Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis: results from a randomised, placebo-controlled, phase 2 trial (EQUATOR)

Philip Mease, Laura C Coates, Philip S Helliwell, Mykola Stanislavchuk, Anna Rychlewska-Hanczewska, Anna Dudek, Walid Abi-Saab, Chantal Tasset, Luc Meuleners, Pille Harrison, Robin Besuyen, Annegret Van der Aa, Neelufar Mozaffarian, Joy M Greer, Rebecca Kunder, Filip Van den Bosch, Dafna D Gladman

Swedish Medical Center and University of Washington, Seattle; WA, USA (P Mease MD); Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK (L Coates MB ChB); Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, UK (Prof PS Helliwell MD); National Pirogov Memorial Medical University, Vinnytsya, Ukraine (Prof M Stanislavchuk MD); ai centrum medyczne sp. z o.o. sp.k., Poznan, Poland (A Rychlewska-Hanczewska MD); Centrum Medyczne AMED, Warszawa, Poland (A Dudek MD); Galapagos NV, Mechelen, Belgium (W Abi-Saab MD, C Tasset PhD, L Meuleners MSc, P Harrison DPhil, A Van der Aa Phd*); Galapagos BV, Leiden, The Netherlands (R Besuyen MD); Gilead Sciences Inc, Foster City, CA, USA (N Mozaffarian MD, JM Greer PhD, R Kunder MD); Ghent University Hospital and VIB UGent Center for Inflammation Research, Ghent University, Ghent, Belgium (F Van den Bosch MD); and University of Toronto and Krembil Research Institute, Toronto Western Hospital, Toronto, Canada (Prof DD Gladman MD FRCPC)

*****The affiliation details listed here indicate the authors' affiliation at the time the study was conducted.

Corresponding author: Dr Philip Mease MD. Director of Rheumatology Research, Swedish Medical Center, 601 Broadway, Seattle, WA 98122, USA. Tel: +12069791943; Email: pmease@philipmease.com.

Summary

Background The EQUATOR trial investigated the efficacy and safety of filgotinib, a selective Janus kinase 1 (JAK1) inhibitor, for the treatment of psoriatic arthritis (PsA).

Methods This completed, randomised, double-blind, placebo-controlled phase 2 trial enrolled adults from 25 centres in seven countries (ClinicalTrials.gov identifier: NCT03101670). Patients had active moderate-to-severe PsA fulfilling Classification for PsA (CASPAR) criteria and insufficient response/intolerance to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). Using an interactive web-based system, patients were randomised 1:1 to filgotinib 200 mg or placebo orally once daily for 16 weeks (stratified by current csDMARD use and prior anti-tumour necrosis factor use). Patients, study team and sponsor were blinded to treatment assignment. The primary endpoint was the proportion of patients achieving 20% improvement in American College of Rheumatology response criteria (ACR20) at week 16; compared between groups using the Cochran-Mantel-Haenszel test and non-responder imputation method. Secondary efficacy outcomes, patient-reported outcomes, and safety were assessed.

Findings Between 9 March and 27 September 2017, 191 patients were screened and 131 randomised (filgotinib: n=65; placebo: n=66). The proportion achieving ACR20 at week 16 was 80% (52/65) and 33% (22/66) in the filgotinib and placebo groups, respectively; treatment difference (95% confidence interval) was 47% (30·2%, 59·6%), p<0·0001. Significant improvements in signs and symptoms of PsA, peripheral arthritis, psoriasis, enthesitis and patient-reported outcomes were observed in filgotinib-treated patients compared with placebo. Treatment-emergent adverse events (TEAEs) were reported in 57% (37/65) and 59% (39/66) of patients on filgotinib and placebo, respectively. The most common events were nasopharyngitis and headache, occurring in similar proportions in each group. One serious TEAE was reported in each group, leading to one fatal TEAE (pneumonia) in the filgotinib group.

Interpretation In this phase 2 study, filgotinib was efficacious in the treatment of active PsA, and no new safety signals were identified.

Funding Galapagos NV/Gilead Sciences.

Research in context panel

Evidence before this study

We conducted a PubMed search for English language articles published between 1 January 2000 and 7 August 2018, containing the term “psoriatic arthritis” in the title. Of the 3990 articles found, 206 described clinical trials in adults. Among these were a number of potential treatments for psoriatic arthritis (PsA), including biological disease-modifying anti-rheumatic drugs (bDMARDs) such as anti-tumour necrosis factor (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), T-cell activation blockers (abatacept, alefacept), anti-interleukin (IL)12/23 (ustekinumab), anti-IL17 (brodalumab, ixekizumab, secukinumab), anti-IL6 (clazakizumab), and anti-CD11a (efalizumab), and targeted synthetic disease-modifying anti-rheumatic drugs, such as phosphodiesterase type-4 inhibitor (apremilast) and Janus kinase (JAK)1/3 inhibitor (tofacitinib). Treatment of PsA is complicated by the heterogeneous nature of the disorder, which is characterised by skin and nail disease, musculoskeletal manifestations (eg peripheral arthritis, axial disease, enthesitis and dactylitis) and other extra-articular manifestations that may involve the bowel, eyes or cardiovascular system. The range of different targets investigated for PsA, and the fact that only a minority of patients achieve desired thresholds of response (such as minimal disease activity), suggests there is a need for an effective treatment that addresses the multiple aspects of this disease.

Added value of this study

To our knowledge, this is the first double-blind, placebo-controlled phase 2 study investigating the efficacy and safety of a selective JAK1 inhibitor in PsA. In addition to the primary endpoint (20%

improvement in American College of Rheumatology response criteria [ACR20]), the study investigated a broad range of secondary and exploratory endpoints including those that assess peripheral arthritis, psoriasis, enthesitis, dactylitis, and overall PsA disease activity, in addition to multiple patient-reported outcomes, such as physical functioning, pain and fatigue. These data provide a detailed picture of the impact of filgotinib on a number of domains of PsA. The results demonstrate that selective inhibition of JAK1 by filgotinib is effective in treating signs and symptoms of active PsA across various disease manifestations. In addition, filgotinib exhibits a favourable safety profile over 16 weeks of treatment that was consistent with findings thus far in trials of other rheumatologic conditions.

Implications of all the available evidence

The results of this study support the development of filgotinib for the treatment of PsA in patients with an inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs. Larger, global phase 3 trials in PsA are needed to confirm these findings and to extend observations over a longer period of time. In addition, the safety of selective JAK1 inhibition should be explored further to determine whether the theoretical advantage of increased selectivity translates to a better safety profile in clinical practice.

Introduction

Psoriatic arthritis (PsA) is a chronic, inflammatory musculoskeletal disease estimated to affect around 30% of patients with psoriasis.[1,2] It is a heterogeneous disorder with a clinical presentation characterised by skin and nail disease, musculoskeletal manifestations such as peripheral arthritis, axial disease, enthesitis and dactylitis, and other extra-articular manifestations that can involve the bowel, eyes, or cardiovascular system.[1,3] In addition to joint pain, PsA can cause irreversible structural damage and disability,[4] leading to impaired daily functioning and reduced quality of life, with progressive worsening over time.[5] The economic burden of PsA is substantial, with the use of biological therapy being an important driver of direct[6] and indirect[7] costs.

There are several therapeutic options available to patients with PsA, which target disease pathogenesis, relieve inflammation, improve health-related quality of life, and/or prevent long-term structural damage.[8,9] These include non-steroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate and leflunomide.[8] Many patients have an inadequate response to NSAIDs and/or csDMARDs. Fortunately, there is now an increasing armamentarium of drugs to treat patients with PsA, including anti-tumour necrosis factor (TNF) agents, other classes of biological DMARDs (bDMARDs), such as those targeting interleukin (IL)17 or IL12/23, and orally administered targeted synthetic DMARDs (tsDMARDs), such as apremilast and tofacitinib.[8,9] Patient-specific disease characteristics, such as the presence of psoriasis and other comorbidities, as well as patient preference for oral versus injectable treatments, may impact clinical decision-making among these drugs.[10] Despite the increased number of therapeutic options for PsA, a lack or loss of response to existing therapies, and safety and tolerability issues, remain problematic and can lead to treatment discontinuation.[11] Therefore, there is still a need for conveniently administered agents with novel and targeted mechanisms of action and an acceptable safety profile that can effectively improve PsA outcomes.

Many cytokines are known to contribute to the skin and joint inflammation in PsA. The Janus kinase (JAK) family of tyrosine kinases (JAK1, JAK2, JAK3, and TYK2 in humans) are key signalling proteins that are vital for downstream intracellular transduction of cytokine-mediated signals.[12] Tofacitinib is a tsDMARD that inhibits JAK1 and JAK3, and also JAK2 to a lesser degree. The drug has demonstrated efficacy in patients with PsA who have an inadequate response to csDMARDs or anti-TNF therapy.[13,14] Drugs that block or reduce the activity of TNF and other cytokines in the IL23 and IL17 pathways have also demonstrated efficacy in PsA.[15] The activity of these cytokines can be directly or indirectly blocked by JAK inhibitors. By reducing the proinflammatory activity of multiple cytokines simultaneously, JAK inhibition is an attractive mechanism for the treatment of PsA.

Filgotinib is an oral JAK inhibitor distinct from previously characterised tsDMARDs in that it is more selective for JAK1 over other JAK family members.[16] Preclinical characterisation of filgotinib demonstrated that it prevents JAK1-mediated Th1 and Th2 differentiation (driven by IFNγ and IL4, respectively), and to a lesser extent Th17 differentiation (driven by transforming growth factor β, IL23, IL6 and IL1β). Filgotinib reduces levels of inflammatory cytokines and chemokines in a rodent collagen-induced arthritis model and signs and symptoms of PsA in a mouse model.[16,17] In the phase 2b DARWIN1 and DARWIN2 trials, which involved over 800 patients with rheumatoid arthritis (RA) treated for 24 weeks, filgotinib improved the signs and symptoms of active RA with significant responses seen as early as week 1.[18,19] Both trials met their primary endpoint of demonstrating a significant improvement in American College of Rheumatology (ACR) 20 response rates at week 12 in filgotinib-treated patients compared with placebo when given as monotherapy or in combination with methotrexate.[18,19] Treatment with filgotinib was also associated with rapid and sustained improvements in patient-reported outcomes through to week 24 compared with placebo.[20] Based on the strength of the phase 2 data in RA (as well as positive data in a phase 2 studies in Crohn's disease[21] and active ankylosing spondylitis)[22], global phase 3 trials have been initiated in RA (NCT02873936; NCT02889796;

NCT02886728, NCT03025308), Crohn's disease (NCT02914561; NCT02914600), and ulcerative colitis (NCT02914522; NCT02914535).

The primary aim of the current study was to evaluate the efficacy of filgotinib on the signs and symptoms of active moderate-to-severe PsA in patients with an inadequate response or intolerance to csDMARDs. Secondary objectives included evaluation of other features of PsA and additional signs and symptoms of peripheral arthritis, psoriasis, enthesitis, dactylitis, safety and tolerability, physical functioning, fatigue, and pain.

Methods

Study design and patients

In this double-blind, randomised, placebo-controlled, phase 2 study, patients were recruited at 25 centres in Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine (appendix p2).

Eligible patients were aged ≥18 years, met classification criteria for PsA (CASPAR),[23] and had a diagnosis of PsA for at least 12 weeks prior to screening. Patients had active moderate-to-severe disease defined as ≥5 swollen joints (from a 66 swollen joint count) and ≥5 tender joints (from a 68 tender joint count), active or a documented history of plaque psoriasis, and an insufficient response or intolerance to at least one csDMARD. Patients were allowed to continue csDMARDs during the study provided they had received this treatment for ≥12 weeks prior to screening and were on a stable dose for 4 weeks prior to baseline.

Patients who had received prior treatment with more than one anti-TNF agent, or any alkylating agent, JAK inhibitor, or other investigational or approved biologic immune-modulator at any time, were excluded from the study. Other exclusion criteria included: receipt of intramuscular/intravenous corticosteroids or intra-articular injection within 4 weeks prior to screening; oral steroids at a dose ≥10

mg/day prednisone or equivalent, or at a dose not stable for 4 weeks prior to baseline; a very poor functional status or inability to perform self-care. Full eligibility criteria are listed in the appendix (p3).

The study conformed to Good Clinical Practice guidelines and Declaration of Helsinki Principles. The protocol was reviewed and approved by the central or individual independent ethics committees in each participating country. All patients provided written informed consent prior to participation. An external data monitoring committee reviewed study progress throughout and conducted interim safety data reviews. A cardiovascular event adjudication committee reviewed and adjudicated major adverse cardiovascular events, including all fatalities. The study protocol and protocol amendments are included in the appendix (p21 and p8, respectively).

Randomisation and masking

Patients were randomised (1:1), using a computerised interactive web response system, to receive either filgotinib 200 mg (Gilead Sciences, Inc, Foster City, California, USA) or matching placebo orally once daily for 16 weeks (additional details in appendix, p12). Randomisation was stratified by current csDMARD use (yes/no) and prior anti-TNF therapy (yes [capped at 30% of enrolled patients]/no). The patient, study team including site staff and investigators, and the sponsor were blinded to treatment assignment.

Procedures

Screening was performed within 4 weeks prior to randomisation. Patients were enrolled by investigators and assessed at baseline (day 1) and at weeks 1, 2, 4, 8, 12, and 16, and at a follow-up visit at week 20. Efficacy assessments included (appendix p13): 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; dactylitis; modified Nail Psoriasis Severity Index (mNAPSI), pruritus numeric rating

scale (NRS); Health Assessment Questionnaire-Disability Index (HAQ-DI); Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue; and Patient's Global Assessment of PsA Pain Intensity. Assessment of PASI and pruritus was performed in patients with ≥3% affected body surface area (BSA) affected at baseline. Assessment of enthesitis and mNAPSI was performed in patients with enthesitis and psoriatic nail involvement, respectively, at baseline. Data on dactylitis were not analysed as it was identified during blinded data review that it was not scored uniformly across all centres. Therefore, analysis of this endpoint is not included here.

Outcomes

The primary endpoint was the proportion of patients achieving ACR20 response at week 16. Key secondary endpoints included: ACR50 and ACR70 response rates; the evolution over time in ACR20, ACR50, and ACR70 response rates; change from baseline in Disease Activity Score in 28 joints (DAS28)(C-reactive protein [CRP]); PsA Response Criteria (PsARC) response rates; the proportion of patients achieving minimal disease activity (MDA); change from baseline in Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index; the proportion of patients achieving a 75% reduction in PASI (PASI75); change from baseline in mNAPSI and pruritus NRS; and change from baseline in the HAQ-DI, FACIT-Fatigue questionnaires, and patient-reported intensity of PsA-related pain. Results for HAQ-DI, fatigue, and PsA-related pain are presented here; data from other patient-reported outcomes will be published subsequently. A full list of secondary endpoints is provided in the appendix (p14). The safety and tolerability of filgotinib were assessed by the incidence of treatment-emergent adverse events (TEAEs), TEAEs of special interest (infection, malignancies, major adverse cardiovascular events), serious TEAEs, and discontinuations due to TEAEs, as well as electrocardiograms (ECGs), physical examination findings, body weight, vital signs, and changes in laboratory results.

Additional exploratory endpoints included the change from baseline in Disease Activity in PsA (DAPSA) score as a measure of peripheral arthritis, PsA Disease Activity Score (PASDAS) as a measure of overall PsA disease, and assessment of enthesitis based on the change from baseline in Leeds Enthesitis Index (LEI). These endpoints were added to the statistical analysis plan after trial commencement, but prior to unblinding of data, as all the necessary components/assessments were included in the trial design.

Statistical analysis

A sample size of 124 was calculated to have 80% power to detect efficacy of filgotinib compared with placebo with respect to the primary endpoint. This was based on a Chi-square test with continuity correction at a 5% two-sided significance level, assuming the proportion of patients with responses at week 16 were 45% and 20% in the filgotinib and placebo groups, respectively.

For the primary endpoint (and other binary endpoints), proportions of responders were compared between treatment groups using the Cochran-Mantel-Haenszel test, controlling for randomisation stratification factors. The proportion of responders in each treatment group was summarised with a point estimate and 95% confidence intervals (CIs). Differences in the proportions of responders between the treatment groups were summarised with a point estimate and 95% Cis using the Newcombe method. Changes from baseline in continuous endpoints were analysed using an analysis of covariance model (ANCOVA) with treatment, baseline value, and randomisation stratification factors as fixed effects. Adjusted least squares means and 95% CIs for analysed measures of efficacy within each treatment group, and differences between treatment groups, were obtained from the corresponding ANCOVA models. Missing data for binary endpoints (including the primary endpoint) were handled using the non-responder imputation (NRI) method. For analysis of continuous endpoints, missing values were imputed using the last observation carried forward (LOCF) method. Sensitivity analyses of the primary endpoint using the observed cases and LOCF imputation methods were also performed. All efficacy and

safety analyses were done on the full analysis set (FAS; all randomised patients who received at least one dose of study drug). Statistical analyses were performed using SAS® software, version 9·4 (SAS Institute Inc., Cary, NC, USA). The trial was registered at ClinicalTrials.gov (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

Of the 191 patients screened between 9 March and 27 September 2017, 131 were enrolled and randomised to receive filgotinib 200 mg (n=65) or placebo (n=66) once daily. Most patients completed the study (filgotinib, n=60 [92%]; placebo, n=64 [97%]; five patients (8%) discontinued treatment in the filgotinib group (withdrew consent, n=2; lack of efficacy, n=1; adverse events, n=1; death, n=1) and two patients (3%) discontinued treatment in the placebo group (withdrew consent, n=1; lack of efficacy, n=1; figure 1). Demographics and baseline disease characteristics were similar between the two treatment groups (table 1). The mean (standard deviation [SD]) age of the study population was 50 (11·5) years and 66/131 (50%) patients were female. At baseline, the mean (SD) duration of PsA was 7 (6·4) years, mean (SD) HAQ-DI was 1·40 (0·6), and the median (interquartile range) PASI in patients with psoriasis ≥3% BSA (82/131 patients; 63%) was 6·6 (3·0, 15·2). The majority (74% [97/131]) of patients received concomitant csDMARD therapy at baseline and during the study, meaning 26% received filgotinib (or placebo) as monotherapy (table 1). Mean (SD) on-treatment adherence was 99.7% (6.3) and 99·9% (10·5) for patients on filgotinib and placebo, respectively.

The proportion of patients achieving an ACR20 response at week 16 was 80% (52/65) and 33% (22/66) in the filgotinib and placebo groups, respectively (figure 2A), with a treatment difference (95% CI) of 47%

(30·2%, 59·6%; p<0·0001; table 2). Sensitivity analyses of the primary endpoint using observed cases and LOCF imputation methods were consistent with those from the primary NRI analysis (table 2). In anti-TNF-naïve patients, ACR20 responses were achieved in 78% (42/54) and 35% (20/57) of patients in the filgotinib and placebo groups, respectively.

Significantly more patients treated with filgotinib than placebo achieved ACR50 (48% [31/65] and 15% [10/66], respectively; treatment difference 33% [95% CI 16·8%, 46·2%]; p<0·0001) and ACR70 responses (23% [15/65] and 6% [4/66]; treatment difference 17% [95% CI 4·9%, 29·2%]; p=0·0037) at week 16 (figure 2). There was a significant difference between the filgotinib and placebo groups in ACR20 and ACR50 response rates starting at week 1 (the earliest timepoint measured) (ACR20: 26% [17/65] and 5% [3/66], p=0·0003; ACR50: 6% [4/65] and 0, p=0·0365, respectively; figure 2). Of those patients who received concomitant csDMARD therapy at baseline, there was a difference between the filgotinib and placebo groups in ACR20 and ACR50 response rates at week 16 (ACR20: 81% [38/47] and 32% [16/50], treatment difference 49%; ACR50: 55% [26/47] and 12% [6/50], treatment difference 43% [95% CI and p-values not available]).

The mean change from baseline in DAPSA score was –27·9 for filgotinib and –18·1 for placebo (least square [LS] mean difference –12·5 [95% CI –17·0, –8·0; p<0·0001; figure 3A). Remission/low disease activity (DAPSA ≤14) was achieved in 49% (32/65) and 15% (10/66) of patients receiving filgotinib and placebo, respectively (treatment difference 34% [95% CI 18·3%, 47·7%]; p<0·0001). Remission (DAPSA ≤4) was achieved in 11% (7/65) and 3% (2/66) of patients, respectively (treatment difference 8% [95% CI –1·4%, 17·8%]; p=0·0678). A greater mean (SD) change from baseline in DAS28(CRP) was observed in patients treated with filgotinib compared with placebo at week 16 (–2·0 [0·9] and –0·9 [1·1], respectively, LS mean difference –1·1 [95% CI –1·5, –0·8]; p<0·0001; appendix p17). PsARC response rate data are provided in figure 3B and appendix p16).

Filgotinib significantly improved the overall control of PsA, with more patients achieving MDA at week 16 in the filgotinib group than those on placebo (23% [15/65] and 9% [6/66], respectively; treatment difference 14% [95% CI 1·3%, 26·5%]; p=0·0212; figure 3C). In addition, the mean (SD) change from baseline in PASDAS at week 16 was –2·5 (1·1) for the filgotinib group, compared with –1·3 (–5·4) for placebo (LS mean difference –1·3 [95% CI –1·7, –0·9]; p<0·0001; figure 3D). Low disease activity (PASDAS ≤3.2) at week 16 was achieved in 37% (24/65) and 9% (6/66) of patients receiving filgotinib and placebo, respectively (treatment difference 28% [95% CI 13·6%, 40·9%]; p<0·0001).

Filgotinib significantly improved enthesitis compared with placebo. Of the 85 (65%) patients with enthesitis at baseline (per SPARCC Enthesitis Index), the mean (SD) change from baseline at week 16 was –2·8 (3·3) and –1·9 (3·2) in the filgotinib and placebo groups, respectively (LS mean difference –1·4 [95% CI –2·6, –0·1]; p=0·0310; figure 4A). Resolution of enthesitis was achieved in 35% (13/37) of patients on filgotinib compared with 23% (11/48) of patients on placebo (treatment difference –12% [95% CI –6·8%, 31·0%]; p=0·1583; figure 4B). When assessed according to LEI in an exploratory analysis, 76 (58%) patients had enthesitis at baseline. In this population, the mean (SD) change from baseline at week 16 was –1·8 (1·5) and –0·7 (1·4) in the filgotinib and placebo groups, respectively (LS mean difference –1·1 [95% CI –1·7, –0·5]; p=0·0004; figure 4C), and resolution of enthesitis was achieved in 52% (17/33) of patients receiving filgotinib compared with 26% (11/43) of patients receiving placebo (treatment difference 26% [95% CI 4·0%, 45·1%]; p=0·0089; figure 4D).

The signs and symptoms of psoriasis improved in patients treated with filgotinib compared with those receiving placebo, as assessed by PASI75. Of the 82 (62%) patients with ≥3% of BSA covered by psoriasis at baseline, PASI75 was achieved in 45% (19/42) of patients on filgotinib compared with 15% (6/40) on placebo (treatment difference 30% [95% CI 10·4%, 47·0%]; p=0·0034; figure 3E). Filgotinib significantly improved the pruritic component of psoriasis with a mean change from baseline in pruritus NRS of –2·5 at week 16 compared with –0·6 in the placebo group (LS mean difference –2·2 [95% CI –3·1, –1·4];

p<0·0001; figure 3F). The proportion of patients with an improvement of ≥3 in pruritus NRS was 58% (21/36) and 22% (8/36) in the filgotinib and placebo groups, respectively (treatment difference 36% [95% CI 13·5%, 54·0%]; p=0·0022). Of the 90 (69%) patients with nail involvement (mNAPSI >0) at baseline, 16% (7/44) and 7% (3/46) in the filgotinib and placebo groups, respectively, achieved complete resolution of all nail symptoms at week 16, although this was not a statistically significant difference (treatment difference 9% [95% CI –4·2%, 23·5%]; p=0·2573).

Filgotinib significantly improved several patient-reported outcomes compared with placebo, including those for physical functioning, fatigue, and pain. Significant improvements in some measures were evident as early as weeks 1 or 2 (table 3). At week 16, HAQ-DI decrease was –0·57 in the filgotinib group compared with –0·28 for placebo (LS mean difference –0·3 [95% CI –0·4, –0·1]; p=0·0009), and 65% (41/63) of patients receiving filgotinib achieved a clinically important improvement from baseline (defined as a change ≥0·35)[24] compared with 42% (26/62) of those receiving placebo (treatment difference 23% [95% CI 5·7%, 38·8%]; p=0·0085). The mean change from baseline in FACIT-Fatigue total score at week 16 was 8·2 for filgotinib and 5·5 for placebo (LS mean difference 3·2 [95% CI 0·8, 5·5]; p=0·0086). The mean decrease from baseline in PsA-related pain intensity was also greater for filgotinib compared with placebo (–31·6 and –11·1 mm, respectively; LS mean difference –18·9 [95% CI –26·7, –11·1]; p<0·0001).

With respect to safety outcomes, the proportion of patients experiencing at least one TEAE was similar between filgotinib (57% [37/65]) and placebo (59% [39/66]; table 4). TEAEs were mostly mild or moderate in severity, with only six events reported at grade 3 or higher (appendix p18). The most common TEAEs were nasopharyngitis and headache, occurring in similar proportions of patients in each treatment group (appendix p18). Treatment was discontinued in one patient in the filgotinib group due to endometrial hypertrophy. The TEAE began three days after first study drug intake but was not considered related to drug (table 4). There were two serious TEAEs reported; pneumonia with a fatal

outcome in a patient receiving filgotinib, and a hip fracture after a fall in a patient on placebo. The case of pneumonia was the only death in the study. The patient (male, aged 44 years) had mild lymphocytopenia at baseline and throughout the study, received methotrexate (15 mg/week) and methylprednisolone acetate (8 mg/day) for PsA, and folic acid for prophylaxis (concomitant medications). The event onset was at day 106 of treatment; the patient died on day 107. No hepatobiliary disorders were reported in the filgotinib group (0/65 patients), whilst 2% [1/66] of patients in the placebo group reported these. Liver function analysis did identify a small number of patients with an increase in gamma-glutamyltransferase (filgotinib 6% [4/65], placebo 0% [0/66]), alanine aminotransferase (filgotinib 2% [1/65], placebo 3% [2/66]), and aspartate amino transferase (filgotinib 2% [1/65], placebo 0% [0/66]).There were no gastric perforations, malignancies, lymphomas, venous thromboembolic events, opportunistic infections, or cases of active tuberculosis reported. There was one case of herpes zoster confined to a single dermatome in the filgotinib group. There was no difference in the overall rate of infections between patients treated with filgotinib (22% [14/65]) and placebo (21% [14/66]).

Key laboratory parameters monitored in this study are listed in the appendix (p19). Of note, creatinine levels were similar to baseline levels at week 16 (mean change from baseline [SD]: filgotinib 5% [11·4] placebo 1% [11·0]) Parameters that differed in the filgotinib group compared with placebo included increased haemoglobin concentrations (mean [SD] +6 [8·2] and +1 [9·2] g/L in the filgotinib placebo groups, respectively) and decreased platelet counts (–16 [62·0] and 7 [57·4] giga/L, respectively) from baseline. In addition, natural killer cell counts were stable in the filgotinib group, as indicated by the percent change from baseline, but increased in the placebo group (–4% [46·9] and 13% [32·5], respectively). Total cholesterol increased from baseline (+0·45 [1·0] mmol/L) in filgotinib-treated patients compared with placebo-treated patients (+0·09 [0·8] mmol/L). This increase in the filgotinib group was driven mainly by high-density lipoprotein (HDL) (+0·37 mmol/L), resulting in a 15% decrease

in the low-density lipoprotein (LDL)/HDL ratio from baseline in the filgotinib group compared with a 6% increase in the placebo group (appendix p19). Changes in other laboratory parameters, vital signs, or ECGs were in line with previously reported data for filgotinib and no new safety signals were identified.

Discussion

To our knowledge, this is the first report of a clinical trial investigating a selective JAK1 inhibitor for the treatment of PsA. This phase 2 study explored the effect of filgotinib on patients with active PsA with regards to disease activity, physical functioning, and safety. Filgotinib performed significantly better than placebo in terms of efficacy, as demonstrated by the greater proportion of patients achieving the primary endpoint of ACR20 response after 16 weeks of treatment (80% and 33%, respectively). The onset of action of filgotinib was rapid, with measurable improvements in disease activity observed after one week of treatment. Compared with placebo, filgotinib significantly improved signs and symptoms of peripheral arthritis, enthesitis, and psoriasis, as well as overall PsA disease control (as determined by PASDAS and fulfilment of MDA criteria). Although the improvement in nail disease observed in filgotinib-treated patients was not significant, week 16 may be too early a timepoint to expect complete resolution of nail disease, and importantly, not all patients had nail disease at baseline. Filgotinib had a beneficial effect on patient-reported outcomes of physical functioning, fatigue, and pain. These effects were also evident at an early timepoint, with significant improvements observed in PsA-related pain intensity at week 1 and in HAQ-DI score at week 2. These time of onset findings for responses to filgotinib in PsA are consistent with those from the previous phase 2 trials in RA,[18,19] and would likely be of importance to future patients.

In this study of adults with active PsA, filgotinib was well tolerated and associated with mostly mild or moderate AEs that required no intervention different from common medical practice. In terms of TEAE and treatment discontinuations due to TEAEs, the safety profile of filgotinib was similar to that of

placebo. This is consistent with safety results from the DARWIN trials in RA after 24 weeks.[18,19] Clinical data on JAK inhibitors have raised potential safety concerns with regards to the risk of infections, particularly herpes zoster, pneumonia, and opportunistic infections.[25] In the present study, infections occurred at a similar rate in both treatment groups through to 16 weeks, however there was one case of serious infection (pneumonia) that led to a fatality in the filgotinib group. In comparison, in DARWIN1, the incidence of treatment-related infections was higher in the filgotinib group (200 mg) than the placebo group (8·1% [7/86] *vs* 1·8% [1/56], respectively), whereas the incidence of serious infections was similar between groups in both DARWIN1 (1·2% [1/86] *vs* 1·8% [1/56]) and DARWIN2 (1·4% [1/69] *vs* 0% [0/70]).[18,19] Thromboembolic AEs have also been highlighted as a potential safety issue with JAK inhibitors, and reports of lymphoma and other malignancies have resulted in warnings for these AEs being included on some drug labels.[26] No malignancies, thromboembolic events, or cases of opportunistic infections, such as tuberculosis, and only a single case of herpes zoster were reported in this study. The study has confirmed previously reported effects of filgotinib on laboratory parameters, including increased haemoglobin and HDL, stable natural killer cell and lymphocyte counts, and decreased platelets.[18,19] No hepatic events of clinical importance were observed. Selective inhibition of JAK1 may theoretically provide an improved safety profile compared with JAK inhibitors that are not or less selective for JAK1. For example, inhibition of JAK1/2 has been shown to induce increases in platelets[26] that may increase the risk of thromboembolic events, which seems to be absent when JAK1 is selectively inhibited. Longer-term follow-up and exposure in larger scale clinical studies is required to further characterise the safety profile of filgotinib and confirm the initial safety findings reported here. An open-label, long-term extension of this study (NCT03320876) is underway in which PsA patients will be treated with filgotinib for up to an additional 148 weeks; results will be reported upon completion.

A number of biological DMARDs have shown efficacy in PsA.[27-29] Although efficacious in some patients, these treatments require parenteral administration and refrigeration, and may be considered

burdensome or problematic in some patient populations or geographies.[11] Oral treatments, such as apremilast (a phosphodiesterase 4 inhibitor) and tofacitinib, can provide a more convenient therapeutic option. Apremilast (30 mg twice-daily), an oral tsDMARD that inhibits phosphodiesterase 4, has been shown to improve ACR20 responses compared with placebo at week 16 in biologic-naïve patients (38% and 20%, p=0·004)[30] and in DMARD- and biologic-naïve patients (31% and 16%, p=0·001).[31] In a phase 3 trial in patients with PsA and an inadequate response to csDMARDs, the ACR20 response rate at 3 months in patients treated with 5 mg tofacitinib twice-daily was 50%, versus 33% in the placebo group (p=0·01).[13] In a similar trial in patients with an inadequate response to anti-TNF therapy, these values were 50% and 24%, respectively (p<0·001).[14] Filgotinib may potentially provide an alternative oral therapeutic option for PsA, which, in this phase 2 trial, has demonstrated significantly improved ACR20 response rates and disease activity in many domains compared with placebo.

This phase 2 study assessed various manifestations of PsA to determine efficacy of a JAK1-selective inhibitor. Consistent with a study of this nature, the centres involved were from a limited geographical location, there was no active comparator and the patient population was relatively small. One limitation is the 16-week study duration; increased patient numbers and a longer trial duration are required to confirm the findings relating to long-term safety and efficacy. In addition, only a single dose of filgotinib was evaluated and no imaging was included to assess effects on structural outcomes. The effect of filgotinib on dactylitis could not be established here; a phase 3 study will be necessary to evaluate this. Filgotinib's effect on axial disease is also important and, although not assessed here, was investigated in a phase 2 trial in patients with ankylosing spondylitis.[22] Also, although previous exposure to one anti-TNF drug was permitted in this study (following an appropriate washout period), the results may not be generalisable to patients with PsA who have failed multiple biological treatments, in whom the need for new pharmacotherapies is highest. Confirmation of these phase 2 results in larger phase 3 trials is

awaited and, until then, comparisons with data from other phase 3 trials should be undertaken with caution.

In conclusion, selective JAK1 inhibition by filgotinib significantly improved signs and symptoms of PsA in patients with active disease. The primary, secondary and exploratory efficacy endpoints demonstrated rapid improvements in multiple domains of PsA disease activity, including enthesitis and patient-reported outcomes. The safety profile of filgotinib after 16 weeks of treatment was in line with previous reports and no new safety signals were identified.

Contributors

PM, CT, LM, PH and DDG were involved in study design. MS, ARH, AD, LM, PH, RN and AVdA were involved in data collection. PSH, CT, LM, RB and AVdA were involved in data analysis. PM, LCC, PSH, AD, WA-S, CT, LM, PH, RB, NM, JMG, RK, FVdB and DDG were involved in data interpretation. All authors reviewed and revised drafts of the manuscript and approved the final draft.

Declaration of interests

PM has received consultancy fees from Galapagos during the conduct of the study and has received consultancy fees from Abbvie, Amgen, BMS, Janssen, Lilly, Novartis, Pfizer, SUN, and UCB, research grants from Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, SUN, and UCB, and speaker fees from Abbvie, Amgen, BMS, Celgene, Genentech, Janssen, Lilly, Novartis, Pfizer and UCB outside the submitted work. **LCC** has received personal fees from Galapagos during the conduct of the study, grants and personal fees from Abbvie, Celgene, Lilly, Novartis, and Pfizer, and personal fees from Amgen, Galapagos, Janssen, Prothena, Sun pharma, and UCB outside the submitted work. **PSH** has received advisory fees from Galapagos during the conduct of the study; and grants, personal fees for educational symposia, research funding and speaker fees, and non-financial support from Abbvie, grants for investigator meetings and speaker fees from Amgen, grants for educational meetings and speaker fees from Janssen, grants and research support from Pfizer, grants for educational symposia from UCB and Novartis, and personal advisory fees from Celgene, outside of the submitted work. **MS** has received fees to conduct the study from Galapagos NV during the conduct of the study and also outside the submitted work, and fees from Astra Zeneca, Celltrion, Eli Lilly, Genentech, GSK, Human Genome, MedImmune, Pfizer, Roche, and UCB for conducting studies outside the submitted work. **ARH** has received a national coordinator fee and her institute received a fee to conduct the study from Galapagos NV during the conduct of the study and also outside the submitted work, and her institute received fees from Gilead

Sciences for conducting a study outside the submitted work. **AD** reports study fees from Galapagos NV paid to her institute during the conduct of the study and also outside the submitted work, and consultancy fees Eli Lilly outside the submitted work. **WA-S**, **CT** and **LM** are employees of and have received warrants from Galapagos NV during the conduct of the study. **RB** is an employee of and has received warrants from Galapagos BV during the conduct of the study. **PH** and **AVdA** were employees of and received warrants from Galapagos NV during the conduct of the study. **NM**, **JMG** and **RK** are employees and have shares from Gilead Sciences. **FVdB** has received consultancy fees from Galapagos during the conduct of the study and has received speaker and/or consultancy fees from Abbvie, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck, Novartis, Pfizer, and UCB outside the submitted work. **DDG** has been involved in trial participation/design for and has received grants, personal fees, consultancy fees from Abbvie, Amgen, Celgene, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, and UCB, and has been involved in trial participation/design for and has personal fees and consultancy fees from BMS and Galapagos outside the submitted work.

Acknowledgements

We wish to thank the study investigators and patients who participated in this study. Gilead Sciences, Inc (Foster City, California, USA) were responsible for data management and statistics. The study was sponsored by Galapagos NV (Mechelen, Belgium), and was co-funded by Galapagos NV and Gilead Sciences, Inc. Medical writing support (including development of a draft outline and subsequent drafts in consultation with the authors, assembling tables and figures, collating author comments, copy-editing, fact-checking and referencing) was provided by Alice Wareham PhD at Aspire Scientific (Bollington, UK), and funded by Galapagos NV.

Data sharing

Data sharing with regard to this study is being managed by Gilead Sciences, Inc. The clinical study report synopsis, protocol, statistical analysis plan, and de-identified patient-level data from clinical trial analysis datasets will be made available from six months after approval of the study compound by the US Food and Drug Administration and European Medicines Agency until an indefinite date. Proposals should be submitted to Gilead. Access to these data will be provided in a secured analysis environment to qualified external researchers approved by Gilead, depending on the nature of the request, the merit of the research proposed, availability of the data and the intended use of the data. To gain access, approved requestors will need to sign a data sharing agreement.

References

1. Ogdie A, Weiss P. The epidemiology of psoriatic arthritis. *Rheum Dis Clin North Am* 2015; **41**(4): 545–68.

2. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005; **64**(suppl 2): ii14–ii7.

3. Peluso R, Iervolino S, Vitiello M, Bruner V, Lupoli G, Di Minno MN. Extra-articular manifestations in psoriatic arthritis patients. *Clin Rheumatol* 2015; **34**(4): 745–53.

4. Kerschbaumer A, Baker D, Smolen JS, Aletaha D. The effects of structural damage on functional disability in psoriatic arthritis. *Ann Rheum Dis* 2017; **76**(12): 2038–45.

5. Gudu T, Gossec L. Quality of life in psoriatic arthritis. *Exp Rev Clin Immunol* 2018; **14**(5): 405–17.

6. D'Angiolella LS, Cortesi PA, Lafranconi A, et al. Cost and cost effectiveness of treatments for psoriatic arthritis: A systematic literature review. *PharmacoEconomics* 2018; **36**(5): 567–89.

7. Kawalec P, Malinowski KP. The indirect costs of psoriatic arthritis: systematic review and meta-analysis. *Expert Rev Pharmacoecon Outcomes Res* 2015; **15**(1): 125–32.

8. Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2016; **75**(3): 499–510.

9. Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. *Arthritis Rheumatol* 2016; **68**(5): 1060–71.

10. Merola JF, Lockshin B, Mody EA. Switching biologics in the treatment of psoriatic arthritis. *Semin Arthritis Rheum* 2017; **47**(1): 29–37.

11. Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol* 2014; **70**(5): 871–81.e1–30.

12. Babon JJ, Lucet IS, Murphy JM, Nicola NA, Varghese LN. The molecular regulation of Janus kinase (JAK) activation. *Biochem J* 2014; **462**(1): 1–13.

13. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med* 2017; **377**(16): 1537–50.

14. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. *N Engl J Med* 2017; **377**(16): 1525–36.

15. Wu D, Yue J, Tam LS. Efficacy and safety of biologics targeting interleukin-6, -12/23 and -17 pathways for peripheral psoriatic arthritis: a network meta-analysis. *Rheumatology (Oxford)* 2018; **57**(3): 563–71.

16. Van Rompaey L, Galien R, van der Aar EM, et al. Preclinical characterization of GLPG0634, a selective inhibitor of JAK1, for the treatment of inflammatory diseases. *J Immunol* 2013; **191**(7): 3568–77.

17. Robin-Jagerschmidt C, Lavazais S, Marsais F, et al. OP0161 The JAK1 selective inhibitor filgotinib regulates both enthesis and colon inflammation in a mouse model of psoriatic arthritis. *Annals of the Rheumatic Diseases* 2017; **76**(Suppl 2): 118–9.

18. Kavanaugh A, Kremer J, Ponce L, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). *Ann Rheum Dis* 2017; **76**(6): 1009–19.

19. Westhovens R, Taylor PC, Alten R, et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). *Ann Rheum Dis* 2017; **76**(6): 998–1008.

20. Genovese M, Westhovens R, Meuleners L, et al. Effect of filgotinib, a selective JAK 1 inhibitor, with and without methotrexate in patients with rheumatoid arthritis: patient-reported outcomes. *Arthritis Res Ther* 2018; **20**(1): 57.

21. Vermeire S, Schreiber S, Petryka R, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. *Lancet* 2017; **389**(10066): 266–75.

22. van der Heijde D, Baraliakos X, Gensler LS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis: results from a randomised, placebo-controlled, phase 2 trial (TORTUGA). *Lancet* 2018; **(Submitted)**.

23. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; **54**(8): 2665–73.

24. Mease PJ, Woolley JM, Bitman B, Wang BC, Globe DR, Singh A. Minimally important difference of Health Assessment Questionnaire in psoriatic arthritis: relating thresholds of improvement in functional ability to patient-rated importance and satisfaction. *J Rheumatol* 2011; **38**(11): 2461–5.

25. Winthrop KL, Yamanaka H, Valdez H, et al. Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2014; **66**(10): 2675–84.

26. US Food and Drug Administration. FDA Briefing document. NDA 207924 Baricitnib, a Janus kinase (JAK) inhibitor for RA. 2018. https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm605061.pdf (accessed August 28, 2018).

27. D'Angelo S, Tramontano G, Gilio M, Leccese P, Olivieri I. Review of the treatment of psoriatic arthritis with biological agents: choice of drug for initial therapy and switch therapy for non-responders. *Open Access Rheumatol* 2017; **9**: 21–8.

28. Mease P, van der Heijde D, Landewé R, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. *Ann Rheum Dis* 2018; **77**(6): 890–7.

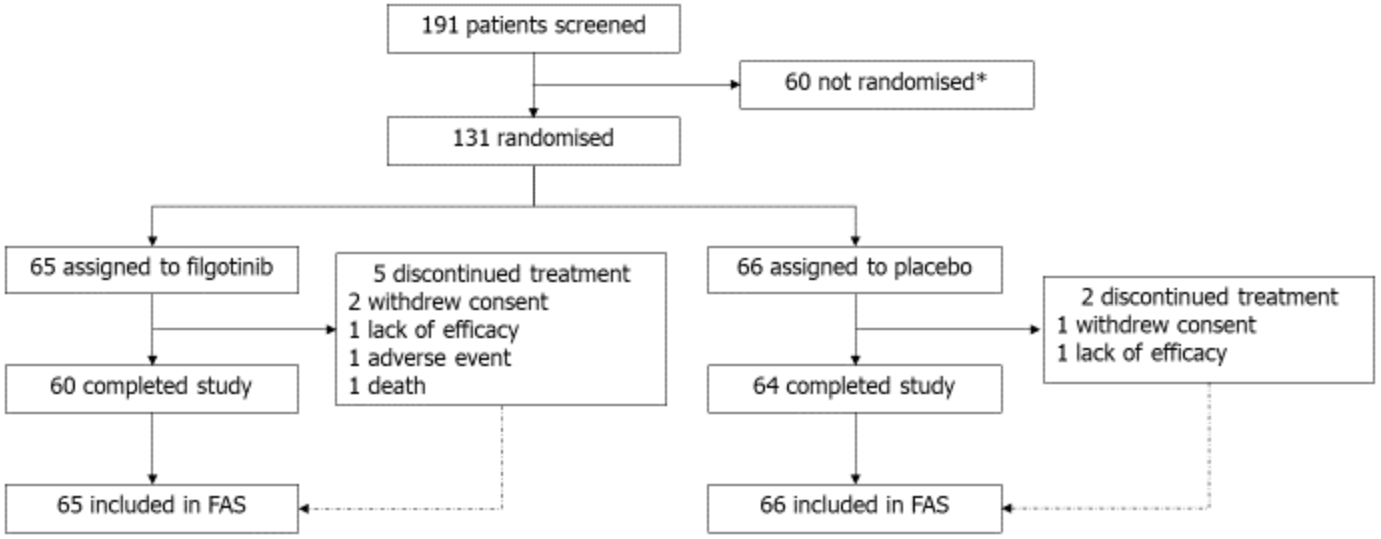
29. Mease PJ, van der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis* 2017; **76**(1): 79–87.

30. Nash P, Ohson K, Walsh J, et al. Early and sustained efficacy with apremilast monotherapy in biological-naive patients with psoriatic arthritis: a phase IIIB, randomised controlled trial (ACTIVE). *Ann Rheum Dis* 2018; **77**(5): 690–8.

31. Wells AF, Edwards CJ, Kivitz AJ, et al. Apremilast monotherapy in DMARD-naive psoriatic arthritis patients: results of the randomized, placebo-controlled PALACE 4 trial. *Rheumatology* 2018; **57**(7): 1253–63.

Figures and tables

Figure 1: **Patient disposition**

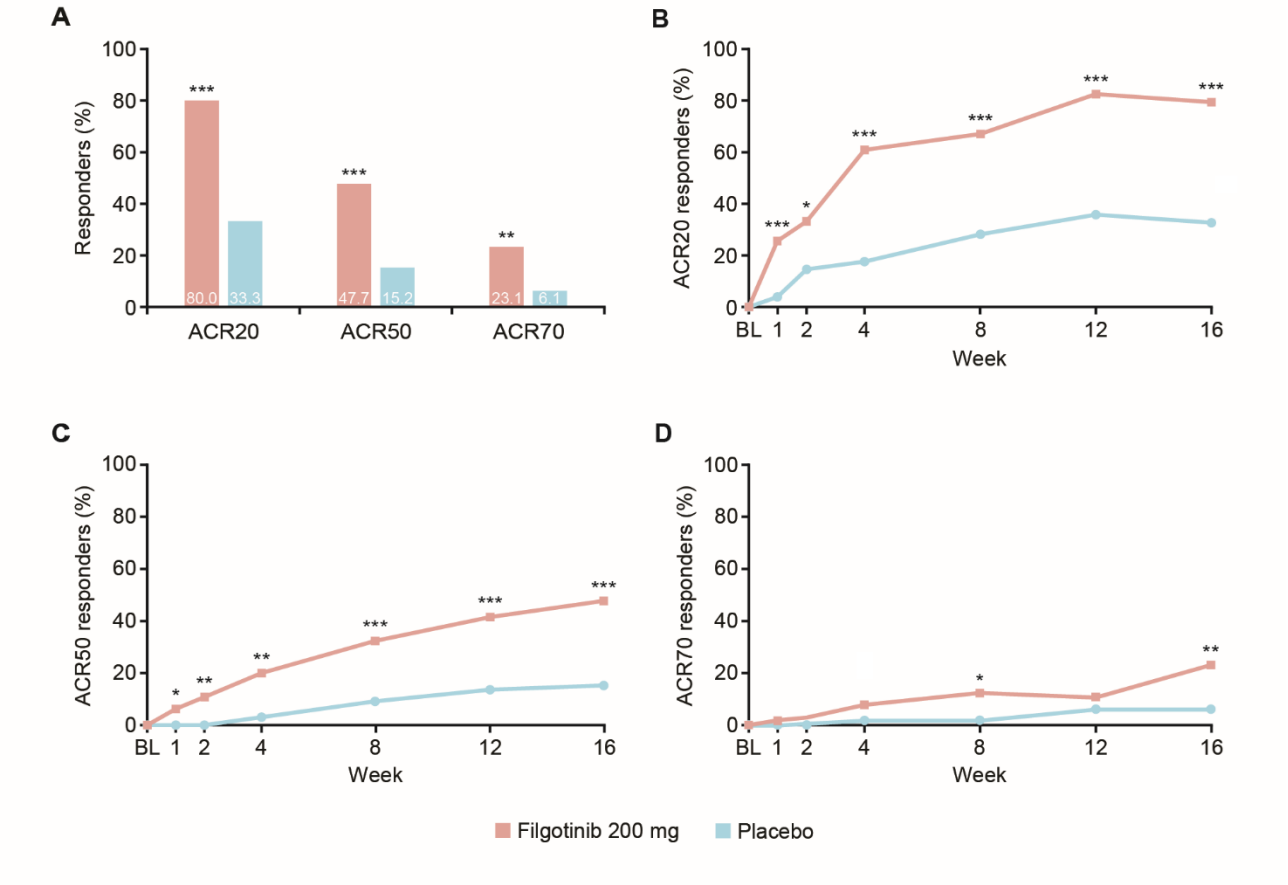


*Most common reasons for screening failure were: positive serology[†] (n=23); out of range laboratory values (n=18); untreated/inadequately treated latent tuberculosis infection (n=9); insufficient response or intolerance to ≥csDMARD (n=3); unconfirmed active psoriatic arthritis defined as ≥5 swollen joints and ≥5 tender joints (n=3); subjects could have more than one reason for screening failure.

[†]Positive serology for human immunodeficiency virus 1 or 2, hepatitis B virus, or hepatitis C virus or any history of infectious hepatitis from any cause with the exception of hepatitis A.

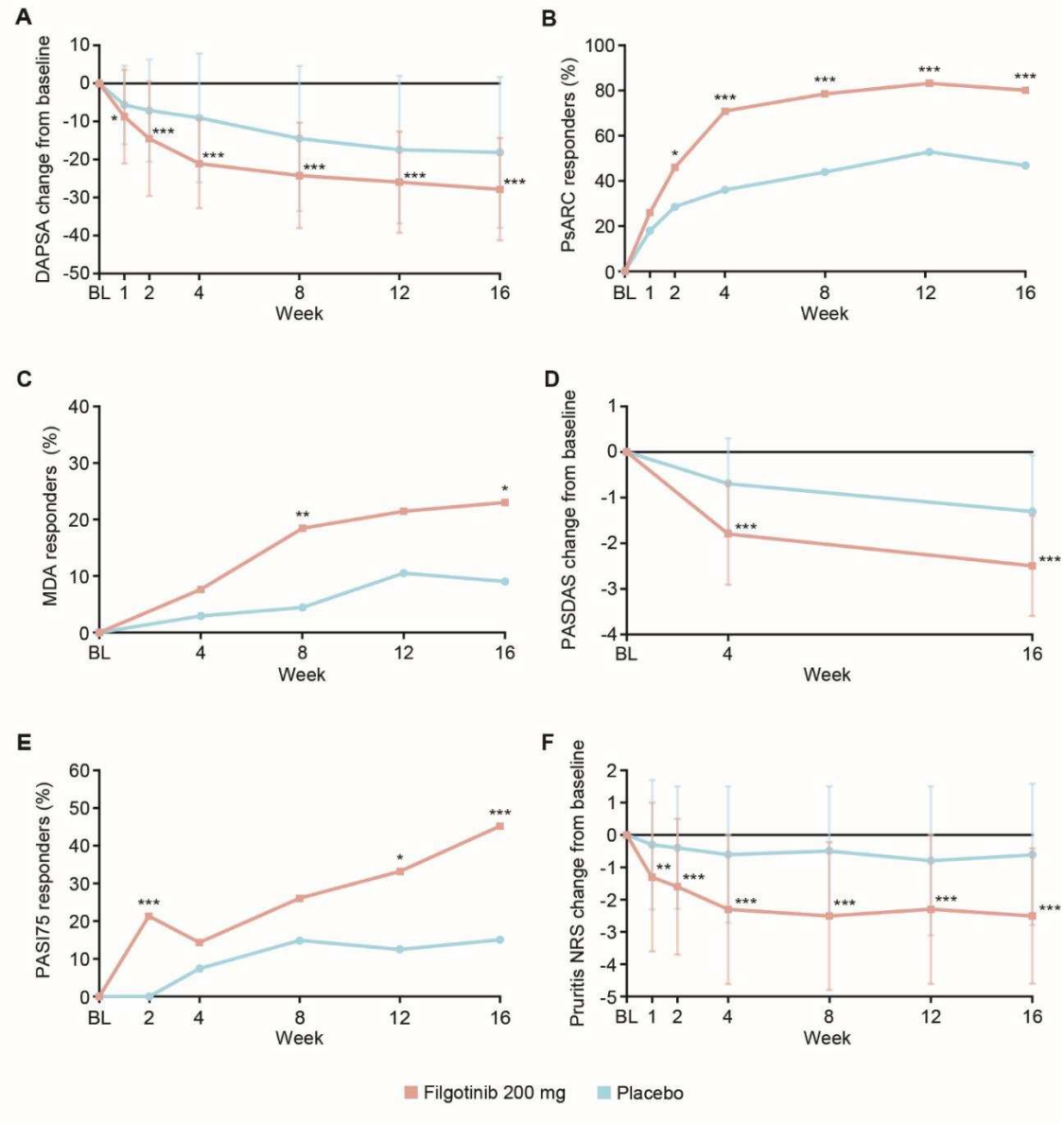
csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; FAS = full analysis set.

Figure 2: **(A) ACR responses at week 16 and (B) ACR20, (C) ACR50 and (D) ACR70 responses over time (NRI; FAS)**



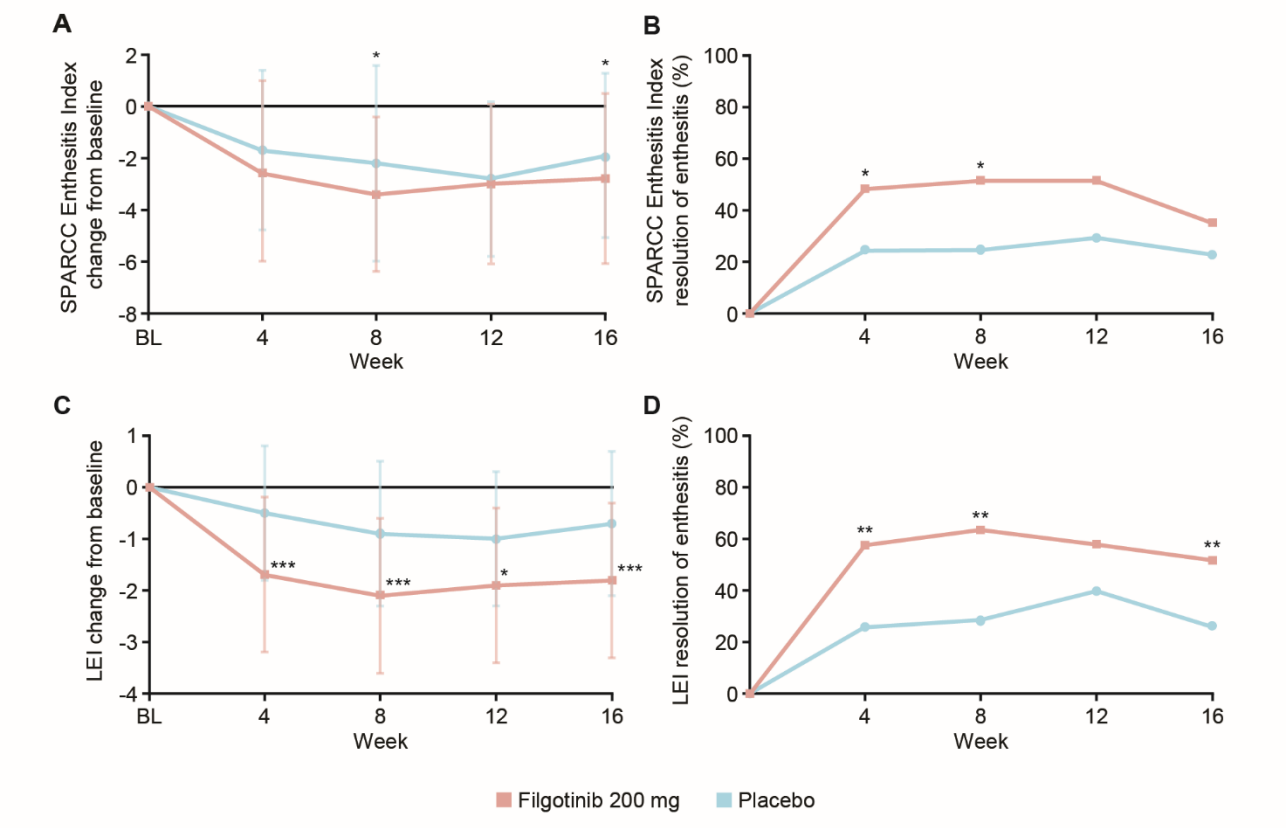
n=65 (filgotinib) and n=66 (placebo). *p<0·05. **p<0·005. ***p<0·001. ACR20 = 20% improvement in the American College of Rheumatology response criteria; ACR50 = 50% improvement in the American College of Rheumatology response criteria; ACR70 = 70% improvement in the American College of Rheumatology response criteria; BL = baseline; FAS = full analysis set; NRI = non-responder imputation.

Figure 3: **Secondary outcomes up to week 16 (FAS)**



(A) Change from baseline in DAPSA [LOCF]. (B) Proportion of PsARC responders [NRI]. (C) Proportion of patients with MDA [NRI] (D) Change from baseline in PASDAS [LOCF]. (E) Proportion of PASI75 responders† [NRI]. (F) Change from baseline in pruritus NRS† [LOCF]. Data are means ± standard deviation (panels A, D, and F) or % of patients (panels B, C and E); n=65 (filgotinib) and 66 (placebo). *p<0·05. **p<0·01. ***p<0·005. †Only assessed in patients with ≥3% body surface area at baseline, n=42 (filgotinib) and n=40 (placebo). BL = baseline; DAPSA = Disease Activity in Psoriatic Arthritis; FAS = full analysis set; LOCF = last observation carried forward; MDA = minimal disease activity; NRI = non-responder imputation; NRS = numerical rating scale; PASDAS = Psoriatic Arthritis Disease Activity Score; PASI75 = 75% reduction in the Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria.

Figure 4: **(A) Change from baseline in SPARCC Enthesitis Index [LOCF]. (B) Proportion of patients with resolution of enthesitis based on SPARCC Enthesitis Index [NRI]. (C) Change from baseline in LEI [LOCF]. (D) Proportion of patients with resolution of enthesitis based on LEI [NRI]†**



Data are means ± standard deviation (panels A and C) or % of patients (panels B and D); 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. *p<0·05. **p<0·01. ***p<0·005. †Only assessed in patients with enthesitis at baseline. BL = baseline; LEI = Leeds Enthesitis Index; SPARCC = Spondyloarthritis Research Consortium of Canada.

Table 1: **Baseline patient and disease characteristics (FAS)**

	Filgotinib (N=65)	**Placebo (N=66)**
Age, years	49 (12·2)	50 (10·9)
Female, n (%)	36 (55)	30 (45)
Weight, kg	81 (19·0)	87 (17·5)
Body mass index, kg/m²	28·6 (6·8)	30·1 (5·7)
Duration of PsA, years	7 (6·7)	7 (6·2)
Tender joint count 68	18·3 (9·2)	21·6 (13·2)
Swollen joint count 66	11·6 (5·1)	12·7 (6·7)
Health Assessment Questionnaire-Disability Index	1·43 (0·5)	1·36 (0·6)
hsCRP, mg/L	13·9 (19·8)	10·9 (17·2)
hsCRP ≥ULN, n (%)	25 (38)	17 (26)
At least 3% body surface area of psoriasis, n (%)	42 (65)	40 (61)
Median Psoriasis Area and Severity Index (IQR)*	6·5 (2·6, 15·0)	6·9 (3·8, 18·6)
PsA Disease Activity Score (PASDAS)	6·1 (0·8)	6·2 (1·0)
Disease Activity Index for PsA (DAPSA)	44·0 (14·3)	47·8 (19·8)
Enthesitis based on SPARCC Enthesitis Index, n (%)	37 (57)	48 (73)
SPARCC Enthesitis Index†	4·9 (3·0)	5·5 (3·8)
Enthesitis based on Leeds Enthesitis Index, n (%)	38 (58)	49 (74)
Leeds Enthesitis Index‡	2·8 (1·4)	2·6 (1·4)
Prior anti-TNF therapy, n (%)	11 (17)	9 (14)
Concurrent csDMARD use, n (%)	47 (72)	50 (76)
Leflunomide, n (%)	2 (3)	4 (6)
Sulfasalazine, n (%)	3 (5)	3 (5)
Methotrexate (oral), n (%)	36 (55)	35 (53)
Methotrexate dose (oral)	1·9 (0·6)	2·3 (0·7)
Methotrexate (subcutaneous), n (%)	5 (8)	8 (12)
Methotrexate dose (subcutaneous)	2·9 (0·9)	2·4 (0·8)
Concurrent steroid use, n (%)	17 (26)	16 (24)
Prednisolone-equivalent dose (oral)	7·8 (2·5)	5·9 (2·6)

All data are mean (standard deviation), unless otherwise indicated. *FAS with baseline body surface area ≥3%. †FAS with enthesitis at baseline (SPARCC Enthesitis Index >0). ‡FAS with enthesitis at baseline (Leeds Enthesitis Index >0). csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; FAS = full analysis set; hsCRP = highly-sensitive C-reactive protein; IQR = interquartile range; PsA = psoriatic arthritis; SPARCC = Spondyloarthritis Research Consortium of Canada; TNF = tumour necrosis factor; ULN = upper limit of normal (≥10 mg/L).

Table 2: **Primary and sensitivity analyses of ACR20 response at week 16 (FAS)**

Imputation method	Filgotinib (N=65)		Placebo (N=66)		Treatment difference		
	Response rate	95% CI	Response rate	95% CI	Response rate	95% CI	p-value*
NRI	80% (52/65)	68·7, 87·9	33% (22/66)	23·2, 45·3	47%	30·2, 59·6	<0·0001
LOCF	83% (54/65)	72·2, 90·3	33% (22/66)	23·2, 45·3	50%	33·5, 62·2	<0·0001
OC	87% (52/60)	75·8, 93·1	34% (22/64)	23·9, 46·6	52%	36·0, 64·6	<0·0001

*p-value was from the Cochran-Mantel-Haenszel test for general association, controlling for randomisation stratification factors. ACR20 = 20% improvement in the American College of Rheumatology response criteria; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; NRI = non-responder imputation; OC = observed cases.

Table 3: **Patient-reported physical functioning, fatigue, and pain outcomes (LOCF; FAS)**

	Filgotinib (N=65)		Placebo (N=66)		Least squares mean difference (95% CI)	p-value*
	Total score	Change from baseline	Total score	Change from baseline		
HAQ-DI						
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, 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, –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, –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, –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, –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, –0·12)	0·0009
FACIT-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, 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, 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, –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, –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, –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, –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, –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, –11·1)	<0·0001

Data are mean (standard deviation) unless otherwise indicated. *Between group p-value calculated from an ANCOVA model on the changes from baseline per visit, with treatment, baseline values and randomisation stratification factors. ANCOVA = analysis of covariance; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire-Disability Index; LOCF = last observation carried forward.

***Table 4*: Safety endpoints and TEAEs of special interest (FAS)**

n (%)	Filgotinib (N=65)	Placebo (N=66)
TEAE	37 (57)	39 (59)
Drug-related TEAE	11 (17)	9 (14)
Serious TEAE	1 (2)*	1 (2)
Drug-related serious TEAE	1 (2)*	0
Serious treatment-emergent infection	1 (2)*	0
Grade ≥3 TEAE	1 (2)*	5 (8)
TEAE leading to permanent discontinuation of study drug	1 (2)†	0
TEAEs of special interest		
Infections	14 (22)	14 (21)
All serious infections	1 (2)*	0
Opportunistic infections	0	0
Herpes zoster	1 (2)	0
Active tuberculosis	0	0
Urinary tract infections	1 (2)	3 (5)
Respiratory tract infections	10 (15)*	10 (15)
Malignancies	0	0
Deep venous thrombosis	0	0
Pulmonary embolism	0	0
Major adverse cardiovascular events	1 (2)*	0
Deaths due to TEAE	1 (2)*	0

*One patient died following onset of pneumonia (the same single case is represented in several categories). †As treatment in the patient that died was not discontinued prior to death, this patient is not counted here. FAS = full analysis set; TEAE = treatment-emergent adverse event.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5–6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Appendix
Participants	4a	Eligibility criteria for participants	7 and appendix
	4b	Settings and locations where the data were collected	7 and appendix
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8–9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	9 and appendix
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			8
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
7Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8
	11b	If relevant, description of the similarity of interventions	A Appendix
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9–10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10

Results			
Participant flow (a diagram is	13a	For each group, the numbers of patients who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10 and figure 1
strongly recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	10
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of patients (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10–13, table 2 and 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	11–12
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	11–12
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13, table 4 and appendix
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15–16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15–16
Other information			
Registration	23	Registration number and name of trial registry	10
Protocol	24	Where the full trial protocol can be accessed, if available	Appendix
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10 and acknowledgements

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

CONSORT Extension for abstracts - Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	2 (page 1)
Authors *	Contact details for the corresponding author	23–24 (page 1)
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	4
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	5–7
Interventions	Interventions intended for each group	8
Objective	Specific objective or hypothesis	2–3
Outcome	Clearly defined primary outcome for this report	10–11
Randomization	How participants were allocated to interventions	7
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	9–10
Results		
Numbers randomized	Number of participants randomized to each group	15
Recruitment	Trial status	4
Numbers analysed	Number of participants analysed in each group	15–16
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	15–17
ack Harms	Important adverse events or side effects	19–22
Conclusions	General interpretation of the results	23–24
Trial registration	Registration number and name of trial register	5
Funding	Source of funding	25

**this item is specific to conference abstracts*