SUPPLEMENTARY MATERIAL

Supplementary methods

Assessment of radiographic progression based on van der Heijde modified total Sharp score

The van der Heijde modified total Sharp score (mTSS) was assigned by 2 central readers blinded to treatment, patient information, and chronological order of the radiographs; average value is reported. Results reported for baseline, week 12, and week 24 were based on readings of radiographs obtained at screening, week 12, and week 24 or pretermination visit before week 24 (Campaign A). Week 52 results were based on readings of radiographs obtained at screening, week 24, and week 52 or pretermination visit after week 24 (Campaign B) combined with Campaign A results.

Statistical analysis

Noninferiority analyses

The noninferiority test of the proportions of patients achieving Disease Activity Score in 28 joints with C-reactive protein (DAS28[CRP]) ≤3.2 and <2.6 at week 12 assessed whether each filgotinib dose preserves more than 50% of the effect of adalimumab compared with placebo (minimum effect fraction = 0.5). The minimum effect fraction of 0.5 was chosen based on published methods suggesting a fraction of 0.5–0.99 for noninferiority and a similar trial of tofacitinib employing a noninferiority margin based on 50% of the treatment difference for adalimumab[1-3].

Sensitivity analyses

The multiple imputation procedure replaced each missing value with a set of plausible values that represented the uncertainty about the right value to impute. Fifty imputed data sets were generated based on logistic regression models for binary efficacy endpoints (eg, ACR20) or linear regression models for continuous efficacy end points (eg, Health Assessment Questionnaire-Disability Index). These multiple imputed data sets were analysed using the same method as for the primary analysis. The results from each set of imputed data sets were combined using Rubin's rule.[4] The stratification factors were included in

the imputation model as covariates, and all available data at postbaseline visits up to the time point of interest were included in the model.

All statistical analyses were done using SAS version 9.4 (SAS Institute).

Supplementary results

Narratives of deaths

1. The acute DVT-associated death occurred in a patient in their 60s with risk factors of obesity, history of tobacco use, African descent, and cardiovascular disease. The patient started placebo on study day 1 and was rerandomised to filgotinib 200 mg (FIL200) on study day 169. The patient received FIL200 for 37 days before study drug discontinuation on day 205 due to persistent anaemia, radiographic finding of pneumoperitoneum, and weight loss. Investigation did not identify an underlying cause. The patient experienced ischaemic stroke and DVT considered related to study drug on day 219 (13 days after the last dose of filgotinib), followed by pulmonary embolism on day 220, and death on day 224. Investigation revealed bilateral pulmonary emboli with scattered interstitial opacities of the bilateral upper and lower lobes concerning for pulmonary infarcts and deep venous thrombosis of the femoral vein (thrombus within the bilateral popliteal veins with extension into the inferior femoral vein on the left). There was no evidence of right heart strain. The patient was also found to have cardiomegaly with patent foramen ovale, which could explain the distal internal carotid artery, middle cerebral artery, and posterior cerebral artery occlusions.

2. The primary varicella infection-associated death occurred in a patient in their 30s with unknown history of childhood chicken pox or varicella vaccination who completed study treatment with filgotinib 100 mg (after rerandomisation from placebo) on day 361—the end of the study—and continued receiving methotrexate and corticosteroids for treatment of rheumatoid arthritis. The patient presented 5 days after study drug discontinuation with a disseminated vascular rash diagnosed as varicella based on appearance. It is unknown if the patient had ever received varicella vaccination; however, the investigator noted that vaccination for chicken pox was uncommon in that region and there were 2 other patients

admitted to the same hospital with varicella infection within ~1 week of this event. The patient's death on day 368 was attributed to varicella and was considered related to study drug. No virology testing or autopsy was performed.

Supplementary References

1. Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet*. 2017;390(10093):457-68.

2. Koch GG, Tangen CM. Nonparametric analysis of covariance and its role in noninferiority clinical trials. *Drug Information Journal*. 1999;33:1145-59.

3. Liu JT, Tzeng CS, Tsou HH. Establishing non-inferiority of a new treatment in a three-arm trial: Apply a step-down hierarchical model in a papulopustular acne study and an oral prophylactic antibiotics study. *International Journal of Statistics in Medical Research*. 2014;3(1):11-20.

4. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons, Inc, 1987.

Table S1. Noninferiority margins based on the difference of proportions of patients achieving DAS28(CRP) ≤3.2 or <2.6 between the adalimumab and placebo groups at weeks 12 and 24

	ADA (%)	PBO (%)	Noninferiority margin[a] (%)
DAS28(CRP) ≤3.2, week 12	43.4	23.4	10.0
DAS28(CRP) ≤3.2, week 24	50.5	33.7	8.4
DAS28(CRP) <2.6, week 12	23.7	9.3	7.2
DAS28(CRP) <2.6, week 24	35.7	16.2	9.8

[a]50% of the difference between ADA vs PBO.

ADA, adalimumab; DAS28(CRP), Disease Activity Score in 28 joints with C-reactive protein; PBO, placebo.

Table S2. Multiple imputation sensitivity analyses: Primary and secondary outcomes

	FIL200 (n = 475)	FIL100 (n = 480)	ADA (n = 325)	PBO (n = 475)
Primary outcome				
ACR20, week 12				
% (95% CI)	79.1 (75.4 to 82.9)	73.9 (69.9 to 77.9)	73.8 (68.9 to 78.6)	53.3 (48.7 to 57.9)
Difference vs PBO (95% CI)	25.9 (20.0 to 31.8)	20.6 (14.5 to 26.7)		
Exploratory p vs PBO	<0.001	<0.001		
Key secondary outcomes				
HAQ-DI change from baseline to week 12				
N	462	460	315	443
Mean ± SD	−0.69 ± 0.61	−0.56 ± 0.57	−0.61 ± 0.56	−0.42 ± 0.54
Difference vs PBO (95% CI)	−0.29 (−0.35 to −0.22)	−0.17 (−0.24 to −0.10)		
Exploratory p vs PBO	<0.001	<0.001		
DAS28(CRP) <2.6, week 12				
% (95% CI)	34.5 (30.2 to 38.8)	25.6 (21.6 to 29.6)	25.0 (20.3 to 29.8)	9.8 (7.1 to 12.5)
Difference vs PBO (95% CI)	24.7 (19.7 to 29.8)	15.8 (11.0 to 20.7)		
Exploratory p vs PBO	<0.001	<0.001		
mTSS change from baseline to week 24				
N	428	429	283	390
Mean ± SD	0.15 ± 1.1	0.17 ± 0.89	0.17 ± 0.94	0.36 ± 1.4
Difference vs PBO (95% CI)	−0.24 (−0.39 to −0.08)	−0.23 (−0.39 to −0.07)		
Exploratory p vs PBO	0.003	0.004		
Noninferiority DAS28(CRP) ≤3.2, week 12				
% (95% CI)	50.6 (46.1 to 55.1)	41.5 (37.0 to 46.0)	45.4 (39.9 to 50.8)	24.3 (20.4 to 28.2)
Difference vs ADA (95% CI)	5.2 (−1.9 to 12.3)	−3.9 (−10.9 to 3.2)		
Exploratory p vs ADA	<0.001	0.02		
SF-36 PCS change from baseline to week 12				
N	465	465	315	448
Mean ± SD	9.1 ± 8.1	8.4 ± 7.7	8.4 ± 7.8	5.7 ± 7.2
Difference vs PBO (95% CI)	3.7 (2.8 to 4.6)	3.1 (2.2 to 4.0)		
Exploratory p vs PBO	<0.001	<0.001		
FACIT-F change from baseline to week 12				

N	458	457	309	440
Mean ± SD	9.2 ± 9.8	9.0 ± 10.2	8.8 ± 9.4	6.6 ± 9.9
Difference vs PBO (95% CI)	3.0 (2.0 to 4.1)	2.8 (1.7 to 3.9)		
Exploratory p vs PBO	<0.001	<0.001		
Superiority DAS28(CRP) ≤3.2, week 12				
Difference vs ADA (95% CI)	5.2 (−1.9 to 12.3)	−3.9 (−10.9 to 3.2)		
Exploratory p vs ADA	0.13	0.27		
Noninferiority DAS28(CRP) <2.6, week 12				
Difference vs ADA (95% CI)	9.5 (3.0 to 15.9)	0.6 (−5.6 to 6.8)		
Exploratory p vs ADA	<0.001	<0.001		
Superiority DAS28(CRP) <2.6, week 12				
Difference vs ADA (95% CI)	9.5 (3.0 to 15.9)	0.6 (−5.6 to 6.8)		
Exploratory p vs ADA	0.004	0.86		

Difference shown as difference in response rates for categorical outcomes and least-squares means difference for continuous outcomes.

ACR20, 20% improvement from baseline in American College of Rheumatology core criteria; ADA, adalimumab; CI, confidence interval; DAS28(CRP), Disease Activity Score in 28 joints with C-reactive protein; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FIL100, filgotinib 100 mg; FIL200, filgotinib 200 mg; HAQ-DI, Health Assessment Questionnaire-Disability Index; mTSS, van der Heijde modified total Sharp score; PBO, placebo; SD, standard deviation; SF-36 PCS, Short Form-36 Physical Component Summary.

Table S3. Additional efficacy data through week 52

	FIL200 (n = 475)	FIL100 (n = 480)	ADA (n = 325)	PBO (n = 475)
ACR20				
% (95% CI), week 24	78.1 (74.3–81.9)	77.7 (73.9–81.5)	74.5 (69.6–79.4)	59.2 (54.6–63.7)
Treatment difference vs PBO (95% CI)	18.9 (13.0–24.9)	18.6 (12.6–24.5)		
Exploratory p vs PBO	<0.001	<0.001		
% (95% CI), week 52	78.3 (74.5–82.1)	75.6 (71.7–79.6)	73.5 (68.6–78.5)	N/A
Treatment difference vs ADA (95% CI)	4.8 (−1.5 to 11.1)	2.1 (−4.3 to 8.5)		
Exploratory p vs ADA	0.10	0.52		
ACR50				
% (95% CI), week 24	57.9 (53.3–62.4)	52.7 (48.1–57.3)	52.3 (46.7–57.9)	33.3 (28.9–37.6)
Treatment difference vs PBO (95% CI)	24.6 (18.3–31.0)	19.4 (13.1–25.8)		
Exploratory p vs PBO	<0.001	<0.001		
% (95% CI), week 52	62.3 (57.9–66.8)	58.5 (54.0–63.1)	59.1 (53.6–64.6)	N/A
Treatment difference vs ADA (95% CI)	3.2 (−3.9 to 10.4)	−0.5 (−7.7 to 6.7)		
Exploratory p vs ADA	0.32	0.87		
ACR70				
% (95% CI), week 24	36.4 (32.0–40.9)	30.2 (26.0–34.4)	30.2 (25.0–35.3)	15.4 (12.0–18.7)
Treatment difference vs PBO (95% CI)	21.1 (15.4–26.7)	14.8 (9.4–20.3)		
Exploratory p vs PBO	<0.001	<0.001		
% (95% CI), week 52	44.2 (39.6–48.8)	37.5 (33.1–41.9)	39.4 (33.9–44.9)	N/A
Treatment difference vs ADA (95% CI)	4.8 (−2.4 to 12.0)	−1.9 (−9.0 to 5.2)		
Exploratory p vs ADA	0.15	0.61		
HAQ-DI change from baseline				
Week 24				
N	418	423	283	376
Mean ± SD	−0.82 ± 0.63	−0.75 ± 0.60	−0.78 ± 0.63	−0.62 ± 0.60
Treatment difference vs PBO, LSM (95% CI)	−0.27 (−0.34 to −0.19)	−0.19 (−0.26 to −0.11)		
Exploratory p vs PBO	<0.001	<0.001		
Week 52				
N	400	398	265	N/A
Mean ± SD	−0.93 ± 0.65	−0.85 ± 0.62	−0.85 ± 0.65	N/A
Treatment difference vs ADA, LSM (95% CI)	−0.09 (−0.17 to −0.01)	−0.01 (−0.09 to 0.08)		
Exploratory p vs ADA	0.036	0.87		

DAS28(CRP) <2.6				
% (95% CI), week 24	48.4 (43.8–53.0)	35.2 (30.8–39.6)	35.7 (30.3–41.1)	16.2 (12.8–19.6)
Treatment difference vs PBO (95% CI)	32.2 (26.4–38.0)	19.0 (13.4–24.6)		
Exploratory p vs PBO	<0.001	<0.001		
% (95% CI), week 52	53.9 (49.3–58.5)	42.9 (38.4–47.4)	46.2 (40.6–51.7)	N/A
Treatment difference vs ADA (95% CI)	7.7 (0.4–15.0)	−3.2 (−10.5 to 4.0)		
Exploratory p vs ADA	0.024	0.38		
DAS28(CRP) ≤3.2				
% (95% CI), week 24	60.6 (56.1–65.1)	53.1 (48.6–57.7)	50.5 (44.9–56.1)	33.7 (29.3–38.0)
Treatment difference vs PBO (95% CI)	26.9 (20.6–33.3)	19.4 (13.1–25.8)		
Exploratory p vs PBO	<0.001	<0.001		
% (95% CI), week 52	65.9 (61.5–70.3)	59.4 (54.9–63.9)	58.8 (53.3–64.3)	N/A
Treatment difference vs ADA (95% CI)	7.1 (0–14.2)	0.6 (−6.6 to 7.8)		
Exploratory p vs ADA	0.031	0.86		
SF-36 PCS change from baseline				
Week 24				
N	424	426	283	376
Mean ± SD	10.4 ± 8.5	10.3 ± 8.6	10.4 ± 8.5	7.7 ± 8.0
Treatment difference vs PBO, LSM (95% CI)	3.1 (2.1–4.1)	3.1 (2.0–4.1)		
Exploratory p vs PBO	<0.001	<0.001		
Week 52				
N	399	398	265	N/A
Mean ± SD	12.0 ± 8.7	11.5 ± 8.7	12.4 ± 9.2	N/A
Treatment difference vs ADA, LSM (95% CI)	0.1 (−1.1 to 1.3)	−0.3 (−1.5 to 0.9)		
Exploratory p vs ADA	0.84	0.64		
FACIT-F change from baseline				
Week 24				
N	413	417	273	369
Mean ± SD	10.5 ± 10.6	10.8 ± 10.8	10.3 ± 9.7	8.4 ± 10.5
Treatment difference vs PBO, LSM (95% CI)	2.6 (1.5–3.8)	2.8 (1.6–3.9)		
Exploratory p vs PBO	<0.001	<0.001		
Week 52				
N	384	376	254	
Mean ± SD	11.9 ± 10.2	12.2 ± 10.9	11.7 ± 10.8	N/A
Treatment difference vs ADA, LSM (95% CI)	0.7 (−0.6 to 2.0)	0.8 (−0.5 to 2.1)		
Exploratory p vs ADA	0.28	0.22		

CDAI ≤10				
% (95% CI), week 12	45.9 (41.3–50.5)	36.7 (32.3–41.1)	38.5 (33.0–43.9)	23.8 (19.9–27.7)
Treatment difference vs PBO (95% CI)	22.1 (16.0–28.2)	12.9 (6.9–18.9)		
Exploratory p vs PBO	<0.001	<0.001		
Exploratory p for noninferiority vs ADA[a]	<0.001	0.045		
% (95% CI), week 24	60.2 (55.7–64.7)	50.8 (46.3–55.4)	49.5 (43.9–55.1)	35.6 (31.2–40.0)
Treatment difference vs PBO (95% CI)	24.6 (18.3–31.0)	15.3 (8.8–21.7)		
Exploratory p vs PBO	<0.001	<0.001		
Exploratory p for noninferiority vs ADA[a]	<0.001	0.004		
% (95% CI), week 52	66.9 (62.6–71.3)	59.2 (54.7–63.7)	61.2 (55.8–66.7)	N/A
Treatment difference vs ADA (95% CI)	5.7 (−1.3 to 12.8)	−2.1 (−9.2 to 5.1)		
Exploratory p vs ADA	0.077	0.55		
SDAI ≤11				
% (95% CI), week 12	46.9 (42.4–51.5)	36.7 (32.3–41.1)	38.5 (33.0–43.9)	24.4 (20.5–28.4)
Treatment difference vs PBO (95% CI)	22.5 (16.4–28.7)	12.2 (6.2–18.2)		
Exploratory p vs PBO	<0.001	<0.001		
% (95% CI), week 24	60.2 (55.7–64.7)	52.5 (47.9–57.1)	50.5 (44.9–56.1)	35.4 (31.0–39.8)
Treatment difference vs PBO (95% CI)	24.8 (18.5–31.2)	17.1 (10.7–23.5)		
Exploratory p vs PBO	<0.001	<0.001		
% (95% CI), week 52	67.4 (63.0–71.7)	59.6 (55.1–64.1)	60.0 (54.5–65.5)	N/A
Treatment difference vs ADA (95% CI)	7.4 (0.3–14.4)	−0.4 (−7.6 to 6.7)		
Exploratory p vs ADA	0.025	0.91		
CDAI ≤2.8				
% (95% CI), week 12	12.4 (9.3–15.5)	11.0 (8.1–13.9)	5.8 (3.1–8.6)	2.7 (1.2–4.3)
Treatment difference vs PBO (95% CI)	9.7 (6.2–13.2)	8.3 (4.9–11.7)		
Exploratory p vs PBO	<0.001	<0.001		
Exploratory p for noninferiority vs ADA[a]	<0.001	<0.001		
% (95% CI), week 24	21.3 (17.5–25.0)	18.5 (15.0–22.1)	16.9 (12.7–21.2)	8.4 (5.8–11.0)
Treatment difference vs PBO (95% CI)	12.8 (8.2–17.5)	10.1 (5.6–14.6)		
Exploratory p vs PBO	<0.001	<0.001		
Exploratory p for noninferiority vs ADA[a]	<0.001	0.006		
% (95% CI), week 52	29.5 (25.3–33.7)	24.2 (20.2–28.1)	22.8 (18.1–27.5)	N/A
Treatment difference vs ADA (95% CI)	6.7 (0.3–13.1)	1.4 (−4.8 to 7.6)		
Exploratory p vs ADA	0.028	0.62		
SDAI ≤3.3				
% (95% CI), week 12	12.8 (9.7–16.0)	9.4 (6.7–12.1)	6.8 (3.9–9.7)	2.9 (1.3–4.6)

Treatment difference vs PBO (95% CI)	9.9 (6.3–13.5)	6.4 (3.2–9.7)		
Exploratory p vs PBO	<0.001	<0.001		
% (95% CI), week 24	23.2 (19.3–27.1)	17.5 (14.0–21.0)	16.9 (12.7–21.2)	7.2 (4.7–9.6)
Treatment difference vs PBO (95% CI)	16.0 (11.3–20.7)	10.3 (6.0–14.7)		
Exploratory p vs PBO	<0.001	<0.001		
% (95% CI), week 52	29.7 (25.5–33.9)	24.6 (20.6–28.5)	24.0 (19.2–28.8)	N/A
Treatment difference vs ADA (95% CI)	5.7 (−0.8 to 12.1)	0.6 (−5.7 to 6.9)		
Exploratory p vs ADA	0.064	0.82		
Boolean remission				
% (95% CI), week 12	9.5 (6.7–12.2)	6.5 (4.2–8.8)	5.2 (2.7–7.8)	1.9 (0.6–3.2)
Treatment difference vs PBO (95% CI)	7.6 (4.5–10.7)	4.6 (1.8–7.3)		
Exploratory p vs PBO	<0.001	<0.001		
% (95% CI), week 24	18.5 (14.9–22.1)	13.8 (10.6–16.9)	13.2 (9.4–17.1)	4.8 (2.8–6.9)
Treatment difference vs PBO (95% CI)	13.7 (9.5–17.9)	8.9 (5.1–12.8)		
Exploratory p vs PBO	<0.001	<0.001		
% (95% CI), week 52	22.5 (18.7–26.4)	19.2 (15.5–22.8)	16.9 (12.7–21.2)	N/A
Treatment difference vs ADA (95% CI)	5.6 (−0.2 to 11.4)	2.2 (−3.4 to 7.9)		
Exploratory p vs ADA	0.044	0.38		

Comparisons vs ADA were for superiority unless otherwise indicated.

[a]Post hoc exploratory analysis.

ACR20, 20% improvement from baseline in American College of Rheumatology core criteria; ADA, adalimumab; CDAI, Clinical Disease Activity Index; CI, confidence interval; DAS28(CRP), Disease Activity Score in 28 joints with C-reactive protein; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FIL100, filgotinib 100 mg; FIL200, filgotinib 200 mg; HAQ-DI, Health Assessment Questionnaire-Disability Index; LSM, least squares mean; N/A, not applicable; PBO, placebo; SD, standard deviation; SDAI, Simplified Disease Activity Index; SF-36 PCS, Short Form-36 Physical Component Summary.

Table S4. Radiographic progression from baseline through week 52

	FIL200 (n = 475)	FIL100 (n = 480)	ADA (n = 325)	PBO (n = 475)
Campaign A				
Patients evaluated, n				
Baseline	467	471	319	466
Change from baseline at week 12	426	438	282	408
Change from baseline at week 24	405	404	271	351
mTSS				
Baseline, mean ± SD	32.5 ± 48.0	36.7 ± 53.1	34.8 ± 55.0	31.6 ± 53.2
Change from baseline at week 12, LSM ± SE	0.08 ± 0.08	0.12 ± 0.08	0.13 ± 0.09	0.25 ± 0.09
Treatment difference vs PBO, LSM (95% CI)	−0.18 (−0.30 to −0.06)	−0.14 (−0.25 to −0.02)		
Exploratory p vs PBO	0.004	0.026		
Change from baseline at week 24, LSM ± SE	0.13 ± 0.09	0.15 ± 0.09	0.19 ± 0.10	0.40 ± 0.09
Treatment difference vs PBO, LSM (95% CI)	−0.27 (−0.43 to −0.12)	−0.25 (−0.40 to −0.10)		
p vs PBO	<0.001	0.001		
Treatment difference vs ADA, LSM (95% CI)	−0.05 (−0.22 to 0.12)	−0.03 (−0.20 to 0.14)		
Exploratory p vs ADA	0.54	0.71		
Erosion score				
Baseline, mean ± SD	13.9 ± 24.2	16.8 ± 27.3	15.2 ± 28.7	14.0 ± 28.1
Change from baseline at week 12, LSM ± SE	0.03 ± 0.05	0.05 ± 0.05	0.05 ± 0.05	0.14 ± 0.05
Treatment difference vs PBO, LSM (95% CI)	−0.11 (−0.18 to −0.05)	−0.10 (−0.16 to −0.03)		
Exploratory p vs PBO	<0.001	0.004		
Change from baseline at week 24, LSM ± SE	0.03 ± 0.05	0.06 ± 0.05	0.06 ± 0.06	0.22 ± 0.05
Treatment difference vs PBO, LSM (95% CI)	−0.19 (−0.27 to −0.10)	−0.16 (−0.24 to −0.07)		
Exploratory p vs PBO	<0.001	<0.001		
Joint space narrowing				
Baseline, mean ± SD	18.5 ± 25.6	19.9 ± 27.3	19.6 ± 28.2	17.6 ± 26.9
Change from baseline at week 12, LSM ± SE	0.05 ± 0.06	0.07 ± 0.06	0.09 ± 0.06	0.11 ± 0.06
Treatment difference vs PBO, LSM (95% CI)	−0.06 (−0.15 to 0.02)	−0.04 (−0.12 to 0.04)		
Exploratory p vs PBO	0.14	0.36		
Change from baseline at week 24, LSM ± SE	0.10 ± 0.06	0.09 ± 0.06	0.12 ± 0.07	0.19 ± 0.07
Treatment difference vs PBO, LSM (95% CI)	−0.09 (−0.19 to 0.02)	−0.09 (−0.20 to 0.01)		
Exploratory p vs PBO	0.11	0.078		

Combined Campaign A and Campaign B				
Patients evaluated at week 52, n[a]	417	411	273	N/A
mTSS				
Change from baseline at week 24, LSM ± SE	0.10 ± 0.10	0.19 ± 0.10	0.17 ± 0.11	0.49 ± 0.10
Treatment difference vs PBO, LSM (95% CI)	−0.39 (−0.54 to −0.24)	−0.30 (−0.45 to −0.15)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−0.07 (−0.23 to 0.09)	0.02 (−0.14 to 0.18)		
Exploratory p vs ADA	0.40	0.80		
Change from baseline at week 52, LSM ± SE	0.18 ± 0.12	0.45 ± 0.12	0.61 ± 0.13	N/A
Treatment difference vs ADA, LSM (95% CI)	−0.43 (−0.66 to −0.20)	−0.15 (−0.38 to 0.08)		
Exploratory p vs ADA	<0.001	0.19		
Erosion score				
Change from baseline at week 24, LSM ± SE	0.04 ± 0.06	0.08 ± 0.06	0.06 ± 0.06	0.27 ± 0.06
Treatment difference vs PBO, LSM (95% CI)	−0.22 (−0.31 to −0.14)	−0.18 (−0.27 to −0.10)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−0.01 (−0.11 to 0.08)	0.03 (−0.07 to 0.12)		
Exploratory p vs ADA	0.76	0.57		
Change from baseline at week 52, LSM ± SE	0.06 ± 0.07	0.19 ± 0.07	0.28 ± 0.08	N/A
Treatment difference vs ADA, LSM (95% CI)	−0.22 (−0.35 to −0.09)	−0.09 (−0.23 to 0.04)		
Exploratory p vs ADA	0.001	0.18		
Joint space narrowing				
Change from baseline at week 24, LSM ± SE	0.06 ± 0.06	0.11 ± 0.06	0.11 ± 0.07	0.23 ± 0.07
Treatment difference vs PBO, LSM (95% CI)	−0.17 (−0.26 to −0.08)	−0.12 (−0.22 to −0.03)		
Exploratory p vs PBO	<0.001	0.012		
Treatment difference vs ADA, LSM (95% CI)	−0.05 (−0.16 to 0.05)	−0.01 (−0.11 to 0.10)		
Exploratory p vs ADA	0.29	0.90		
Change from baseline at week 52, LSM ± SE	0.12 ± 0.07	0.26 ± 0.07	0.32 ± 0.08	N/A
Treatment difference vs ADA, LSM (95% CI)	−0.21 (−0.34 to −0.07)	−0.06 (−0.19 to 0.07)		
Exploratory p vs ADA	0.002	0.36		

[a]Patient numbers are not reported for the combined analyses due to the change from baseline including both Campaign A and Campaign B.
ADA, adalimumab; CI, confidence interval; FIL100, filgotinib 100 mg; FIL200, filgotinib 200 mg; LSM, least squares mean; mTSS, van der Heijde modified total Sharp score; N/A, not applicable; PBO, placebo; SD, standard deviation; SE, standard error.

Table S5. Change from baseline in other ACR and DAS28(CRP) core measure components at weeks 12, 24, and 52

	FIL200 (n = 475)	FIL100 (n = 480)	ADA (n = 325)	PBO (n = 475)
TJC68				
Week 12				
N	458	458	311	435
Mean ± SD	−17 ± 11.1	−15 ± 10.7	−15 ± 9.9	−13 ± 11.6
Treatment difference vs PBO, LSM (95% CI)	−4 (−5 to −2)	−3 (−4 to −1)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−1 (−3 to −0)	−0 (−2 to 1)		
Exploratory p vs ADA	0.015	0.47		
Week 24				
N	418	423	283	375
Mean ± SD	−20 ± 12.1	−19 ± 10.9	−18 ± 11.1	−17 ± 11.7
Treatment difference vs PBO, LSM (95% CI)	−3 (−4 to −2)	−2 (−3 to −1)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−2 (−3 to −1)	−1 (−2 to 0)		
Exploratory p vs ADA	0.001	0.16		
Week 52				
N	400	397	265	
Mean ± SD	−21 ± 12.2	−21 ± 11.4	−20 ± 11.4	
Treatment difference vs ADA, LSM (95% CI)	−1 (−2 to −0)	−0 (−1 to 1)		
Exploratory p vs ADA	0.015	0.68		
TJC28				
Week 12				
N	458	458	311	435
Mean ± SD	−10 ± 6.4	−9 ± 6.2	−9 ± 5.7	−8 ± 6.7
Treatment difference vs PBO, LSM (95% CI)	−2 (−3 to −2)	−1 (−2 to −1)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−1 (−2 to −0)	−0 (−1 to 1)		
Exploratory p vs ADA	0.026	0.83		
Week 24				
N	418	423	283	375
Mean ± SD	−12 ± 6.2	−12 ± 6.1	−11 ± 6.1	−11 ± 6.2
Treatment difference vs PBO, LSM (95% CI)	−2 (−3 to −2)	−2 (−2 to −1)		

Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−1 (−2 to −0)	−0 (−1 to 0)		
Exploratory p vs ADA	0.002	0.19		
Week 52				
N	400	397	265	
Mean ± SD	−13 ± 6.0	−12 ± 6.0	−12 ± 5.8	
Treatment difference vs ADA, LSM (95% CI)	−1 (−1 to −0)	−0 (−0 to 0)		
Exploratory p vs ADA	0.012	0.99		
SJC66				
Week 12				
N	458	458	311	435
Mean ± SD	−11 ± 7.5	−11 ± 8.1	−11 ± 7.1	−10 ± 8.4
Treatment difference vs PBO, LSM (95% CI)	−2 (−3 to −1)	−2 (−2 to −1)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−1 (−2 to 0)	−0 (−1 to 0)		
Exploratory p vs ADA	0.060	0.38		
Week 24				
N	418	423	283	375
Mean ± SD	−13 ± 7.8	−13 ± 7.4	−13 ± 6.9	−12 ± 7.7
Treatment difference vs PBO, LSM (95% CI)	−2 (−3 to −1)	−1 (−2 to −1)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−1 (−2 to −0)	−0 (−1 to 0)		
Exploratory p vs ADA	0.004	0.52		
Week 52				
N	400	397	265	
Mean ± SD	−14 ± 8.1	−13 ± 7.6	−14 ± 7.5	
Treatment difference vs ADA, LSM (95% CI)	−1 (−1 to −0)	−0 (−1 to 0)		
Exploratory p vs ADA	0.018	0.60		
SJC28				
Week 12				
N	458	458	311	435
Mean ± SD	−8 ± 5.2	−8 ± 5.4	−8 ± 4.9	−7 ± 5.5
Treatment difference vs PBO, LSM (95% CI)	−2 (−2 to −1)	−1 (−2 to −1)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−0 (−1 to 0)	−0 (−1 to 0)		
Exploratory p vs ADA	0.088	0.60		

Week 24				
N	418	423	283	375
Mean ± SD	−10 ± 5.0	−9 ± 5.0	−9 ± 4.7	−8 ± 5.2
Treatment difference vs PBO, LSM (95% CI)	−2 (−2 to −1)	−1 (−1 to −1)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−1 (−1 to −0)	−0 (−1 to 0)		
Exploratory p vs ADA	0.001	0.71		
Week 52				
N	400	397	265	
Mean ± SD	−10 ± 5.1	−9 ± 5.0	−10 ± 4.7	
Treatment difference vs ADA, LSM (95% CI)	−0 (−1 to −0)	−0 (−0 to 0)		
Exploratory p vs ADA	0.010	0.68		
SGA, mm				
Week 12				
N	457	458	311	435
Mean ± SD	−33 ± 24.8	−28 ± 24.7	−28 ± 23.2	−21 ± 24.8
Treatment difference vs PBO, LSM (95% CI)	−13 (−16 to −10)	−10 (−12 to −7)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−5 (−8 to −1)	−1 (−4 to 2)		
Exploratory p vs ADA	0.005	0.43		
Week 24				
N	418	423	283	376
Mean ± SD	−39 ± 25.8	−36 ± 24.9	−36 ± 24.9	−31 ± 26.9
Treatment difference vs PBO, LSM (95% CI)	−11 (−14 to −7)	−8 (−11 to −5)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−3 (−6 to 1)	−1 (−4 to 3)		
Exploratory p vs ADA	0.097	0.69		
Week 52				
N	400	398	265	
Mean ± SD	−44 ± 24.4	−41 ± 25.4	−42 ± 25.7	
Treatment difference vs ADA, LSM (95% CI)	−2 (−5 to 1)	1 (−3 to 4)		
Exploratory p vs ADA	0.28	0.75		
PGA, mm				
Week 12				
N	457	450	308	433
Mean ± SD	−41 ± 20.2	−39 ± 20.3	−39 ± 20.4	−34 ± 22.4

Treatment difference vs PBO, LSM (95% CI)	−8 (−10 to −6)	−7 (−10 to −5)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−3 (−5 to −0)	−2 (−5 to 1)		
Exploratory p vs ADA	0.030	0.14		
Week 24				
N	413	419	283	373
Mean ± SD	−48 ± 19.2	−46 ± 19.6	−47 ± 19.4	−42 ± 20.4
Treatment difference vs PBO, LSM (95% CI)	−8 (−11 to −6)	−7 (−10 to −5)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−2 (−4 to 0)	−1 (−3 to 1)		
Exploratory p vs ADA	0.11	0.43		
Week 52				
N	400	398	265	
Mean ± SD	−53 ± 18.2	−50 ± 19.2	−52 ± 18.9	
Treatment difference vs ADA, LSM (95% CI)	−1 (−3 to 1)	1 (−2 to 3)		
Exploratory p vs ADA	0.32	0.63		
Patient pain assessment, mm				
Week 12				
N	457	458	311	435
Mean ± SD	−31 ± 26.9	−29 ± 25.3	−27 ± 23.6	−21 ± 26.0
Treatment difference vs PBO, LSM (95% CI)	−12 (−15 to −9)	−10 (−13 to −7)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−4 (−7 to −1)	−2 (−5 to 2)		
Exploratory p vs ADA	0.018	0.32		
Week 24				
N	418	423	283	376
Mean ± SD	−38 ± 27.0	−37 ± 25.6	−35 ± 24.2	−30 ± 27.0
Treatment difference vs PBO, LSM (95% CI)	−11 (−14 to −7)	−9 (−12 to −6)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−3 (−6 to 1)	−2 (−5 to 2)		
Exploratory p vs ADA	0.096	0.35		
Week 52				
N	400	398	265	
Mean ± SD	−43 ± 26.2	−41 ± 25.9	−41 ± 25.6	
Treatment difference vs ADA, LSM (95% CI)	−2 (−5 to 2)	−0 (−4 to 3)		
Exploratory p vs ADA	0.31	0.83		

hsCRP, mg/L				
Week 12				
N	456	454	308	431
Mean ± SD	−11.0 ± 18.7	−9.6 ± 21.3	−7.8 ± 20.6	−3.3 ± 22.7
Treatment difference vs PBO, LSM (95% CI)	−8.0 (−9.9 to −6.1)	−6.5 (−8.3 to −4.6)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−1.8 (−3.8 to 0.3)	−0.2 (−2.3 to 1.9)		
Exploratory p vs ADA	0.094	0.84		
Week 24				
N	416	419	281	370
Mean ± SD	−11.8 ± 20.7	−10.5 ± 22.2	−6.2 ± 24.2	−4.0 ± 19.6
Treatment difference vs PBO, LSM (95% CI)	−7.9 (−9.9 to −5.9)	−6.6 (−8.6 to −4.6)		
Exploratory p vs PBO	<0.001	<0.001		
Treatment difference vs ADA, LSM (95% CI)	−4.5 (−6.6 to −2.3)	−3.2 (−5.3 to −1.0)		
Exploratory p vs ADA	<0.001	0.004		
Week 52				
N	396	386	259	
Mean ± SD	−12.2 ± 20.8	−11.3 ± 23.1	−9.6 ± 16.5	
Treatment difference vs ADA, LSM (95% CI)	−0.4 (−1.8 to 0.9)	0.8 (−0.5 to 2.2)		
Exploratory p vs ADA	0.53	0.23		

Missing change scores were not imputed.

Comparisons vs ADA were for superiority.

ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; DAS28(CRP), Disease Activity Score in 28 joints with C-reactive protein; FIL100, filgotinib 100 mg; FIL200, filgotinib 200 mg; hsCRP, high-sensitivity C-reactive protein; LSM, least squares mean; PBO, placebo; PGA, Physician Global Assessment; SD, standard deviation; SGA, Subject Global Assessment; SJC28, swollen joint count in 28 joints; SJC66, swollen joint count in 66 joints; TJC28, tender joint count in 28 joints; TJC68, tender joint count in 68 joints.

Table S6. Proportions of patients achieving ACR20 at week 12 by region grouped by standard of care

	FIL200	FIL100	ADA	PBO
Group A	77/108 (71.3)	66/104 (63.5)	46/73 (63.0)	39/105 (37.1)
Group B	199/259 (76.8)	193/267 (72.3)	132/175 (75.4)	146/261 (55.9)
Group C	40/48 (83.3)	37/50 (74.0)	28/35 (80.0)	29/49 (59.2)
Group D	17/20 (85.0)	12/18 (66.7)	8/14 (57.1)	9/22 (40.9)
Group E	31/40 (77.5)	27/41 (65.9)	15/28 (53.6)	14/38 (36.8)

Data shown as n/N (%).

Group A, United States of America, Australia, New Zealand, Republic of Korea, Belgium, Germany, Italy, United Kingdom, South Africa, Canada, Spain, Ireland, Israel, and The Netherlands; Group B, Bulgaria, Czech Republic, Hungary, Slovakia, India, Ukraine, Poland, Romania, Russia, and Serbia; Group C, Argentina and Mexico; Group D, Hong Kong, Thailand, and Taiwan; Group E, Japan.

See **Figure S2** for enrolment by country within each group.

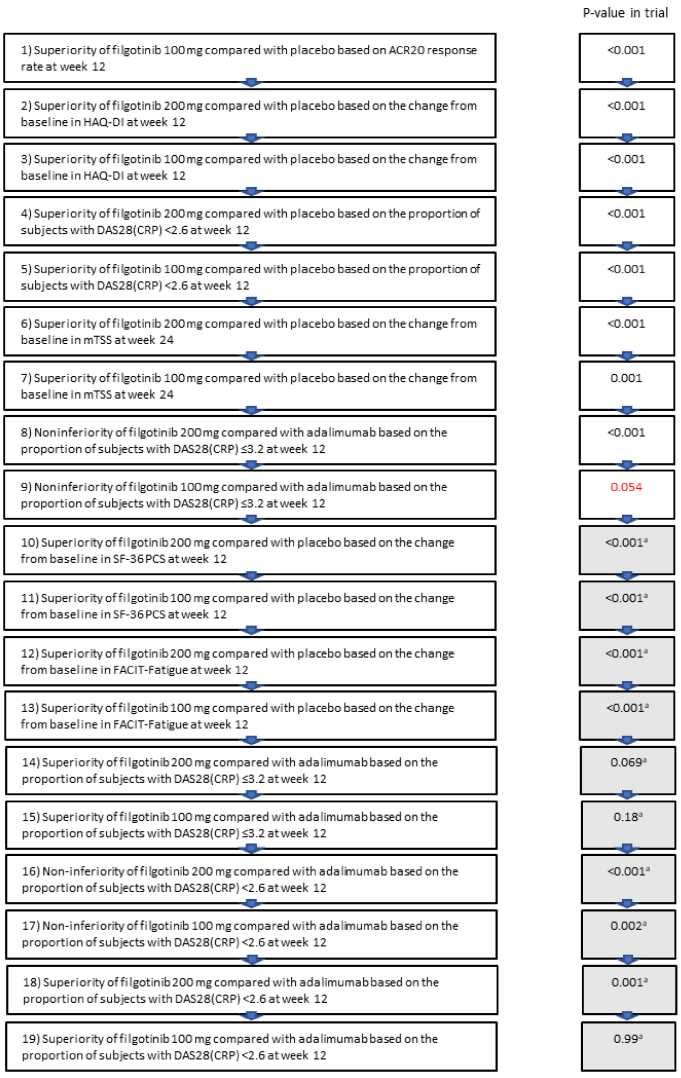
ACR20, 20% improvement from baseline by American College of Rheumatology core criteria; ADA, adalimumab; FIL100, filgotinib 100 mg; FIL200, filgotinib 200 mg; PBO, placebo.

Table S7. ACR20, ACR50, and ACR70 response rates from Figure 2

	FIL200 (n = 475)			FIL100 (n = 480)			ADA (n = 325)			PBO (n = 475)		
Week	**ACR20**	**ACR50**	**ACR70**	**ACR20**	**ACR50**	**ACR70**	**ACR20**	**ACR50**	**ACR70**	**ACR20**	**ACR50**	**ACR70**
2	37.3	9.1	2.7	27.5	5.8	1.3	33.5	6.8	0.9	14.9	1.1	0.4
4	51.6	22.3	9.1	45.6	12.9	3.3	47.1	17.2	3.7	31.8	5.9	1.5
8	69.7	35.6	17.3	63.3	26.9	11.5	61.2	27.7	11.7	42.5	16.8	4.4
12	76.6	47.2	26.1	69.8	36.5	18.5	70.5	35.1	14.2	49.9	19.8	6.7
14	81.5	52.8	32.4	76.9	46.7	23.3	73.5	44.6	21.2	62.1	27.8	10.3
16	80.2	55.4	33.9	76.7	49.2	25.2	72.9	45.5	22.8	60.4	30.7	12.4
20	81.5	55.6	34.1	77.7	50.8	26	73.5	51.4	25.2	59.4	33.7	12.8
24	78.1	57.9	36.2	77.7	52.7	29.6	74.5	52.3	29.5	59.2	33.3	14.9
26	77.9	59.8	38.1	75.8	52.9	29.4	74.2	54.8	31.1			
30	80.2	60.4	38.7	77.5	55.6	32.1	74.2	54.8	32			
36	79.6	61.3	39.8	76.5	56.5	34.4	73.8	56.3	32			
44	79.4	62.1	42.1	77.7	57.1	35.8	71.7	56	39.1			
52	78.3	62.3	44.2	75.6	58.5	37.5	73.5	59.1	39.4			

ACR20/50/70, 20%/50%/70% improvement from baseline based on American College of Rheumatology Criteria; ADA, adalimumab; FIL100, filgotinib 100 mg; FIL200, filgotinib 200 mg; PBO, placebo.

Figure S1. Hierarchical testing of secondary endpoints



First non-significant result shown in red. Subsequent results not adjusted for multiplicity are shaded gray.

[a]Exploratory p value.

ACR20, 20% improvement from baseline in American College of Rheumatology core criteria; DAS28(CRP), Disease Activity Score in 28 joints with C-reactive protein; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire-Disability Index; mTSS, van der Heijde modified total Sharp score; SF-36, Short Form-36 Physical Component Summary.

Figure S2. Treated patients by country of enrollment and group

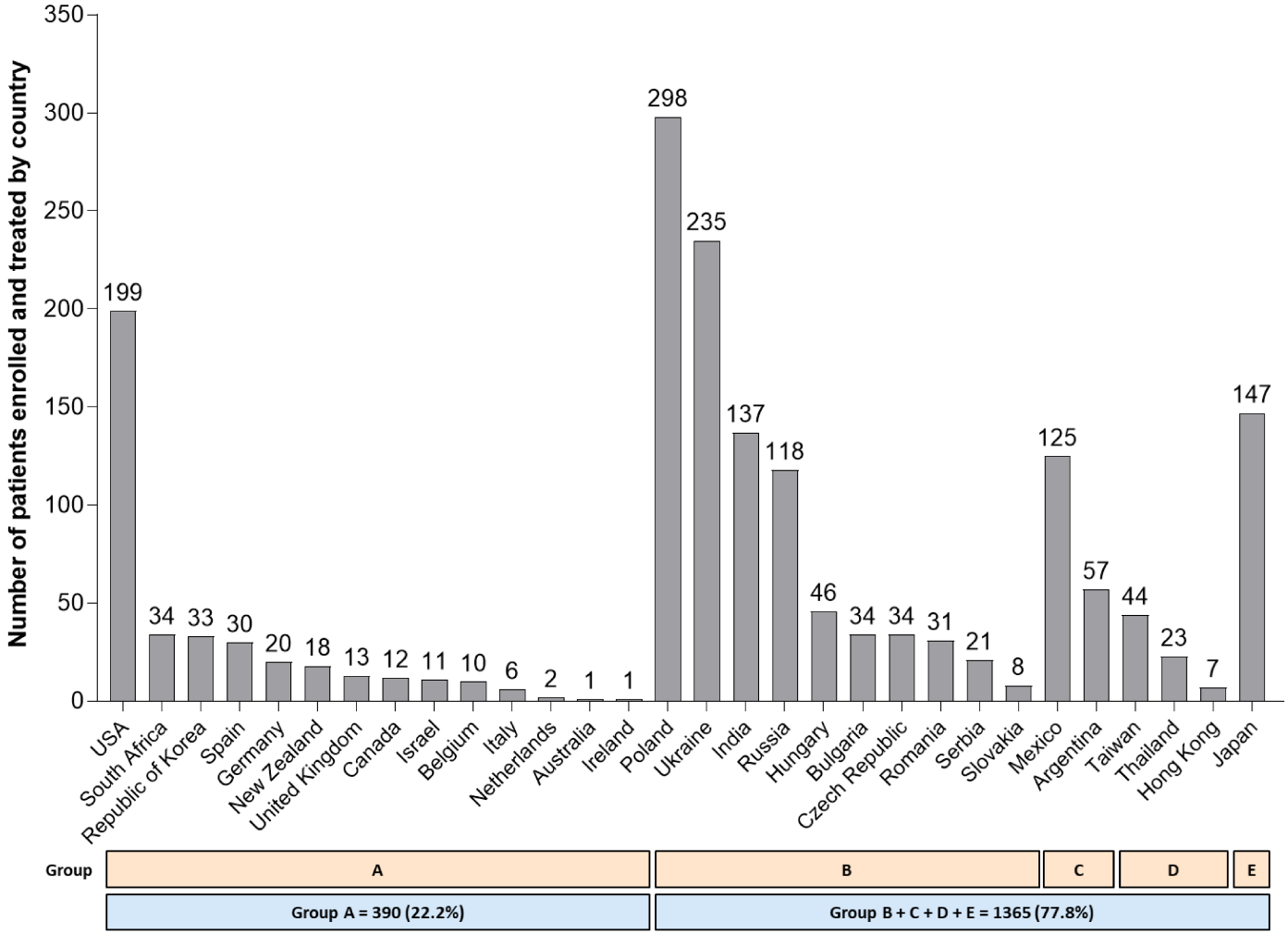
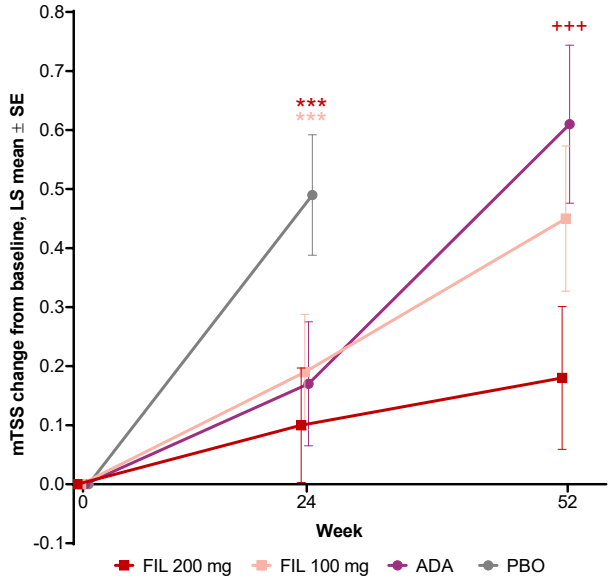
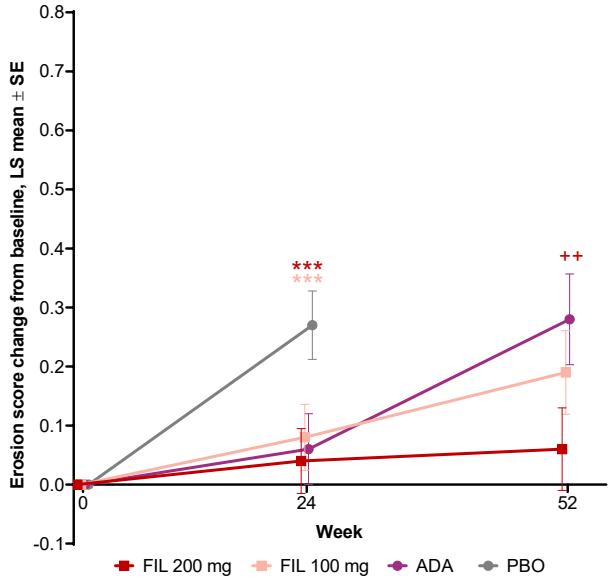


Figure S3. Radiographic progression through week 52. **A)** mTSS change from baseline, **B)** erosion score change from baseline, and **C)** joint space narrowing change from baseline

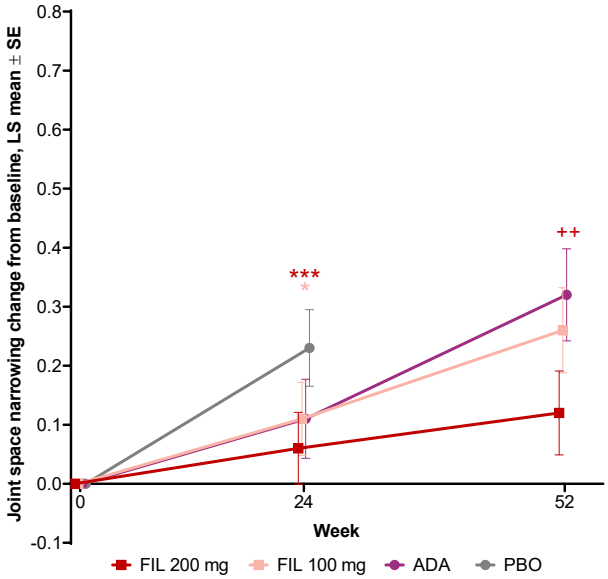
A)



B)



C)



Combined data from Campaign A (through week 24) and Campaign B (through week 52 including rereading of baseline and week 24) are shown. Supporting values are shown in **Table S4**.

Error bars represent the SE of the LS mean.

*Exploratory p <0.05, ***exploratory p <0.001 vs PBO.

++Exploratory p <0.01, +++exploratory p <0.001 vs ADA.

ADA, adalimumab; FIL, filgotinib; LS, least-squares; mTSS, van der Heijde modified total Sharp score; PBO, placebo; SE, standard error.