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

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Summary

Background At present, biological disease-modifying anti-rheumatic drugs (DMARDs) are the only treatment recommended for patients with ankylosing spondylitis who have not responded to first-line treatment with non-steroidal anti-inflammatory drugs (NSAIDs). The TORTUGA trial investigated the efficacy and safety of filgotinib, an oral selective Janus kinase 1 (JAK1) inhibitor, for the treatment of patients with active ankylosing spondylitis.

Methods In this completed, randomised, double-blind, placebo-controlled, phase 2 trial, we enrolled adult patients from 30 sites in seven countries (Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine). Eligible patients had active ankylosing spondylitis and an inadequate response or intolerance to two or more NSAIDs. Patients were randomly assigned (1:1) with an interactive web-based response system to receive filgotinib 200 mg or placebo orally once daily for 12 weeks. Randomisation was stratified by current use of conventional synthetic DMARDs and previous receipt of anti-tumour necrosis factor therapy. The patients, study team, and study sponsor were masked to treatment assignment. The primary endpoint was the change from baseline in ankylosing spondylitis disease activity score (ASDAS) at week 12, which was assessed in the full analysis set (ie, all randomised patients who received at least one dose of study drug). Safety was assessed according to actual treatment received. This trial is registered with ClinicalTrials.gov, number NCT03117270.

Findings Between March 7, 2017, and July 2, 2018, 263 patients were screened and 116 randomly assigned to filgotinib (n=58) or placebo (n=58). 55 (95%) patients in the filgotinib group and 52 (90%) in the placebo group completed the study; three (5%) patients in the filgotinib group and six (10%) in the placebo group discontinued treatment. The mean ASDAS change from baseline to week 12 was –1·47 (SD 1·04) in the filgotinib group and –0·57 (0·82) in the placebo group, with a least squares mean difference between groups of –0·85 (95% CI –1·17 to –0·53; p<0·0001). Treatment-emergent adverse events were reported in 18 patients in each group, the most common being nasopharyngitis (in two patients in the filgotinib group and in four patients in the placebo group). Treatment-emergent adverse events led to permanent treatment discontinuation in two patients (a case of grade 3 pneumonia in the filgotinib group and of high creatine kinase in the placebo group). No deaths were reported during the study.

Interpretation Filgotinib is efficacious and safe for the treatment of patients with active ankylosing spondylitis who have not responded to first-line pharmacological therapy with NSAIDs. Further investigation of filgotinib for ankylosing spondylitis is warranted.

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Introduction

Ankylosing spondylitis is a chronic, immune-mediated disease that is characterised by inflammation of the sacroiliac joints and spine and a young age of onset (20–40 years).[1] Some patients also experience signs and symptoms in their peripheral joints (eg, synovitis, enthesitis, and dactylitis), as well as extra-articular manifestations, including anterior uveitis, psoriasis, and inflammatory bowel disease.[1,2] Ankylosing spondylitis has a worldwide prevalence of about 0·5% and is more common in men than in women.[1,3] The disease can be progressive and associated with chronic pain and functional impairment, leading to substantial loss of quality of life and work productivity.[4–6] Ankylosing spondylitis (also known as radiographic axial spondyloarthritis), together with non-radiographic axial spondyloarthritis, comprise the entire spectrum of axial spondyloarthritis.[1]

The primary aim of therapy for patients with ankylosing spondylitis is to maximise physical function and long-term health-related quality of life.[7] Non-steroidal anti-inflammatory drugs (NSAIDs) are the recommended

Research in context

Evidence before this study

We searched PubMed without language restrictions for articles published between Jan 1, 2000, and Aug 30, 2018, that contained the term "ankylosing spondylitis" in the title. Of 4849 articles retrieved, 376 described clinical trials in adults and reported on the safety and efficacy of several potential therapies for ankylosing spondylitis. These included biological disease-modifying anti-rheumatic drugs (DMARDs) that target tumour necrosis factor (TNF; adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), interleukin (IL)-17 (secukinumab), IL-12 and IL-23 (ustekinumab), IL-23 only (risankizumab), IL-6 (sarilumab and tocilizumab), and T-cell activation (abatacept), and targeted synthetic DMARDs, such as a phosphodiesterase type-4 inhibitor (apremilast) and a Janus kinase (JAK)1/3 inhibitor (tofacitinib). To date, the only DMARDs to be approved for ankylosing spondylitis have been anti-TNF agents and secukinumab. Several drugs, including abatacept, apremilast, risankizumab, ustekinumab, tocilizumab, and sarilumab, have not shown efficacy in patients with ankylosing spondylitis compared with placebo. Moreover, currently approved biological DMARDs require injection, which can be inconvenient, and patients with ankylosing spondylitis can experience a lack or loss of response to existing therapies. Therefore, new oral treatments with different modes of action and acceptable routes of administration are needed.

Added value of this study

To our knowledge, this is the first randomised, placebo-controlled, phase 2 study to show the efficacy of a selective JAK1 inhibitor in patients with ankylosing spondylitis, supporting use of selective JAK1 inhibition as a viable new treatment option for these patients. Filgotinib significantly reduced the ankylosing spondylitis disease activity score after 12 weeks compared with placebo in patients with active ankylosing spondylitis. We also assessed the safety and tolerability of filgotinib and its effect on several secondary endpoints, including signs and symptoms of ankylosing spondylitis, physical function, spinal mobility, peripheral arthritis, enthesitis, spinal and sacroiliac joint inflammation (assessed with MRI), fatigue, and quality-of-life measures. We showed that filgotinib was well tolerated over 12 weeks of treatment. The safety profile was consistent with findings from trials of filgotinib in patients with other conditions, including rheumatoid arthritis, Crohn's disease, and psoriatic arthritis.

Implications of all the available evidence

Selective inhibition of JAK1 by filgotinib is effective in treating active ankylosing spondylitis and can be considered for use in patients who have had an inadequate response to first-line pharmacological therapy with non-steroidal anti-inflammatory drugs. The findings of our study might ultimately lead to an increase in the number of treatment options with alternative mechanisms of action available for patients with ankylosing spondylitis. Confirmation of these findings in larger phase 3 trials with longer-term follow-up is needed. Such studies are also necessary to establish the long-term safety profile of selective JAK1 inhibition by filgotinib in patients with active ankylosing spondylitis.

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first-line pharmacological therapy for patients with ankylosing spondylitis.[7] In patients with persistently high disease activity who have had an inadequate response to conventional therapy, the use of biological disease-modifying anti-rheumatic drugs (bDMARDs) is recommended.[7] Current practice is to start with anti-tumour necrosis factor (TNF) therapy; secukinumab, an inhibitor of interleukin (IL)-17, is the only approved bDMARD for ankylosing spondylitis that has an alternative mechanism of action.[7]

The advent of anti-TNF drugs, and more recently of IL-17 inhibitors, represents an important step forwards in the treatment of ankylosing spondylitis. However, a lack or loss of response to existing therapies remains problematic for some patients, especially given the limited availability of drugs with different modes of action.[8] Therapies with alternative mechanisms of action, such as inhibitors of IL-6 or IL-23 pathways, have not shown efficacy.[9,10] Therefore, additional targeted drugs that can effectively improve ankylosing spondylitis outcomes with an acceptable safety profile are needed.

The IL-23/IL-17 immune axis has been implicated in the pathogenesis of ankylosing spondylitis.[11] Several cytokines, including those involved in the IL-23/IL-17 axis, signal through the Janus kinase (JAK) family of tyrosine kinases.[8] Intracellular inhibition of the JAK pathway, therefore, offers the potential to reduce the proinflammatory signalling implicated in the pathogenesis of ankylosing spondylitis.[12,13] Tofacitinib, a JAK inhibitor that preferentially inhibits signalling via JAK3 and JAK1, has shown efficacy in the treatment of patients with active ankylosing spondylitis, including favourable MRI changes; a phase 3 clinical trial of tofacitinib in patients with ankylosing spondylitis is currently recruiting (NCT03502616).[14] Filgotinib is an oral, selective JAK1 inhibitor currently under investigation for the treatment of several inflammatory diseases. Clinical studies have shown the therapeutic potential and acceptable safety profile of filgotinib in rheumatoid arthritis,[15–17] Crohn's disease,[18] and psoriatic arthritis.[19] Several global phase 3 trials of filgotinib are ongoing or have recently been completed, including in patients with rheumatoid arthritis (NCT02873936, NCT02889796, NCT02886728, and NCT03025308), Crohn's disease (NCT02914561 and NCT02914600), or ulcerative colitis (NCT02914522 and NCT02914535). We aimed to investigate the efficacy and safety of filgotinib compared with

placebo for the treatment of patients with ankylosing spondylitis.

Methods

Study design and patients

In this double-blind, randomised, placebo-controlled, phase 2 study, we recruited patients with ankylosing spondylitis at 30 sites in Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine (appendix p 2). Eligible patients were aged 18 years and older with a diagnosis of ankylosing spondylitis that fulfilled the modified New York classification criteria (with sacroiliitis confirmed by radiography within 12 months of screening; appendix p 3).[20] Patients had to have active ankylosing spondylitis, defined as a Bath ankylosing spondylitis disease activity index (BASDAI) of 4 or higher and spinal pain scored as 4 or more at screening and baseline; a high-sensitivity C-reactive protein (CRP) concentration of 3·0 mg/L or higher at screening; and an inadequate response to two or more NSAIDs given at the therapeutic dose range for 4 weeks or more. Permitted conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) during the study (which must have been taken for at least 12 weeks before screening, with a stable dose for at least 4 weeks before baseline) were methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. Use of one NSAID or a cyclooxygenase-2 inhibitor was permitted provided that the drug was used at a stable dose for at least 2 weeks before baseline. Previous use of one TNF inhibitor was allowed (capped at 30% of enrolled patients), with a minimum washout period before screening of 4 weeks (for etanercept), 8 weeks (for adalimumab, certolizumab pegol, and golimumab), or 12 weeks (for infliximab). Patients who were receiving high-potency opioid analgesics (methadone, hydromorphone, morphine, or oxycodone) at the time of the study or had received previous treatment with more than one TNF inhibitor, any alkylating agent, JAK inhibitors, or other investigational or approved biological drug at any time were excluded from the study. Full eligibility criteria are listed in the appendix (pp 4–6).

See Online for appendix

The study protocol was reviewed and approved by the central or individual independent ethics committee in each participating country. The study conformed to Good Clinical Practice guidelines and Declaration of Helsinki Principles. All patients provided written informed consent. An external data monitoring committee reviewed study progress and conducted interim reviews of safety data. A separate cardiovascular event adjudication committee reviewed major adverse cardiovascular events, as well as all deaths. The study protocol and protocol amendments are in the appendix (pp 7–10, 23–138).

Randomisation and masking

Patients were randomly assigned (1:1) with a computerised interactive web-response system, to receive filgotinib 200 mg or matching placebo once a day for 12 weeks. Randomisation was stratified by current use of csDMARDs and previous receipt of TNF inhibitor therapy. Drug kits were identified by a unique number. At baseline and weeks 4 and 8, the site staff contacted the interactive web-response system for the appropriate kit number to dispense; the kit contained the relevant study drugs for the next 4 weeks. Filgotinib and placebo were presented as visually identical, orally administered tablets. The patients, site staff, investigators, study team, and sponsor were masked to treatment assignment.

Procedures

Screening was done within 4 weeks before randomisation. Eligible patients were assessed at baseline (day 1), at weeks 1, 2, 4, 8, and 12, and at a follow-up visit at week 16 (or 4 weeks after the last dose of study drug). Patients were instructed to take their study drugs at the same time each day. Study assessments and their timings are summarised in the appendix (p 11).

Outcomes

The primary endpoint was change from baseline to week 12 in the ankylosing spondylitis disease activity score (ASDAS). ASDAS is a composite score of five domains: total back pain; patient's global assessment of disease activity; peripheral joint pain, joint swelling, or both; duration of morning stiffness; and CRP concentration. The components were scored on a scale of 0 (none) to 10 (very severe) by the patient, except for CRP concentration, which was assessed at a central laboratory. The composite score was calculated centrally by the sponsor. Investigators, study staff, and sponsors were unaware of post-baseline CRP concentrations.

Secondary endpoints included change over time in the ASDAS and in the proportion of patients achieving Assessment of SpondyloArthritis international Society response criteria (ASAS20, ASAS40, ASAS5/6, and ASAS partial remission; full definitions in appendix p 12). As secondary endpoints, we also assessed change over time in 44 tender joint counts and 44 swollen joint counts (assessed only in patients with one or more affected joints at baseline); the proportion of patients with clinically important improvement (decrease of ASDAS from baseline ≥1·1), major improvement (decrease of ASDAS from baseline ≥2·0), or inactive disease (ASDAS <1·3); individual components of the ASAS response criteria and the ASDAS; the BASDAI, including analysis of the individual items; the Bath ankylosing spondylitis functional index (BASFI); the Bath ankylosing spondylitis metrology index (BASMI); the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI score (assessment of 23 spinal discovertebral units) of the spine and of the sacroiliac joints; and scores on the Short-Form Health Survey (SF-36) and the Ankylosing Spondylitis Quality of Life questionnaire (ASQoL). Further information about the assessments of the secondary endpoints is provided in the appendix (p 12).

Safety endpoints were the incidence of adverse events, serious adverse events, and adverse events of special interest (appendix p 94); treatment discontinuations due to adverse events; and changes in laboratory results, electrocardiograms, physical examination results, and vital signs over time. The severity of adverse events was graded with the modified Common Terminology Criteria for Adverse Events (CTCAE), version 4.03; if CTCAE criteria did not exist, grades were allocated according to definitions provided in the appendix (p 14).

Statistical analysis

We calculated that a total sample size of 100 patients would have 81% power to detect a difference of –0·6 in the primary endpoint between filgotinib and placebo. This calculation was based on an unequal variances *t* test, with a two-sided significance level of 5%, and assumed, on the basis of previous studies, that the mean change from baseline to week 12 would be –0·65 (SD 0·83) in the placebo group and –1·25 (1·2) in the filgotinib group.

We analysed the primary endpoint and other continuous variables (ie, changes from baseline) using an ANCOVA model that included factors for treatment, baseline values, and stratification factors. Normality assumptions were met for all changes in ASDAS from baseline at all timepoints in both groups except for the placebo group at week 1. ANCOVA models produced adjusted least squares means, SDs, and 95% CIs for between-group comparisons. Two-sided p values are provided for between-group comparisons at all timepoints. Binary endpoints (proportions of patients who had a response) were compared between treatment groups using the Cochran-Mantel-Haenszel test for general association, controlling for stratification factors. Proportions of patients who had a response in each treatment group and differences in the proportions of patients who had a response between treatment groups were summarised with point estimates. Missing data for continuous variables (including the primary endpoint) were assigned with the last observation carried forward method. Missing data for binary endpoints were handled with the non-responder imputation method. For both continuous and binary endpoints, a predefined secondary analysis was performed using observed cases only. Adherence to treatment was recorded on the patient's diary card and confirmed by recording numbers of study drugs that were dispensed and returned.

All efficacy and safety analyses were done in the full analysis set (ie, all randomised patients who received at least one dose of study drug, which was equal to the intention-to-treat set). Safety analyses were based on actual treatment received. The primary endpoint and selected secondary endpoints (ASAS20 and ASAS40) were additionally analysed in the per-protocol set, which included all patients in the full analysis set who did not experience a major protocol deviation relevant to efficacy. SAS version 9.4 was used for all statistical analyses. The full statistical analysis plan is available in the appendix (pp 139–216). The trial is registered with ClinicalTrials.gov (NCT03117270).

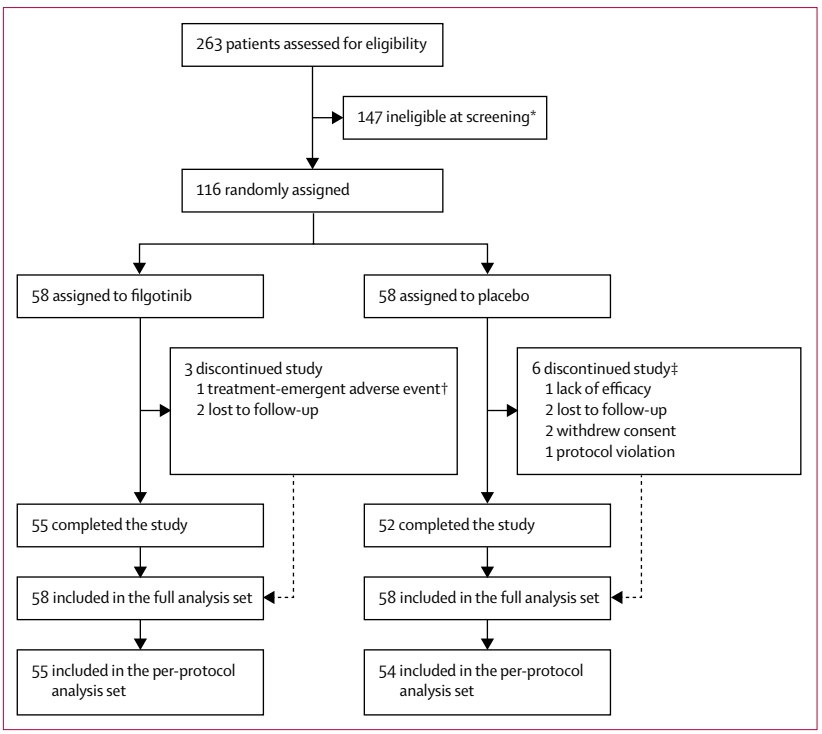

Figure 1: **Trial profile**
*Patients could be ineligible for more than one reason, the most common reasons being not fulfilling criteria for active ankylosing spondylitis (n=67; of whom 58 did not fulfil the Modified New York criteria based on the central reading and nine did not fulfil the diagnosis or criteria for another reason); having concentrations of high-sensitivity C-reactive protein <3·0 mg/L (n=45); having positive serology for HIV-1, HIV-2, hepatitis B virus (HBV), or hepatitis C virus (HCV), or any history of infection with HBV or HCV (n=30); having out-of-range laboratory values (n=13); and having untreated or inadequately treated tuberculosis infection (n=9). †Case of grade 3 pneumonia in a woman aged 49 years who was a current smoker. ‡One patient temporarily discontinued treatment because of an adverse event (grade 3 neutropenia) but restarted treatment and completed all study visits.

Role of the funding source

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

Results

263 patients were screened for eligibility between March 7, 2017, and July 2, 2018. Of these, 116 were enrolled and randomly assigned to receive filgotinib 200 mg (n=58) or placebo (n=58). 55 (95%) patients in the filgotinib group and 52 (90%) in the placebo group completed the study. Reasons for discontinuation are shown in figure 1. Demographic and baseline disease characteristics were similar between the treatment groups, apart from the mean baseline SPARCC spine score, which was higher in the filgotinib group than in the placebo group (table 1). 56 (97%) patients in the

	Filgotinib (n=58)	Placebo (n=58)
Age (years)	41 (11·6)	42 (9·0)
Sex		
Female	13 (22%)	17 (29%)
Male	45 (78%)	41 (71%)
Weight (kg)	75 (11·9)	77 (18·2)
Body-mass index (kg/m²)	25·3 (3·7)	26·4 (5·2)
Time since diagnosis (years)	6 (5·5)	8 (7·6)
HLA-B27 positivity	51 (88%)	51 (88%)
ASDAS	4·2 (0·6)	4·2 (0·8)
BASDAI	6·9 (1·2)	7·0 (1·3)
BASFI	7·0 (1·5)	6·9 (1·6)
BASMI (linear)	5·1 (1·7)	5·3 (1·6)
High-sensitivity CRP (mg/L)	19·6 (13·3)	21·2 (23·0)
High-sensitivity CRP ≥ULN*	41 (71%)	34 (59%)
MRI SPARCC spine	19·0 (19·7)	13·8 (19·9)
MRI SPARCC sacroiliac joint	6·8 (10·9)	5·3 (6·9)
Enthesitis at baseline†	47 (81%)	48 (83%)
MASES enthesitis	4·9 (2·8)	4·1 (2·9)
csDMARD use	23 (40%)	22 (38%)
Methotrexate	9 (16%)	4 (7%)
Sulfasalazine (oral)	14 (24%)	18 (31%)
NSAID use	43 (74%)	38 (66%)
Steroid use	7 (12%)	10 (17%)
Previous TNF inhibitor therapy	4 (7%)	7 (12%)

Data are mean (SD) or n (%). ASDAS=ankylosing spondylitis disease activity score. BASDAI=Bath ankylosing spondylitis disease activity index. BASFI=Bath ankylosing spondylitis functional index. BASMI=Bath ankylosing spondylitis metrology index. csDMARD=conventional synthetic disease-modifying anti-rheumatic drug. CRP=C-reactive protein. MASES=Maastricht ankylosing spondylitis enthesitis score. NSAID=non-steroidal anti-inflammatory drug. SPARCC=Spondyloarthritis Research Consortium of Canada. TNF=tumour necrosis factor. ULN=upper limit of normal. *The ULN for high-sensitivity CRP is 10 mg/L. †Data are shown for patients with one or more tender enthesis at baseline.

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

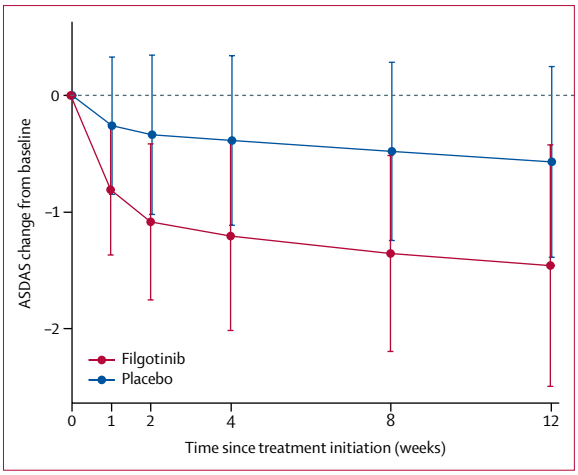

Figure 2: **ASDAS change over time (full analysis set)**
Mean values are shown with SDs. p<0·0001 for the difference between groups at all timepoints. ASDAS=ankylosing spondylitis disease activity score.

filgotinib group and 55 (95%) in the placebo group continued on at least one concomitant medication; the most common concomitant medications were NSAIDs (table 1). Mean on-treatment adherence during the study was 99·3% (SD 5·9) for the filgotinib group and 99·2% (3·5) for the placebo group.

The mean change from baseline to week 12 in ASDAS was –1·47 (SD 1·04) in the filgotinib group and –0·57 (0·82) in the placebo group (figure 2), with a least squares mean difference between groups of –0·85 (95% CI –1·17 to –0·53; p<0·0001; appendix p 15). Analysis of the primary outcome in the per-protocol population confirmed this result: the mean change from baseline to week 12 in the per-protocol population was –1·4 (SE 0·13) in the filgotinib group and –0·5 (0·10) in the placebo group (least squares mean difference –0·88, 95% CI –1·19 to –0·57; p<0·0001).

The difference between groups in the effect on ASDAS was significant as of week 1 (figure 2). A major improvement in ASDAS at week 12 was observed in 19 (33%) of 58 patients in the filgotinib group and in one (2%) of 58 patients in the placebo group (difference 31%, 95% CI 18 to 44; p<0·0001; figure 3). A clinically significant improvement in ASDAS at week 12 was observed in 38 (66%) patients in the filgotinib group compared with 15 (26%) patients in the placebo group (40%, 22 to 54; p<0·0001). Inactive disease at week 12 was achieved in three (5%) patients treated with filgotinib and in no patients treated with placebo (5%, –2 to 14; p=0·092; figure 3). Values for all primary and secondary efficacy endpoints at baseline and week 12 are shown in the appendix (p 15–17).

At week 12, an ASAS20 response was achieved by 44 (76%) of 58 patients assigned to filgotinib and by 23 (40%) of 58 patients assigned to placebo (difference 36%, 95% CI 18 to 51; p<0·0001; figure 3). ASAS40 was achieved by 22 (38%) patients assigned to filgotinib and by 11 (19%) patients assigned to placebo (19%, 3 to 34; p=0·019; figure 3). ASAS5/6 was achieved in 34 (59%) patients in the filgotinib group and in 12 (21%) patients in the placebo group (38%, 20 to 52; p<0·0001; figure 3), and ASAS partial remission in seven (12%) patients in the filgotinib group and in two (3%) patients in the placebo group (9%, –2 to 20; p=0·10; figure 3). Analysis of ASAS20 and ASAS40 in the per-protocol population confirmed these results (appendix p 18).

The mean change from baseline to week 12 in 44 tender joint counts was –2·85 (SD 3·00) in the filgotinib group (n=41) and –1·49 (2·49) in the placebo group (n=47; least squares mean difference –0·79, 95% CI –1·68 to 0·11; p=0·085). The mean change from baseline to week 12 in 44 swollen joint counts was –1·67 (1·88) for the filgotinib group (n=15) and –1·75 (1·65) for the placebo group (n=20; –0·31, –0·76 to 0·15; p=0·18).

At week 12, the BASDAI score had significantly decreased in the filgotinib group compared with the

placebo group (mean change from baseline –2·41 [SD 2·01] *vs* –1·44 [2·02]; least squares mean difference –1·00, 95% CI –1·69 to –0·30; p=0·0052), and this difference was significant from week 8 onwards (figure 4). The results for the individual components of the BASDAI are in the appendix (p 15).

There was also a significant improvement in the overall BASFI at week 12 in the filgotinib group compared with the placebo group (–2·45 [SD 1·90] *vs* –1·23 [1·88]; –1·11, 95% CI –1·78 to –0·43; p=0·0015); the difference was significant from week 8 (figure 4). Spinal mobility, as assessed with the BASMI, improved significantly from baseline to week 12 in the filgotinib group compared with the placebo group (–0·75 [1·02] *vs* –0·39 [0·70]; –0·39, –0·68 to –0·10; p=0·0093), and the difference was significant from week 4 onwards (figure 4). SPARCC spine (–5·76 [11·13] *vs* 0·52 [7·47]; –5·69, –9·75 to –1·62; p=0·0066) and SPARCC sacroiliac joint (–3·52 [7·31] *vs* 0·06 [3·51]; –2·33, –4·20 to –0·46; p=0·0150) scores were also significantly decreased in the filgotinib group at week 12 compared with the placebo group (figure 5).

The change from baseline to week 12 in high-sensitivity CRP concentrations was –10·84 mg/L (SD 13·91) in the filgotinib group and –2·24 mg/L (17·35) in the placebo group, with a least squares mean difference between groups of –9·32 mg/L (95% CI –14·01 to –4·62; p<0·0001). The effect of filgotinib on concentration of high-sensitivity CRP was significant compared with placebo at all timepoints (figure 4). The proportion of patients whose high-sensitivity CRP concentration changed from high at baseline to normal at 12 weeks was significantly higher in the filgotinib group than in the placebo group (66% [27/41] *vs* 18% [6/34]; difference 48%, 95% CI 26 to 64; p<0·0001).

At week 12, patients in the filgotinib group also had significantly improved scores on the ASQoL and the physical components of the SF-36 compared with patients in the placebo group (appendix p 15). Mean changes in ASQoL scores were –4·76 (SD 4·50) in the filgotinib group and –2·24 (3·97) in the placebo group, with a least squares mean difference between groups of –2·35 (95% CI –3·92 to –0·77; p=0·0038). The mean change from baseline in the SF-36 physical component score was 8·44 (SD 8·18) for the filgotinib group versus 3·84 (7·10) for the placebo group, with a least squares mean difference between groups of 4·41 (1·88 to 6·93; p=0·0008). The mean change from baseline in the SF-36 mental component score was 3·95 (SD 7·05) for the filgotinib group versus 1·00 (9·83) for the placebo group (least squares mean difference 2·54, 95% CI –0·21 to 5·29; p=0·070).

The proportion of patients who had at least one treatment-emergent adverse event was the same in both groups (31% [18/58] in both; table 2). These events were generally mild or moderate in severity, with only two events reported as grade 3 or higher, both in the filgotinib group (appendix p 19). The most common treatment-emergent adverse event was nasopharyngitis (two patients in the filgotinib group and four in the placebo group; appendix p 19). The one serious treatment-emergent adverse event was a case of grade 3 pneumonia in a woman aged 49 years in the filgotinib group who was a current smoker; she discontinued the study drug and recovered after antibiotic treatment in hospital. The only other treatment-emergent adverse event to lead to permanent discontinuation of study drug, high creatine kinase, was in the placebo group (table 2). There was one other treatment-emergent adverse event of special interest reported: a non-serious, grade 2 deep vein thrombosis in the calf musculature of a man aged 53 years who had a heterozygous factor V Leiden mutation, diagnosed 3 days after the patient's last dose of filgotinib. There were no malignancies (including lymphomas), opportunistic infections, cases of active tuberculosis, extra-articular manifestations (inflammatory bowel disease, psoriasis, or uveitis), or deaths reported in the study. Reports of any infection did not differ significantly between the groups (12% [7/58] of patients in both groups).

Key laboratory parameters monitored in this study are listed in the appendix (p 20). Compared with patients in

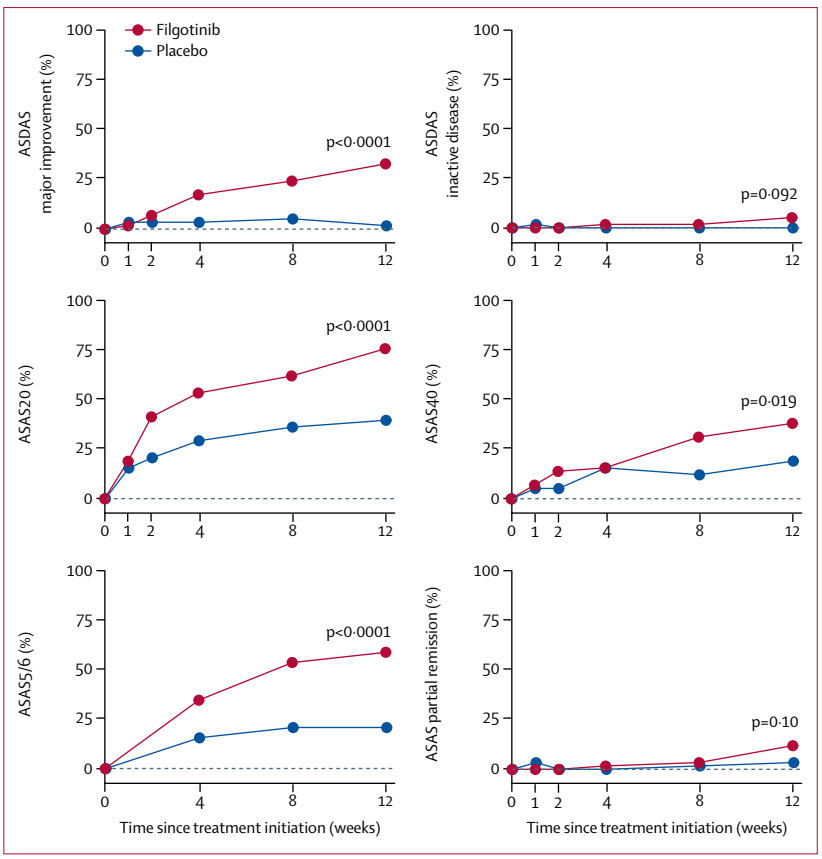

Figure 3: **Proportions of patients reporting major improvements, inactive disease, and fulfilment of ASAS response criteria over time (full analysis set)**

Definitions of ASAS response criteria are in the appendix (p 12). p values for the difference between groups at week 12 are shown; p values for all other timepoints are in the appendix (p 16). ASAS=Assessment of SpondyloArthritis international Society. ASDAS=ankylosing spondylitis disease activity score.

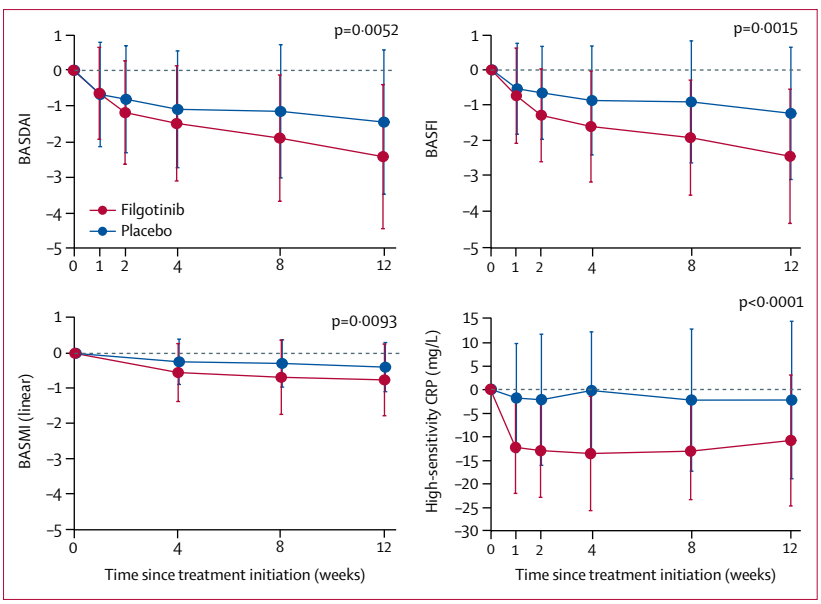

Figure 4: **Change over time in BASDAI, BASFI, BASMI (linear), and high-sensitivity CRP (full analysis set)**
Mean values are shown with SDs. p values for the difference between groups at week 12 are shown; p values for all other timepoints are in the appendix (p 17). BASDAI=Bath ankylosing spondylitis disease activity index. BASFI=Bath ankylosing spondylitis functional index. BASMI=Bath ankylosing spondylitis metrology index. CRP=C-reactive protein.

the placebo group at 12 weeks, patients in the filgotinib group had increased haemoglobin concentrations, decreased platelet counts, and increased creatine kinase concentrations. No patient had thrombocytopenia or thrombocytosis. There were no clinically significant changes in mean neutrophil counts with filgotinib, although five patients in that group had grade 2 or above neutropenia during the study (compared with no patients in the placebo group), with grade 3 neutropenia in one patient leading to temporary study drug discontinuation; all events were resolved without intervention by the next study visit. There was no clinically significant change in either group in the mean number of circulating natural killer cells compared with baseline. No case of liver toxicity was observed during the study; one patient treated with filgotinib had grade 2, asymptomatic hyperbilirubinemia. Total cholesterol, LDL, and HDL increased between baseline and week 12 in the filgotinib group and decreased during that time in the placebo group. The ratio of LDL to HDL had decreased in both groups at week 12 but to a greater extent in the filgotinib group than in the placebo group. Grade 2 or higher increases in creatine kinase concentration were reported in one patient on filgotinib (resulting in a treatment-emergent adverse event) and two patients on placebo (asymptomatic).

Discussion

To our knowledge, the TORTUGA trial is the first clinical trial to investigate a selective JAK1 inhibitor for the treatment of adult patients with active ankylosing spondylitis. This phase 2 study explored the effect of oral filgotinib on ankylosing spondylitis in terms of disease activity (including MRI-documented inflammation), signs and symptoms, physical function, quality of life, and safety. The study met its primary endpoint, with patients in the filgotinib group having a significantly greater reduction in disease activity, as assessed by change in ASDAS from baseline to week 12, than patients in the placebo group. Significantly more patients experienced a clinically important or major improvement in ASDAS with filgotinib than with placebo through week 12. Moreover, the onset of therapeutic effect with filgotinib was rapid, with significant improvements in disease activity observed as of week 1. This observation is consistent with the previously observed rapid onset of action reported in the DARWIN1 and DARWIN2 trials of filgotinib in rheumatoid arthritis.[15,16] We found that filgotinib consistently performed better than placebo in terms of secondary efficacy outcomes, including MRI-assessed inflammation.

The safety profile of filgotinib in patients with ankylosing spondylitis was consistent with that described in clinical trials in patients with other indications.[15,16,18] We found that filgotinib was well tolerated and adverse events were mostly mild or moderate. The proportions of patients who had treatment-emergent adverse events or discontinued treatment early because of a treatment-emergent adverse event during the study were the same in both groups. Clinical data on JAK inhibitors have raised potential class-related safety concerns, including risk of infection, tuberculosis, pneumonia, malignancies, and thromboembolic events.[15,16,21] In this study, infections occurred in 12% of patients in both treatment groups over 12 weeks; however, serious pneumonia was reported for one patient in the filgotinib group who had additional risk factors (she was a current smoker). This patient recovered after antibiotic treatment. Additionally, non-serious deep vein thrombosis was reported in one patient in the filgotinib group who was heterozygous for factor V Leiden mutation. An increased risk of some thromboembolic events, such as pulmonary thrombosis, but not deep vein thrombosis or pulmonary embolism, has been reported for JAK1/2 and JAK1/3 inhibitors in patients with rheumatoid arthritis,[22,23] but a clear mechanistic explanation for this effect is lacking. Such findings are confounded by the increased risk of thromboembolic events, compared with the general population, in patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or undifferentiated spondyloarthritis[24,25] and patients receiving biologics and csDMARDs.[22] In line with other studies of filgotinib,[15,16] our laboratory results showed that mean haemoglobin and creatine kinase concentrations were increased, and mean platelet counts and LDL to HDL ratios were decreased, at week 12 in patients treated with filgotinib compared with patients treated with placebo, which was primarily driven by an increase in HDL

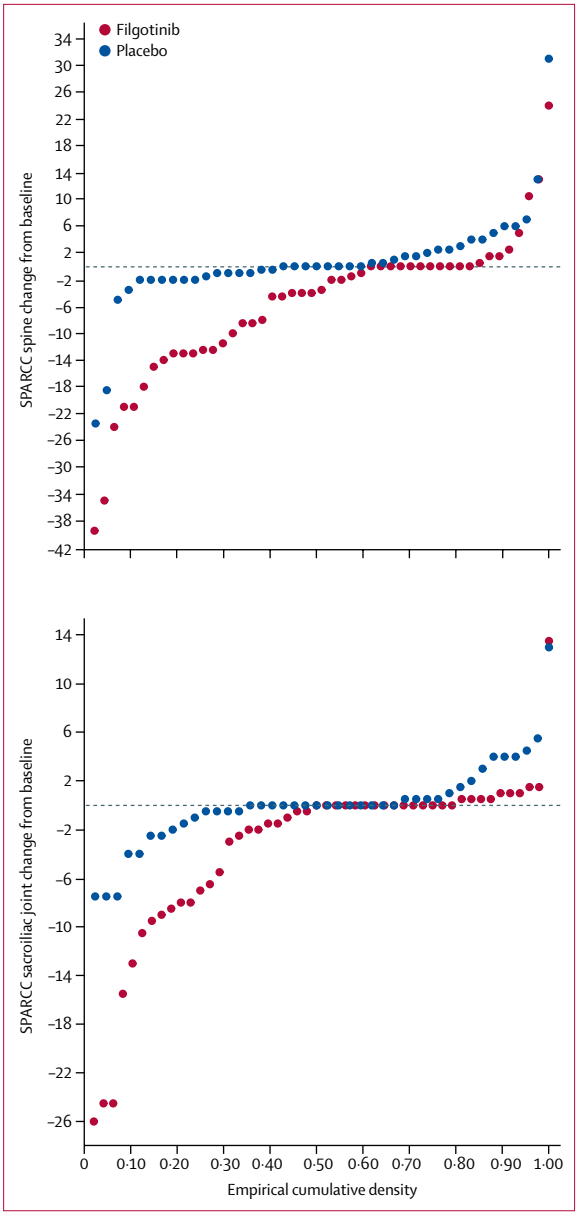

Figure 5: **Cumulative probability of change in MRI SPARCC spine and sacroiliac joint scores (observed cases in the full analysis set)**
SPARCC=Spondyloarthritis Research Consortium of Canada.

	Filgotinib (n=58)	Placebo (n=58)
Treatment-emergent adverse event	18 (31%)	18 (31%)
Drug-related	7 (12%)	8 (14%)
Grade 3 or higher	2 (3%)	0
Leading to permanent discontinuation of study drug	1 (2%)	1 (2%)
Serious treatment-emergent adverse event	1 (2%)	0
Drug-related	0	0
Serious treatment-emergent infection	1 (2%)	0
Treatment-emergent adverse event of special interest	2 (3%)	0
Pneumonia (serious)	1 (2%)	0
Deep vein thrombosis (non-serious)	1 (2%)	0
Deaths	0	0

Data are n (%).

Table 2: **Treatment-emergent adverse events and deaths (full analysis set)**

cholesterol. Longer-term follow-up in patients with ankylosing spondylitis is required to confirm the initial safety findings reported here.

Anti-TNF drugs are the standard of care in patients with ankylosing spondylitis with persistently high disease activity after treatment with NSAIDs. Drugs targeting the IL-17 immune axis have been recently approved for this indication, and drugs targeting JAK signalling are being assessed in clinical studies (NCT03502616 and NCT03178487). In this study, we assessed the efficacy of filgotinib, a JAK1 inhibitor, and showed that it significantly decreased ASDAS at week 12 compared with placebo in patients with active ankylosing spondylitis. The efficacy of filgotinib in reducing ASDAS in our study is encouraging and in line with that reported for other therapies under investigation for the treatment of ankylosing spondylitis.[14,26,27]

The effects of filgotinib on secondary endpoints in this study are generally consistent with those seen in previous studies[14,26–30] of other therapies for this indication, including anti-TNF drugs, a JAK1/3 inhibitor, and therapies targeting IL-17. The low proportions of patients with inactive disease and partial remission at 12 weeks in this study were probably due to the high level of disease activity at baseline (eg, high baseline scores for ASDAS, BASDAI, and SPARCC spine) and the short trial length; a longer trial duration would be needed to more thoroughly investigate the effect of filgotinib on these endpoints. There were greater decreases in 44 tender and 44 swollen joint counts with filgotinib than with placebo at week 12, although the differences between groups in these changes were not significant. This finding might be related to the small number of patients included in these analyses (only patients with one or more affected joints at baseline were included), and the low number of joints at baseline meant that there was limited opportunity to show a significant benefit (so-called floor effect[31]). In phase 2 studies that focused on the effects of filgotinib in patients with rheumatoid arthritis (DARWIN1 and DARWIN2[15,16]) or psoriatic arthritis (EQUATOR[19]), this treatment was shown to have a positive effect on the symptoms of peripheral arthritis.

The number of patients, duration of follow-up, and use of one dose of filgotinib in this study are consistent with other phase 2 studies of drugs. Our study has some limitations. No formal dose-finding study for filgotinib in patients with ankylosing spondylitis was done before study initiation; instead, we selected the highest dose currently being tested in phase 3 trials (NCT02873936,

NCT03025308, NCT02886728, and NCT02889796) in patients with rheumatoid arthritis. A high proportion of patients in our study had elevated CRP at baseline, which is a known predictor of a good response to some therapies;[7] this might have, in part, contributed to the observed findings for filgotinib. However, the mean baseline CRP concentration and proportion of patients with elevated CRP in this study is in line with values reported in previous studies.[10,27,28] Additionally, patient-reported outcomes, such as the BASDAI, confirmed the findings of the other endpoints that included a CRP component, such as the ASDAS. The small sample size restricted analysis of the activity of filgotinib in patient subgroups, such as those receiving different concomitant DMARDs at baseline or by previous receipt of TNF inhibitor therapy. Moreover, the effect of filgotinib in patients with the entire spectrum of axial spondyloarthritis, including non-radiographic axial spondyloarthritis, should be studied. The results of this phase 2 study should be interpreted in the context of these considerations and confirmed in larger phase 3 trials.

In conclusion, selective inhibition of JAK1 by filgotinib reduced disease activity and signs and symptoms more effectively than did placebo in patients with active ankylosing spondylitis. Filgotinib was well tolerated through 12 weeks of treatment, and new safety signals were not seen. The results of this study add to the weight of evidence supporting the benefit of selective JAK1 inhibition by filgotinib in a range of inflammatory diseases.[32,33]

Contributors

DvdH, CT, LM, and RL were involved in study design. VT, ON, LM, and RB were involved in data collection. LM, RB, and KL were involved in data analysis. DvdH, XB, LSG, WPM, WA-S, CT, LM, RB, TH, NM, JMG, AD, and RL were involved in data interpretation. All authors reviewed and revised drafts of the manuscript and approved the final draft.

Declaration of interests

DvdH has received consulting fees from AbbVie, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb (BMS), Boehringer Ingelheim, Celgene, Daiichi, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, and UCB and is the director of Imaging Rheumatology BV. XB has received grants or research support and consultation fees from AbbVie, BMS, Celgene, Chugai, Eli Lilly, Galapagos, Hexal, Janssen, Merck, Novartis, Pfizer, Sandoz, and UCB, outside of the submitted work. LSG has received grants from AbbVie, Amgen, Novartis, and UCB and consulting fees from Eli Lilly, Galapagos, Janssen, Novartis, and Pfizer during the conduct of the study. WPM has received personal fees from Galapagos during the conduct of the study, and grants and consulting fees from AbbVie, Janssen, Novartis, and Pfizer, and consulting fees from, Boehringer Ingelheim, Celgene, Eli Lilly, and UCB, outside of the submitted work. VT and ON have received fees for performance of this study from Galapagos. WA-S, CT, LM, RB, and TH are employees of and have received warrants from Galapagos during the conduct of the study. NM, KL, and JMG are employees of and hold stock, stock options, or shares with Gilead Sciences. AD has received consultancy fees from Galapagos during the conduct of the study, and consultancy fees from BMS and research grants and consultancy fees from AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, and UCB, outside of the submitted work. RL has received consulting fees from Galapagos during the conduct of the study, and consulting fees from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Novartis, Merck, Pfizer, Roche, Schering, TiGenix, and UCB outside of the submitted work. RL is also a director of Rheumatology Consultancy BV.

Data sharing

Data sharing with regard to this study is being managed by Gilead Sciences. The clinical study report synopsis and de-identified patient-level data from clinical trial analysis datasets will be made available 6 months after approval of the study drug by the US Food and Drug Administration and European Medicines Agency until an indefinite date. Research proposals should be submitted to Gilead Sciences at datarequest@gilead.com. Access to these data will be provided in a secured analysis environment to qualified external researchers who have been approved by Gilead Sciences, depending on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. To gain access, approved requestors will need to sign a data-sharing agreement.

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