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).

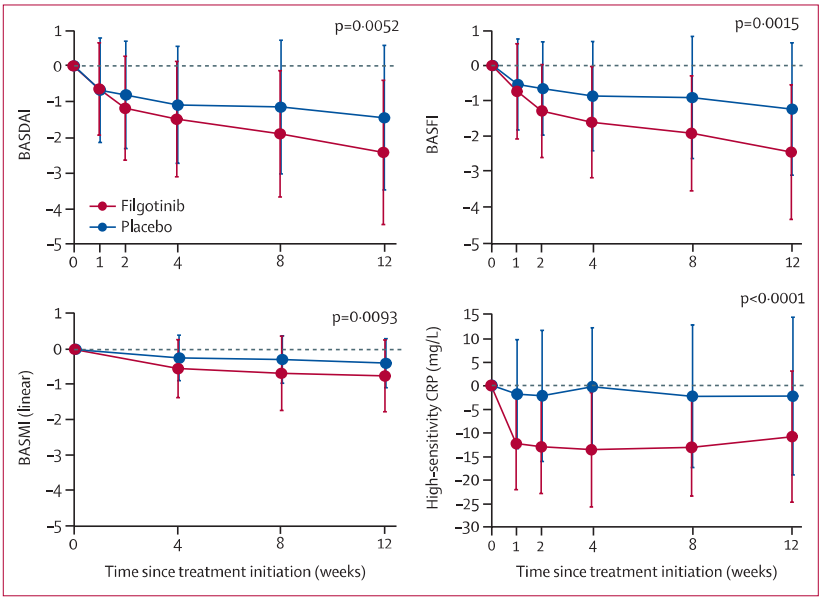

Figure 4: **Change over time in BASDAI, BASFI, BASMI (linear), and high-sensitivity CRP (full analysis set)**
Mean values are shown with SDs. p values for the difference between groups at week 12 are shown; p values for all other timepoints are in the appendix (p 17). BASDAI=Bath ankylosing spondylitis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

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

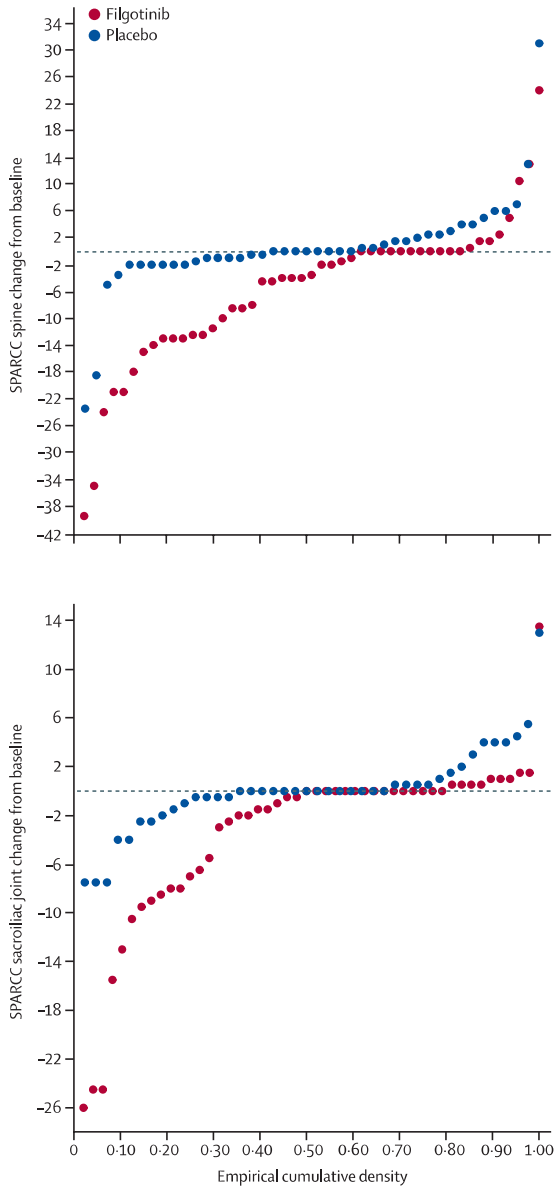

Figure 5: **Cumulative probability of change in MRI SPARCC spine and sacroiliac joint scores (observed cases in the full analysis set)**
SPARCC=Spondyloarthritis Research Consortium of Canada.

	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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