	Filgotinib (n=65)	Placebo (n=66)
Treatment-emergent adverse events		
All	37 (57%)	39 (59%)
Nasopharyngitis	8 (12%)	10 (15%)
Headache	3 (5%)	5 (8%)
Blood cholesterol increased	5 (8%)	0
Diarrhoea	2 (3%)	2 (3%)
Dizziness	2 (3%)	2 (3%)
Drug-related	11 (17%)	9 (14%)
Serious	1 (2%)*	1 (2%)
Drug-related serious	1 (2%)*	0
Serious treatment-emergent infection	1 (2%)*	0
Grade 3 or worse	1 (2%)*	5 (8%)
Led to permanent discontinuation of study drug	1 (2%)†	0
Treatment-emergent adverse events 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 treatment-emergent adverse event	1 (2%)*	0

Data are n (%). The top five most common treatment-emergent adverse events are shown. *One patient died following onset of pneumonia (the same single case is represented in several categories). †Since treatment in the patient that died was not discontinued before, this patient is not included here.

Table 4: **Safety endpoints (full analysis set)**

Filgotinib improved the patient-reported outcomes for physical functioning (p=0·0009), fatigue (p=0·0086), and pain (p<0·0001; table 3). Improvements in some measures were evident as early as week 1 (pain) or week 2 (physical functioning; table 3). At week 16, Health Assessment Questionnaire-Disability Index scores decreased by 0·57 in the filgotinib group compared with a decrease of 0·28 for placebo (LS mean difference –0·3 [95% CI –0·4 to –0·1], p=0·0009). 41 (65%) of 63 patients who received filgotinib achieved a clinically important improvement from baseline (defined as a change ≥0·35),[25] compared with 26 (42%) of 62 patients who received placebo (treatment difference 23% [95% CI 5·7–38·8]; p=0·0085). The mean change from baseline in Functional Assessment of Chronic Illness Therapy–Fatigue total score at week 16 was 8·2 (SD 7·3) for filgotinib and 5·5 (8·1) for placebo (LS mean difference 3·2 [0·8–5·5]; p=0·0086). The mean decrease from baseline in psoriatic arthritis-related pain intensity was also greater for filgotinib compared with placebo (–31·6 mm [SD 21·3] *vs* –11·1 mm [29·7]; LS mean difference –18·9 [95% CI –26·7 to –11·1], p<0·0001).

The proportion of patients who had at least one treatment-emergent adverse event was similar between the two groups (table 4). Treatment-emergent adverse events were mostly mild or moderate in severity, with only six events at grade 3 or worse (table 4, appendix p 18). The most common treatment-emergent adverse events were nasopharyngitis and headache, the incidences of which were similar between the two groups (table 4, appendix p 18). Treatment was discontinued in one patient in the filgotinib group due to endometrial hypertrophy. This treatment-emergent adverse event began 3 days after first study drug intake but was not considered related to drug (table 4). Two serious treatment-emergent adverse events were reported: pneumonia with a fatal outcome in a patient receiving filgotinib and a hip fracture after a fall in a patient receiving 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. He received methotrexate (15 mg/week) and methylprednisolone acetate (8 mg/day) for psoriatic arthritis, and folic acid for prophylaxis (concomitant medications). Pneumonia onset was at day 106 of treatment; the patient died on day 107. No hepatobiliary disorders were reported in the filgotinib group, compared with one (2%) of 66 patients in the placebo group. Liver function analysis did show that a small number of patients had increased γ-glutamyltransferase (filgotinib four [6%] of 65], placebo none [0%] of 66), alanine aminotransferase (filgotinib one (2%) of 65, placebo two [3%] of 66), and aspartate amino transferase (filgotinib one [2%] of 65, placebo none [0%] of 66). No gastric perforations, malignancies, lymphomas, venous thromboembolic events, opportunistic infections, or cases of active tuberculosis were reported. There was one case of herpes zoster confined to a single dermatome in the filgotinib group. The incidence of infections was similar between the two groups (table 4).

Key laboratory parameters from baseline to week 16 are listed in the appendix (p 19). At week 16, creatinine concentrations were similar to baseline (mean change from baseline: filgotinib 3 [SD 8·3], placebo 0 [7·9]). Mean change in haemoglobin concentrations (filgotinib 6 g/L [8·2] *vs* placebo 1 g/L [9·2]) and platelet counts (–16 giga/L [62·0] *vs* 7 giga/L [57·4]) differed between the filgotinib and placebo groups. Natural killer cell counts (indicated by percent change from baseline) were stable in the filgotinib group (–4·2% [46·9]), but increased in the placebo group (12·9% [32·5]). Mean total cholesterol increased from baseline in patients treated with filgotinib (0·45 mmol/L [1·0]) compared with placebo (0·09 mmol/L [0·8]). This increase in the filgotinib group was driven mainly by HDL (0·37 mmol/L [0·3]), resulting in a 15·0% decrease in the LDL:HDL ratio from baseline compared with a 5·5% increase in the LDL:HDL ratio in

the placebo group (appendix p 19). Changes in other laboratory parameters, vital signs, or ECGs were similar to reported data for filgotinib and no new safety signals were found.

Discussion

To our knowledge, EQUATOR is the first clinical trial to investigate a selective JAK1 inhibitor for the treatment of psoriatic arthritis. This phase 2 study explored the effect of filgotinib on patients with active psoriatic arthritis with regards to disease activity, physical functioning, and safety. Filgotinib did significantly better than placebo in terms of efficacy, as shown by the greater proportion of patients who met the primary endpoint of ACR20 response after 16 weeks of treatment (filgotinib 80% *vs* placebo 33%). Filgotinib's onset of action was rapid, with measurable improvements in disease activity after 1 week of treatment. Compared with placebo, filgotinib significantly improved signs and symptoms of peripheral arthritis, enthesitis, and psoriasis, and overall psoriatic arthritis disease control (according to PASDAS and fulfilment of minimal disease activity criteria). Although the improvement in nail disease with filgotinib was not significant, week 16 might be too early a timepoint to expect complete resolution of nail disease and, notably, not all patients had nail disease at baseline. Filgotinib had a beneficial effect on patient-reported outcomes of physical functioning, fatigue, and pain, with significant improvements in psoriatic arthritis-related pain intensity at week 1 and in HAQ-DI at week 2. These time of onset findings for responses to filgotinib in psoriatic arthritis are similar to those reported by phase 2 trials in rheumatoid arthritis,[19,20] and are probably of interest to prospective patients.

Filgotinib was well tolerated and associated with mostly mild or moderate adverse events that required no intervention different from routine medical practice. For treatment-emergent adverse events and treatment discontinuations due to such events, the safety profile of filgotinib was similar to that of placebo. This finding is consistent with safety results from the DARWIN trials in rheumatoid arthritis over 24 weeks.[19,20] Clinical data on JAK inhibitors have raised potential safety concerns with regards to the risk of infections, particularly herpes zoster, pneumonia, and opportunistic pathogens.[26] In the present study, incidence of infections was similar between the groups through to 16 weeks; however, there was one case of serious infection (pneumonia) that led to death in the filgotinib group. The incidence of serious infections was similar between the filgotinib (200 mg once daily) and placebo groups in both DARWIN1 (one [1%] of 86 patients *vs* one [2%] of 56) and DARWIN2 (one [1%] of 69 *vs* none).[19,20] Thromboembolic adverse events 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 adverse events being included on some drug labels.[27] No malignancies, thromboembolic events, or cases of opportunistic infections, including tuberculosis, were reported in this study. There was a single case of uncomplicated herpes zoster. Our findings are consistent with previously reported effects of filgotinib on laboratory parameters, including increased haemoglobin and HDL, stable natural killer cell and lymphocyte counts, and decreased platelets.[19,20] No hepatic events of clinical importance were seen. Selective inhibition of JAK1 might theoretically provide an improved safety profile compared with less selective JAK inhibitors. For example, inhibition of JAK1/2 increases platelets,[27] which might be related to the risk of thromboembolic events; this effect is not seen 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 corroborate the initial safety findings reported here. An open-label, long-term extension of this study (NCT03320876) is underway, in which psoriatic arthritis patients are treated with filgotinib for up to an additional 148 weeks; results will be reported upon completion.

Several bDMARDs have efficacy in psoriatic arthritis.[28–30] Although efficacious in some patients, these treatments require parenteral administration and refrigeration, and might be considered burdensome or problematic in some patient populations or geographical areas.[11] Oral treatments, such as apremilast (a phosphodiesterase 4 inhibitor) and tofacitinib, can provide a more convenient therapeutic option. Apremilast (30 mg twice daily), which is an oral tsDMARD that inhibits phosphodiesterase 4, has improved ACR20 responses compared with placebo at week 16 in biologic-naive patients (38% *vs* 20%, p=0·004)[31] and in DMARD-naive and biologic-naive patients (31% *vs* 16%, p=0·001).[32] In a phase 3 trial[14] in patients with psoriatic arthritis 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). In a similar trial[15] in patients with an inadequate response to anti-TNF therapy, these values were 50% and 24%, respectively (p<0·001). Filgotinib might be an alternative oral therapeutic option for psoriatic arthritis, which, in this phase 2 trial, has shown significantly improved ACR20 response rates and disease activity in many domains compared with placebo.

This phase 2 study assessed various manifestations of psoriatic arthritis to determine efficacy of a JAK1-selective inhibitor. As is common in a study of this nature, the centres involved were from a restricted geographical location, there was no active comparator, and the patient population was relatively small. Furthermore, no multiplicity correction was done because the study had one primary endpoint and all other endpoints gave only secondary, supporting data. This study has some limitations. First, the study duration of 16 weeks; increased patient numbers and trial duration are required to confirm the findings. Second, we only studied a single dose of filgotinib and no imaging was included to assess effects