	Filgotinib (n=65)	Placebo (n=66)
Mean age, years	49 (12·2)	50 (10·9)
Sex		
Female	36 (55%)	30 (45%)
Male	29 (45%)	36 (55%)
Mean weight, kg	81 (19·0)	87 (17·5)
Mean body-mass index, kg/m²	28·6 (6·8)	30·1 (5·7)
Mean duration of psoriatic arthritis, years	7 (6·7)	7 (6·2)
Tender joint count 68 score	18·3 (9·2)	21·6 (13·2)
Swollen joint count 66 score	11·6 (5·1)	12·7 (6·7)
Mean Health Assessment Questionnaire-Disability Index score	1·43 (0·5)	1·36 (0·6)
Mean hsCRP, mg/L	13·9 (19·8)	10·9 (17·2)
hsCRP ≥10 mg/L	25 (38%)	17 (26%)
At least 3% body surface area of psoriasis	42 (65%)	40 (61%)
Median PASI*	6·5 (2·6–15·0)	6·9 (3·8–18·6)
Mean PASDAS	6·1 (0·8)	6·2 (1·0)
Mean DAPSA score	44·0 (14·3)	47·8 (19·8)
Enthesitis based on SPARCC Enthesitis Index	37 (57%)	48 (73%)
Mean SPARCC Enthesitis Index score†	4·9 (3·0)	5·5 (3·8)
Enthesitis based on Leeds Enthesitis Index	38 (58%)	49 (74%)
Mean Leeds Enthesitis Index score‡	2·8 (1·4)	2·6 (1·4)
Prior anti-TNF therapy§	11 (17%)	9 (14%)
Concurrent use of csDMARD	47 (72%)	50 (76%)
Leflunomide	2 (3%)	4 (6%)
Sulfasalazine	3 (5%)	3 (5%)
Methotrexate (oral)	36 (55%)	35 (53%)
Mean methotrexate dose (oral)	1·9 (0·6)	2·3 (0·7)
Methotrexate (subcutaneous)	5 (8%)	8 (12%)
Mean methotrexate dose (subcutaneous)	2·9 (0·9)	2·4 (0·8)
Concurrent use of steriods	17 (26%)	16 (24%)
Prednisolone-equivalent dose (oral)	7·8 (2·5)	5·9 (2·6)

Data are mean (SD), n (%), or median (IQR). csDMARD=conventional synthetic disease-modifying anti-rheumatic drug. DAPSA=Disease Activity Index for Psoriatic Arthritis. hsCRP=highly-sensitive C-reactive protein. PASDAS=Psoriatic Arthritis Disease Activity Score. PASI=Psoriasis Area and Severity Index. SPARCC=Spondyloarthritis Research Consortium of Canada. TNF=tumour necrosis factor. *Full analysis set with baseline body surface area of at least 3%. †Full analysis set with enthesitis at baseline (SPARCC Enthesitis Index >0). ‡Full analysis set with enthesitis at baseline (Leeds Enthesitis Index >0). §Patients might have stopped treatment with anti-TNF medication because of an insufficient response, adverse events, or financial constraints.

Table 1: **Baseline patient and disease characteristics (full analysis set)**

(Gilead Sciences, Foster City, CA, USA) or matching placebo orally once daily for 16 weeks (appendix p 12). Randomisation was stratified by current use of csDMARDs (yes or no) and prior anti-TNF therapy (yes [capped at 30% of enrolled patients] or no). The patient, study team (ie, site staff and investigators), and the sponsor were blinded to treatment assignment.

Procedures

Screening was performed within 4 weeks before randomisation. Assessments were done at baseline (day 1), at weeks 1, 2, 4, 8, 12, and 16, and at a follow-up visit at week 20. Efficacy assessments included swollen and tender joint counts, Physician's Global Assessment of Disease Activity, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Psoriasis, Patient's Global Assessment of Psoriasis, Psoriasis Area and Severity Index (PASI), enthesitis (in patients with enthesitis at baseline), dactylitis, modified Nail Psoriasis Severity Index (in patients with psoriatic nail involvement at baseline), pruritus numeric rating scale, Health Assessment Questionnaire-Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy–Fatigue, and Patient's Global Assessment of psoriatic arthritis Pain Intensity (appendix p 13). PASI and pruritus was assessed in patients with at least 3% body surface area affected at baseline. Data on dactylitis were not analysed because blinded data review showed that it was not scored uniformly across all centres. Full details of study assessments are given in the appendix (p 13).

Outcomes

The primary endpoint was the proportion of patients achieving ACR20 response at week 16 in the full analysis set (patients who received at least one dose of study drug). Secondary endpoints included ACR50 and ACR70 response rates; changes over time (baseline to week 16) in ACR20, ACR50, and ACR70 response rates; change from baseline in Disease Activity Score in 28 joints (DAS28)(C-reactive protein [CRP]); Psoriatic Arthritis Response Criteria (PsARC) response rates; proportion of patients achieving minimal disease activity; change from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index; proportion of patients achieving a 75% reduction in PASI (PASI75); change from baseline in modified Nail Psoriasis Severity Index and pruritus numeric rating scale; and change from baseline in the HAQ-DI, Functional Assessment of Chronic Illness Therapy–Fatigue questionnaires, and patient-reported intensity of psoriatic arthritis-related pain. Results for HAQ-DI, fatigue, and psoriatic arthritis-related pain are presented here; data for other patient-reported outcomes will be published separately. A full list of secondary endpoints is given in the appendix (p 14). The safety and tolerability of filgotinib were assessed by the incidence of treatment-emergent adverse events, treatment-emergent adverse events of special interest (infection, malignancies, and major adverse cardiovascular events), serious treatment-emergent adverse events, discontinuations due to treatment-emergent adverse events, ECG, physical examination findings, body weight, vital signs, and changes in laboratory results.

Additional exploratory endpoints included change from baseline at week 16 in Disease Activity in psoriatic arthritis (DAPSA) score to measure peripheral arthritis, psoriatic arthritis Disease Activity Score (PASDAS) to measure overall psoriatic arthritis disease, and assessment of enthesitis based on the change from baseline in Leeds Enthesitis Index (appendix p 61). These endpoints were added to the statistical analysis plan (appendix p 153) after the trial started, and before data were unblinded,

because all the necessary components and assessments were included in the trial design.

Statistical analysis

We calculated that a sample size of 124 would have 80% power to show efficacy of filgotinib compared with placebo for the primary endpoint. This calculation was done using a χ^2 test with continuity correction at a 5% two-sided significance level, assuming the proportion of patients with responses at week 16 were 45% in the filgotinib group and 20% in the placebo group.

For the primary endpoint (and other binary endpoints reported as proportion of patients), we compared proportions of participants between treatment groups using the Cochran–Mantel–Haenszel test, controlling for randomisation stratification factors. The proportion of participants who responded to treatment in each treatment group was summarised with a point estimate and 95% CI. We used the Newcombe method to calculate differences in the proportions of participants between the treatment groups, summarised with a point estimate and 95% CI. We analysed changes from baseline in continuous endpoints using an analysis of covariance model with treatment, baseline value, and randomisation stratification factors as fixed effects. Corresponding analysis of covariance models were used to produce adjusted least squares means and 95% CIs for measures of efficacy within each treatment group and differences between treatment groups. We used the non-responder imputation method for missing data for binary endpoints (including the primary endpoint). For analysis of continuous endpoints, we imputed missing values imputed using the last observation carried forward method. We also did sensitivity analyses of the primary endpoint using the observed cases and last observation carried forward imputation methods. The analysis of ACR20 and ACR50 response rates in patients who received concomitant therapy with csDMARDs was not prespecified and, as such, 95% CIs and p values are not available. All efficacy and safety analyses were done on the full analysis set (patients who received at least one dose of study drug). We used SAS software (version 9.4; SAS Institute, Cary, NC, USA) for all statistical analyses. This trial was registered with ClinicalTrials.gov, number NCT03101670.

Role of the funding source

The study sponsor supervised study design, study execution, data collection, statistical analyses, data interpretation, and the writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 9, and Sept 27, 2017, 191 patients were screened, of whom 131 were enrolled and randomly assigned to receive filgotinib 200 mg (n=65) or placebo (n=66) once daily. 60 (92%) patients in the filgotinib group and 64 (97%) patients in the placebo group completed the study; five patients (8%) in the filgotinib group and two patients (3%) in the placebo group discontinued treatment (figure 1). Baseline characteristics were similar between the two groups (table 1). 97 [74%] of 131 patients received concomitant therapy with csDMARDs at baseline and during the study, meaning that 34 (26%) patients received filgotinib or placebo as monotherapy (table 1). Mean on-treatment adherence was 99·7% (SD 6·3) for filgotinib and 99·9% (10·5) for placebo.

52 (80%) of 65 patients in the filgotinib group and 22 (33%) of 66 patients in the placebo group had an ACR20 response at week 16 (figure 2), with a treatment difference of 47% (95% CI 30·2–59·6, p<0·0001; table 2). Sensitivity analyses of the primary endpoint using observed cases and last observation carried forward imputation methods were consistent with those from the primary non-responder imputation analysis (table 2). In patients who had not previously had anti-TNF therapy, 42 (78%) of 54 patients in the filgotinib group and 20 (35%) of 57 patients in the placebo group had ACR20 responses.

More patients treated with filgotinib than with placebo achieved ACR50 (treatment difference 33% [95% CI 16·8–46·2]; p<0·0001) and ACR70 responses (treatment

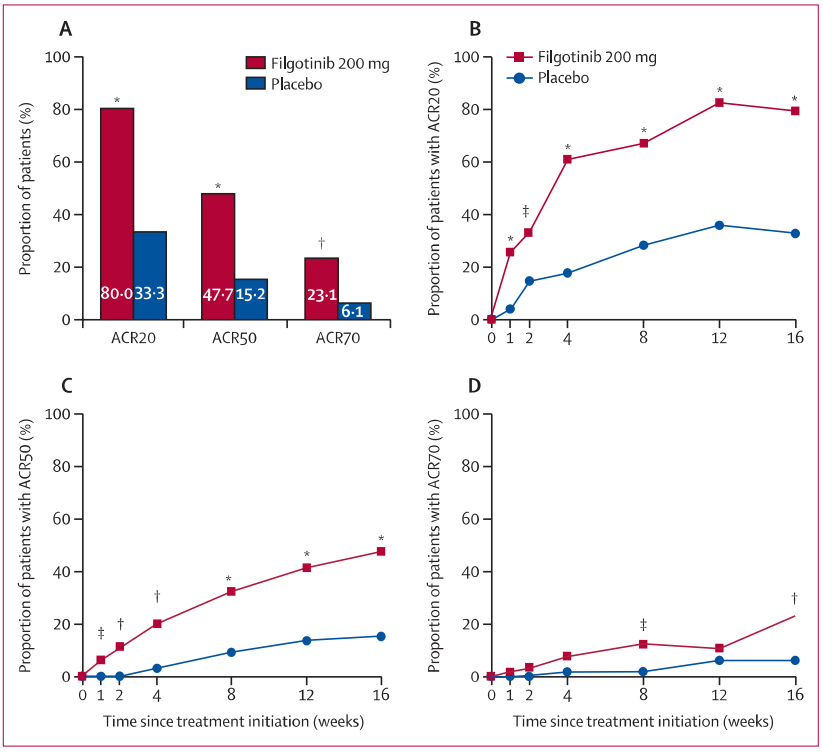

Figure 2: **ACR responses (non-responder imputation; full analysis set)**
n=65 (filgotinib) and n=66 (placebo). ACR20=20% improvement in the American College of Rheumatology response criteria. ACR50=50% improvement in the American College of Rheumatology response criteria. ACR70=70% improvement in the American College of Rheumatology response criteria. *p<0·001. †p<0·005. ‡p<0·05.

	Filgotinib (n=65)		Placebo (n=66)		Treatment difference		
	Response rate	95% CI	Response rate	95% CI	Response rate (%)	95% CI	p value*
Non-responder imputation	52 (80%) of 65	68·7–87·9	22 (33%) of 66	23·2–45·3	47%	30·2–59·6	p<0·0001
Last observation carried forward	54 (83%) of 65	72·2–90·3	22 (33%) of 66	23·2–45·3	50%	33·5–62·2	p<0·0001
Observed cases	52 (87%) of 60	75·8–93·1	22 (34%) of 64	23·9–46·6	52%	36·0–64·6	p<0·0001

Data are n (%) unless otherwise stated. ACR20=20% improvement in the American College of Rheumatology response criteria. *Calculated with the Cochran-Mantel-Haenszel test for general association, controlling for randomisation stratification factors.

Table 2: **Primary and sensitivity analyses of ACR20 response at week 16, by imputation method (full analysis set)**

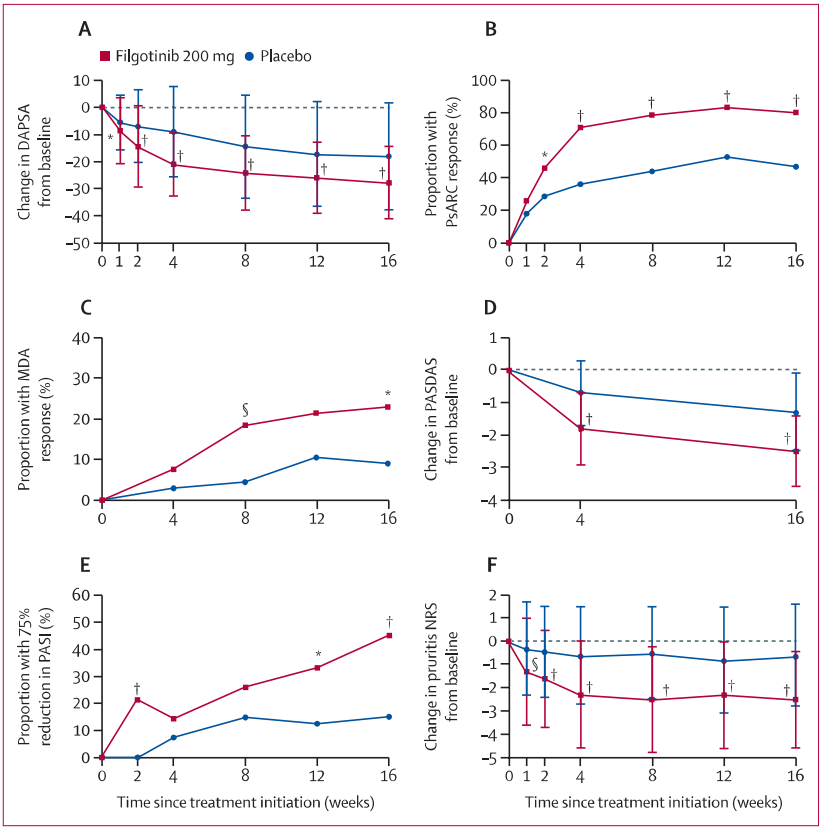

Figure 3: **Secondary outcomes up to week 16 (full analysis set)**
Data are mean, with SD error bars (panels A, D, and F; last observation carried forward) or proportion of patients (panels B, C and E; non-responder imputation); n=65 (filgotinib) and 66 (placebo). 75% reduction in PASI and pruritus NRS were only assessed in patients with at least 3% of their body surface area covered with psoriasis at baseline (filgotinib, n=42; placebo, n=40). DAPSA=Disease Activity in Psoriatic Arthritis. MDA=minimal disease activity. NRS=numerical rating scale. PASDAS=Psoriatic Arthritis Disease Activity Score. PASI=Psoriasis Area and Severity Index. PsARC=Psoriatic Arthritis Response Criteria. *p<0·05. †p<0·005. §p<0·01.

difference 17% [4·9–29·2]; p=0·0037) at week 16 (figure 2). ACR20 and ACR50 response rates starting at week 1 (the earliest timepoint measured) differed between the filgotinib and placebo groups (ACR20 p=0·0003, ACR50 p=0·0365; figure 2). In patients who received concomitant therapy with csDMARDs at baseline and throughout the study, ACR20 and ACR50 response rates at week 16 differed between the filgotinib and placebo groups (ACR20: 38 [81%] of 47 *vs* 16 [32%] of 50, treatment difference 49%; ACR50: 26 [55%] of 47 *vs* six [12%] of 50, treatment difference 43%).

The mean change from baseline in DAPSA score at week 16 was –27·9 (SD 13·6) for filgotinib and –18·1 (19·9) for placebo (least square [LS] mean difference –12·5 [95% CI –17·0 to –8·0, p<0·0001; figure 3A). 32 (49%) of 65 patients receiving filgotinib and ten (15%) of 66 patients receiving placebo achieved remission or low disease activity (DAPSA ≤14; treatment difference 34% [95% CI 18·3–47·7]; p<0·0001); seven (11%) patients on filgotinib and two (3%) patients on placebo achieved remission (DAPSA ≤4; treatment difference 8% [95% CI –1·4 to 17·8]; p=0·0678). A greater mean change from baseline in DAS28(CRP) was seen in patients treated with filgotinib compared with placebo at week 16 (–2·0 [SD 0·9] *vs* –0·9 [1·1]; LS mean difference –1·1 [95% CI –1·5 to –0·8], p<0·0001; appendix p 17).

The proportion of patients with PsARC response was higher in the filgotinib group than in the placebo group (52 [80·0%] of 65 *vs* 31 [47·0%] of 66; treatment difference 33% [95% CI 16·7 to 47·0], p<0·0001; figure 3B, appendix p 16).

Filgotinib improved the overall control of psoriatic arthritis, with more patients achieving minimal disease activity at week 16 in the filgotinib group than in the placebo group (treatment difference 14% [95% CI 1·3–26·5], p=0·0212; figure 3C). In addition, the mean change from baseline in PASDAS at week 16 was higher for the filgotinib group than for placebo (LS mean difference –1·3 [95% CI –1·7 to –0·9], p<0·0001; figure 3D). 24 (37%) of 65 patients who received filgotinib and six (9%) of 66 patients who received placebo had low disease activity (PASDAS ≤3·2) at week 16 (treatment difference 28% [95% CI 13·6–40·9]; p<0·0001).

The signs and symptoms of psoriasis improved in patients treated with filgotinib compared with those receiving placebo (assessed by PASI75). Of the 82 (62%) patients with 3% of their body surface area covered by psoriasis at baseline, more patients on filgotinib than on placebo had a reduction in PASI75 by week 16 (treatment difference 30% [95% CI 10·4–47·0], p=0·0034; figure 3E). Filgotinib improved the pruritic component of psoriasis (assessed via pruritus numeric rating scale) (LS mean difference –2·2 [95% CI –3·1 to –1·4], p<0·0001; figure 3F). 21 (58%) of 36 participants in the filgotinib group and eight (22%) of

36 in the placebo group had an improvement in pruritus numeric rating scale of at least 3 points (treatment difference 36% [95% CI 13·5–54·0], p=0·0022). Of the 90 (69%) patients with nail involvement (modified Nail Psoriasis Severity Index >0) at baseline, seven (16%) of 44 in the filgotinib group and three (7%) of 46 in the placebo group had complete resolution of all nail symptoms at week 16, although the difference was not significant (treatment difference 9% [95% CI –4·2 to 23·5]; p=0·2573).

Filgotinib improved enthesitis compared with placebo. Of the 85 (65%) patients with enthesitis at baseline (per SPARCC Enthesitis Index), the mean change from baseline at week 16 was greater for filgotinib compared with placebo (LS mean difference –1·4 [95% CI –2·6 to –0·1], p=0·0310; figure 4A). Resolution of enthesitis did not differ between the two groups (treatment difference 12% [–6·8 to 31·0], p=0·1583; figure 4B). When assessed according to Leeds Enthesitis Index in an exploratory analysis, 76 (58%) patients had enthesitis at baseline. In this population, the mean change from baseline at week 16 was greater for filgotinib than for placebo (LS mean difference –1·1 [95% CI –1·7 to –0·5], p=0·0004; figure 4C), and enthesitis was resolved in more patients who received filgotinib than received placebo (treatment difference 26% [95% CI 4·0–45·1], p=0·0089; figure 4D).

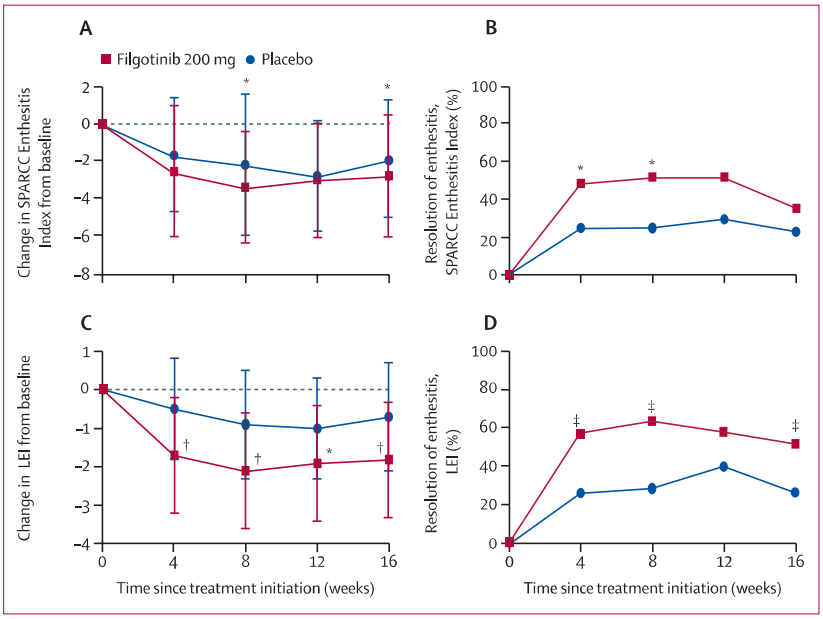

Figure 4: **Enthesitis according to SPARCC Enthesitis Index and LEI**
Enthesitis was only assessed in those with enthesitis at baseline. Data are mean, with SD error bars (panels A and C; last observation carried forward) or proportion of patients (panels B and D; non-responder imputation). n=37 (filgotinib) and n=48 (placebo) in panels A and B, and n=33 (filgotinib) and n=43 (placebo) in panels C and D. LEI=Leeds Enthesitis Index. SPARCC=Spondyloarthritis Research Consortium of Canada. *p<0·05. †p<0·005. ‡p<0·01.

	Filgotinib (n=65)		Placebo (n=66)		Least squares mean difference (95% CI)	p value*
	Total score	Change from baseline	Total score	Change from baseline		
Health Assessment Questionnaire-Disability Index						
Baseline	1·43 (0·5)	..	1·36 (0·6)	..	..	..
Week 1	1·23 (0·5)	–0·19 (0·3)	1·26 (0·6)	–0·09 (0·3)	–0·09 (–0·20 to 0·01)	0·0781
Week 2	1·13 (0·4)	–0·30 (0·4)	1·22 (0·6)	–0·14 (0·3)	–0·14 (–0·25 to –0·04)	0·0078
Week 4	0·99 (0·5)	–0·44 (0·4)	1·23 (0·7)	–0·13 (0·5)	–0·29 (–0·44 to –0·15)	0·0001
Week 8	0·93 (0·6)	–0·50 (0·5)	1·23 (0·7)	–0·13 (0·6)	–0·35 (–0·52 to –0·19)	<0·0001
Week 12	0·90 (0·6)	–0·53 (0·5)	1·08 (0·7)	–0·28 (0·6)	–0·23 (–0·40 to –0·06)	0·0090
Week 16	0·86 (0·6)	–0·57 (0·5)	1·09 (0·6)	–0·28 (0·5)	–0·28 (–0·44 to –0·12)	0·0009
Functional Assessment of Chronic Illness Therapy–Fatigue						
Baseline	27·8 (9·6)	..	26·8 (11·1)	..	..	..
Week 4	34·9 (9·3)	7·1 (6·8)	29·3 (10·9)	2·7 (9·1)	4·9 (2·3 to 7·4)	0·0003
Week 16	36·0 (8·8)	8·2 (7·3)	32·2 (9·9)	5·5 (8·1)	3·2 (0·8 to 5·5)	0·0086
Psoriatic arthritis-related pain intensity						
Baseline	65·2 (16·7)	..	61·5 (21·6)	..	..	..
Week 1	52·4 (21·9)	–12·8 (21·2)	57·8 (21·0)	–3·4 (15·7)	–8·5 (–14·4 to –2·5)	0·0055
Week 2	49·8 (21·2)	–15·4 (20·9)	57·0 (20·4)	–4·5 (17·7)	–9·8 (–15·8 to –3·7)	0·0018
Week 4	40·0 (23·6)	–25·2 (22·3)	56·2 (23·7)	–5·3 (22·9)	–19·0 (–26·1 to –12·0)	<0·0001
Week 8	36·1 (24·8)	–29·1 (23·3)	53·8 (25·0)	–7·7 (27·2)	–20·3 (–28·1 to –12·5)	<0·0001
Week 12	34·1 (22·2)	–31·1 (23·5)	49·7 (26·0)	–11·8 (28·5)	–17·3 (–25·4 to –9·2)	<0·0001
Week 16	33·6 (21·7)	–31·6 (21·3)	50·5 (25·6)	–11·1 (29·7)	–18·9 (–26·7 to –11·1)	<0·0001

Data are mean (SD) unless otherwise indicated. *Between-group p value calculated from an analysis of covariance model on the changes from baseline per visit, with treatment, baseline values and randomisation stratification factors.

Table 3: **Patient-reported physical functioning, fatigue, and pain outcomes (last observation carried forward; full analysis set)**