets



C) Neutrophils



D) Lymphocytes



Data are as observed for the safety analysis set. Supporting data are provided in **Table S4.**

FIL, filgotinib; MTX, methotrexate.

Table S3. Proportion of patients who achieved ACR20 over time

Week	FIL 200 + MTX (n=416)	FIL 100 + MTX (n=207)	FIL 200 (n=210)	MTX (n=416)
0	0 (0,0)	0 (0,0)	0 (0,0)	0 (0,0)
2	42.1 (37.2, 46.9)	37.2 (30.4, 44.0)	39.5 (32.7, 46.4)	16.6 (12.9, 20.3)
4	62.3 (57.5, 67.0)	55.6 (48.5, 62.6)	52.4 (45.4, 59.4)	33.4 (28.8, 38.1)
8	74.8 (70.5, 79.1)	66.2 (59.5, 72.9)	63.3 (56.6, 70.1)	51.0 (46.0, 55.9)
12	76.7 (72.5, 80.9)	72.0 (65.6, 78.3)	71.4 (65.1, 77.8)	59.4 (54.5, 64.2)
16	75.7 (71.5, 80.0)	74.9 (68.7, 81.0)	79.5 (73.8, 85.2)	65.9 (61.2, 70.5)
20	77.9 (73.8, 82.0)	80.7 (75.1, 86.3)	77.6 (71.7, 83.5)	69.0 (64.4, 73.6)
24	81.0 (77.1, 84.9)	80.2 (74.5, 85.9)	78.1 (72.3, 83.9)	71.4 (66.9, 75.9)
30	75.2 (71.0, 79.5)	77.3 (71.3, 83.2)	71.9 (65.6, 78.2)	68.3 (63.7, 72.9)
36	75.5 (71.2, 79.7)	73.4 (67.2, 79.7)	76.2 (70.2, 82.2)	68.3 (63.7, 72.9)
44	75.5 (71.2, 79.7)	72.0 (65.6, 78.3)	76.7 (70.7, 82.6)	66.8 (62.2, 71.5)
52	75.0 (70.7, 79.3)	73.4 (67.2, 79.7)	74.8 (68.6, 80.9)	61.8 (57.0, 66.6)

Data are percent of patients (95% confidence interval).

ACR20, 20% improvement in American College of Rheumatology criteria; FIL, filgotinib; MTX, methotrexate.

Table S4. Mean laboratory results over 52 weeks

	FIL 200 mg + MTX n=416	FIL 100 mg + MTX n=207	FIL 200 mg n=210	MTX n=416
Haemoglobin (g/dL)				
Baseline	12.7	12.9	12.6	12.8
Week 12	12.9	12.9	13.0	12.6
Week 24	13.0	12.9	12.9	12.8
Week 52	13.2	13.1	13.1	13.0
Platelets ($\times 10^3$/µL)				
Baseline	309	301	314	308
Week 12	277	272	265	297
Week 24	270	269	266	291
Week 52	278	276	271	290
Neutrophils ($\times 10^3$/µL)				
Baseline	5.40	5.60	5.29	5.40
Week 12	4.20	4.37	4.17	4.84
Week 24	4.06	4.25	4.16	4.61
Week 52	4.01	4.42	4.07	4.62
Lymphocytes ($\times 10^3$/µL)				
Baseline	1.84	1.95	1.91	1.88
Week 12	1.75	1.75	1.97	1.75
Week 24	1.65	1.73	1.84	1.74
Week 52	1.55	1.61	1.75	1.70

FIL, filgotinib; MTX, methotrexate.

REFERENCES

1. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569-81.

2. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-83.

3. Ware JE, Jr., Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol*. 1998;51(11):903-12.

4. Cella D. FACIT Measurement System. https://www.facit.org/FACITOrg/Questionnaires. Accessed Sept 27, 2019.

5. Hewlett S, Dures E, Almeida C. Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for severity, effect, and coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi-Dimensional Assessment of Fatigue (MAF), Multi-Dimensional Fatigue Inventory (MFI), Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). *Arthritis Care Res (Hoboken)*. 2011;63 Suppl 11:S263-86.

6. Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther*. 2005;7(4):R796-806.

7. Smolen JS, Breedveld FC, Schiff MH, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford)*. 2003;42(2):244-57.

8. Smolen JS, Aletaha D. Scores for all seasons: SDAI and CDAI. *Clin Exp Rheumatol*. 2014;32(5 Suppl 85):S-75-9.

9. Fries JF, Spitz P, Kraines RG, et al. Measurement of patient outcome in arthritis. *Arthritis Rheum*. 1980;23(2):137-45.

10. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol*. 1982;9(5):789-93.

11. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum*. 1995;38(6):727-35.

12. 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(1):44-8.

13. van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Radiographic progression on radiographs of hands and feet during the first 3 years of rheumatoid arthritis measured according to Sharp's method (van der Heijde modification). *J Rheumatol*. 1995;22(9):1792-6.