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)

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ABSTRACT

Objectives To evaluate the efficacy and safety of different doses and regimens of filgotinib, an oral Janus kinase 1 inhibitor, as add-on treatment to methotrexate (MTX) in patients with active rheumatoid arthritis (RA) and inadequate response to MTX.

Methods In this 24-week phase IIb study, patients with moderate-to-severe active RA receiving a stable dose of MTX were randomised (1:1:1:1:1:1:1) to receive placebo or 50, 100 or 200 mg filgotinib, administered once daily or twice daily. Primary end point was the percentage of patients achieving a week 12 American College of Rheumatology (ACR)20 response.

Results Overall, 594 patients were randomised and treated. At week 12, significantly more patients receiving filgotinib 100 mg once daily or 200 mg daily (both regimens) achieved an ACR20 response versus placebo. For other key end points at week 12 (ACR50, ACR-N, Disease Activity Score based on 28 joints and C reactive protein value, Clinical Disease Activity Index, Simplified Disease Activity Index and Health Assessment Questionnaire-Disability Index), differences in favour of 100 or 200 mg filgotinib daily were seen versus placebo; responses were maintained or improved through to week 24. Rapid onset of action and dose-dependent responses were observed for most efficacy end points and were associated with an increased haemoglobin concentration. No significant differences between once-daily and twice-daily regimens were seen. Treatment-emergent adverse event rates were similar in placebo and filgotinib groups. Serious infections occurred in one and five patients in the placebo and filgotinib groups, respectively. No tuberculosis or opportunistic infections were reported.

Conclusions Filgotinib as add-on to MTX improved the signs and symptoms of active RA over 24 weeks and was associated with a rapid onset of action. Filgotinib was generally well tolerated.

Trial registration number: NCT01888874.

INTRODUCTION

Current rheumatoid arthritis (RA) guidelines advise treat-to-target strategies, with a focus on patient involvement in treatment decisions.¹ ² With the emergence of novel and effective therapeutic agents for the treatment of RA, patients and physicians are able to consider factors alongside efficacy and safety, including the rapidity with which agents reduce pain and inflammation and the convenience of administration. Since conventional disease-modifying antirheumatic drugs (cDMARDs) are often slow acting, and biological DMARDs (bDMARDs) are limited to intravenous or subcutaneous use, and also have the potential for immuno-genicity (responsible both for immune-related side effects and loss of efficacy),³ there remains a need for novel, rapidly acting agents that can be orally administered.³ ⁴ In addition to improved convenience for patients, such agents may reduce the need for glucocorticoid-bridging therapy.

The Janus kinase (JAK) receptor JAK1 is implicated in the RA disease process through its role in cytokine signalling. For example, the pro-inflammatory cytokine interleukin-6, which is known to play a major role in RA pathogenesis, acts through a JAK1/JAK2 heterodimer-mediated signalling cascade.⁵ ⁶ By contrast, other signal transduction pathways can function independently of JAK1, such as erythropoietin signalling in erythrocyte precursors, which exclusively uses a JAK2 homodimer. JAK inhibitors are low-molecular-weight products that can be administered orally. The pan-JAK inhibitor tofacitinib has been approved by the US Food and Drug Administration for use in patients with moderately to severely active RA as a second-line agent after methotrexate (MTX), and other JAK inhibitors are in development.⁸ ⁹ Filgotinib (GLPG0634/GS-6034) is a potent and selective inhibitor of JAK1, ¹⁰ ¹¹ currently under investigation for the treatment of RA and inflammatory bowel disease. Pharmacokinetic–pharmacodynamic studies of filgotinib and its active metabolite indicate that both moieties contribute to pharmacodynamic effects, resulting in a relatively long duration of JAK1 inhibition,¹² suggesting that filgotinib has the potential to be active not only in twice-daily dosing but also in a once-daily regimen. The efficacy and safety of filgotinib in patients with RA has previously been investigated in two 4-week phase Ila
Outcomes and assessments

Efficacy assessments were performed at screening (joint counts and Patient’s Global Assessment of Disease Activity only), baseline and at weeks 1, 2, 4, 8, 12, 16, 20 and 24. The primary efficacy end point was the percentage of patients achieving an ACR20 response at week 12. Key secondary end points were the percentages of patients achieving ACR20, ACR50, ACR70 and ACR-N responses, Disease Activity Score based on 28 joints and CRP value (DAS28 (CRP), including remission and low-disease activity (LDA)/remission), EULAR response and ACR/EULAR remission, Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) at every visit from baseline to week 24. Health-related quality of life (HRQoL) was evaluated to week 24 using the Health Assessment Questionnaire-Disability Index (HAQ-DI).

Safety variables included adverse events (AEs) throughout the study period; vital signs (at each visit); physical examinations (at screening, baseline, week 12 and week 24); and 12-lead ECG (at screening, week 12 and week 24). Haematology and clinical chemistry laboratory assessments were performed at each visit. The National Institute of Health Common Terminology Criteria for Adverse Events (CTCAE) V3.0 was used to describe laboratory changes during the study.

Sample sizes and statistical analyses

All randomised patients who received at least one dose of study drug were included in the intent-to-treat (ITT) and safety populations. Patients who discontinued the study prior to week 12 were treated as non-responders for the primary analysis, and those who switched treatments at week 12 were handled as discontinuations and data were imputed from week 12 onwards.

Efficacy data were analysed using non-responder imputation (NRI) for the ITT population and confirmed using last observation carried forward (LOCF) and observed case imputations in the ITT population; NRI and LOCF imputations were used for efficacy data in the per-protocol population.

The primary analysis was conducted using a logistic regression model including treatment, geographical region and previous use of bDMARDs as covariates. Continuous parameters were analysed using analysis of covariance. Time-to-first response (ACR20/50/70) was analysed using Kaplan-Meier survival techniques, with treatment groups compared with placebo using a Cox proportional hazard regression model. Treatment versus placebo comparisons were carried out for each dose group versus placebo using Hommel’s closed-testing correction procedure to adjust for multiplicity. Differences between the oncedaily and twice-daily regimens were analysed exploratively.

A sample size of n=85 per study group (N=595) was estimated to provide 90% power to detect minimum 28–30% treatment difference versus placebo, assuming a 20–40% placebo ACR20 response at week 12.

RESULTS

The study was initiated in July 2013 and completed in May 2015. Of the 1255 patients screened, 599 were randomised and 594 received at least one dose of study drug and were included in the ITT and safety populations. At week 12, 66 non-responders were re-randomised to 100 mg daily dose of filgotinib (figure 1). The overall treatment discontinuation rate was low (n=61, 10.3%), and there was no significant difference in the number of patients who discontinued between the filgotinib and placebo groups. In addition, dropout rates did not increase with increasing doses of filgotinib or over time (weeks 0–12 vs weeks 12–24).
At week 24, such that a significant placebo effect was maintained or improved to week 24. The percentage of ACR50 (ACR20, ACR50 and ACR70; response criteria was also significant in the majority of patients who were naive to biological treatments. As detailed in table 2, a dose–response relationship was also significantly higher compared with placebo across all filgotinib dose groups and regimens at weeks 12; this response was maintained or improved to week 24 (figure 2B) and 100 mg twice-daily dose groups compared with placebo at week 12; this response was improved or maintained at week 24, such that a significant response was observed across all filgotinib dose groups and regimens at week 24 (figure 2C).

Statistically significant improvements compared with placebo were observed after 1 week of treatment in the filgotinib 200 mg daily dose group for some components of the ACR index (TJC and serum CRP) (data not shown). ACR20/50/70 responses improved up to week 24 in non-responders who switched to 100 mg daily filgotinib at week 12 (see online supplementary table S2).

At both weeks 12 and 24, disease activity (CDAI) had decreased to a significant extent versus placebo in all dose groups, with the exception of the lowest dose of filgotinib at week 12. An effect was observed early, with significant reductions versus placebo noted by week 2 in the 100 mg once-daily and 100 mg twice-daily dose groups (figure 2D). Similarly, at both weeks 12 and 24, the mean decrease in DAS28 (CRP) was statistically significantly greater across all filgotinib dose groups and regimens compared with placebo (figure 2E). An early onset of effect was observed in DAS28 (CRP) (from week 1 in the 100 mg once-daily, 200 mg once-daily and 100 mg twice-daily dose groups (figure 2F). Raw data for each of the secondary efficacy end points illustrated in figure 2 are presented in online supplementary table S1.

As detailed in table 2, a dose–response relationship was observed for all other efficacy variables. There were too few patients in each dose group who had previously received and responded to a biological agent to make valid comparisons of the efficacy of filgotinib in this patient population versus patients who were naive to biological treatments.

Safety
Adverse events
Treatment-emergent adverse events (TEAEs) were reported at similar frequencies across all dose groups and treatment
regimens (table 3). Fifteen patients (in the filgotinib 100 mg twice-daily group) died due to pneumonia and septic shock; this was the only death in the study and was considered by the investigator as possibly related treatment. Two patients had serious cardiovascular events: one patient (with a history of myocardial infarction and cardiac failure) experienced unstable angina and a subsequent myocardial infarction and cardiac failure) experienced unstable angina and a subsequent myocardial infarction and cardiac failure) experienced unstable angina and a subsequent myocardial infarction and cardiac failure) experienced unstable angina and a subsequent myocardial infarction and cardiac failure) experienced unstable angina and a subsequent myocardial infarction and cardiac failure) experienced unstable angina and a subsequent myocardial infarction and cardiac failure) experienced unstable angina and a subsequent myocardial infarction and cardiac failure) experienced unstable angina and a subsequent myocardial infarction and cardiac failure) experienced unstable angina and a subsequent myocardial infarction and cardiac failure) experienced unstable angina and a subsequent myocardial infarction and cardiac 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HDL) and low-density lipoprotein (LDL) cholesterol were observed in all filgotinib groups, which stabilised thereafter. The LDL:HDL ratio decreased over this period, indicating a greater proportional increase in HDL versus LDL.

**DISCUSSION**

In this study, clinical efficacy in patients treated with filgotinib added to a stable dose of background MTX was evident in a dose-dependent manner, with an early onset of action. By week 12, statistically significantly higher proportions of patients who received 100 mg once daily, or 200 mg daily, regardless of the dose regimen used, achieved ACR20 response, compared with placebo. This response was maintained at week 24. Baseline imbalances in CRP level between the active treatment groups and placebo were explored in a logistic regression model: the discrepancy in baseline levels of inflammation did not influence the primary efficacy time point (non-responder imputation (NRI) (intent-to-treat population)). Patients who switched at week 12 were handled as if they discontinued at week 12 and were imputed using NRI (A–C) or last observation carried forward (D and E). *p<0.05; **p<0.01; ***p<0.001. b.i.d., twice daily; N, number of subjects per group; q.d., once daily.

Figure 2 Efficacy end points: the percentage of patients achieving an improvement in American College of Rheumatology (ACR) of (A) 20% (ACR20), (B) 50% (ACR50) or (C) 70% (ACR70) over time though 24 weeks; (D) mean change from baseline in Clinical Disease Activity Index (CDAI) over time; (E) mean change from baseline in Disease Activity Score based on 28 joints and C reactive protein value (DAS28) (CRP) over time; (F) mean change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) over time. The vertical line at 12 weeks in (A) indicates the primary efficacy time point (non-responder imputation (NRI) (intent-to-treat population)). Patients who switched at week 12 were handled as if they discontinued at week 12 and were imputed using NRI (A–C) or last observation carried forward (D and E). *p<0.05; **p<0.01; ***p<0.001. b.i.d., twice daily; N, number of subjects per group; q.d., once daily.
### Table 2  Efficacy assessments and disease activity assessments at weeks 12 and 24 (NRI (ITT population) and LOCF (ITT population))

| Time point             | Placebo (N=86) | Filgotinib once-daily dose groups | Filgotinib twice-daily dose groups |
|------------------------|----------------|----------------------------------|-----------------------------------|
|                        |                | 50 mg (N=82) | 100 mg (N=85) | 200 mg (N=86) | 2×25 mg (N=86) | 2×50 mg (N=85) | 2×100 mg (N=84) |
| **ACR20†**             |                |              |              |              |              |              |                   |
| Week 12, n (%)         | 38 (44.2)      | 46 (56.1)    | 54 (63.5)*   | 59 (68.6)**  | 49 (57.0)    | 51 (60.0)    | 66 (78.6)**       |
| Week 24, n (%)         | 36 (41.9)      | 45 (54.9)*   | 52 (61.2)**  | 63 (73.3)    | 48 (55.8)    | 51 (60.0)*    | 67 (79.8)**       |
| **ACR50†**             |                |              |              |              |              |              |                   |
| Week 12, n (%)         | 13 (15.1)      | 27 (32.9)*   | 32 (37.6)**  | 37 (43.0)**  | 24 (27.9)*   | 29 (34.1)*   | 46 (54.8)**       |
| Week 24, n (%)         | 14 (16.3)      | 29 (35.4)**  | 40 (47.1)**  | 43 (50.0)**  | 30 (34.9)**  | 30 (35.3)**  | 46 (54.8)**       |
| **ACR70†**             |                |              |              |              |              |              |                   |
| Week 12, n (%)         | 7 (8.1)        | 13 (15.9)    | 18 (21.2)    | 21 (24.4)*   | 12 (14.0)    | 16 (18.8)    | 26 (31.0)**       |
| Week 24, n (%)         | 8 (9.3)        | 18 (22.0)*   | 28 (32.9)**  | 25 (29.1)**  | 18 (20.9)*   | 20 (23.5)*   | 33 (39.3)**       |
| **ACR-N1**             |                |              |              |              |              |              |                   |
| Week 12, mean (SE)     | 23.09 (2.911)  | 34.03 (3.335)* | 39.87 (3.449)** | 42.10 (3.277)** | 34.12 (3.144)* | 35.86 (3.290)** | 51.17 (3.379)** |
| Week 24, mean (SE)     | 22.06 (2.846)  | 37.13 (3.582)** | 50.86 (3.645)** | 50.40 (3.291)** | 38.56 (3.384)** | 40.50 (3.299)** | 58.69 (3.204)** |
| **CRP‡**               |                |              |              |              |              |              |                   |
| Week 12, mean (mg/L)   | 2.67 (2.219)   | -13.15 (2.890)* | -13.57 (2.771)** | -17.24 (3.322)** | -10.26 (2.873)* | -12.97 (2.277)** | -20.54 (2.665)** |
| Week 24, mean (mg/L)   | 2.00 (1.776)   | -15.22 (3.316)** | -14.89 (2.712)** | -15.57 (4.112)** | -11.68 (3.020)* | -11.96 (2.488)* | -20.82 (2.264)** |
| **Change from baseline in CJC68‡** |                |              |              |              |              |              |                   |
| Week 12, mean (SE) change | -9.2 (1.35) | -12.2 (1.34)* | -14.1 (1.33)** | -17.6 (1.33)** | -14.2 (1.37)** | -15.0 (1.37)** | -18.0 (1.31)**    |
| Week 24, mean (SE) change | -8.9 (1.43) | -12.7 (1.42)* | -17.1 (1.32)** | -20.6 (1.49)** | -15.9 (1.51)** | -18.1 (1.44)** | -21.4 (1.38)**    |
| **Change from baseline in SJC68‡** |                |              |              |              |              |              |                   |
| Week 12, mean (SE) change | -7.6 (0.89) | -8.5 (1.01)  | -9.8 (0.97)  | -11.0 (0.95)* | -8.8 (0.87)  | -11.0 (1.10) | -12.2 (0.84)**    |
| Week 24, mean (SE) change | -7.3 (1.00) | -9.2 (1.05)  | -12.6 (0.91)** | -13.2 (0.87)** | -10.2 (0.93)* | -12.9 (1.29)** | -13.8 (0.85)**    |
| **Change from baseline in HAQ-DI** |                |              |              |              |              |              |                   |
| Week 12, mean (SE) change | -0.383 (0.0691) | -0.577 (0.789) | -0.653 (0.0728)* | -0.753 (0.0648)** | -0.590 (0.0659) | -0.584 (0.0677) | -0.840 (0.0726)** |
| Week 24, mean (SE) change | -0.365 (0.0671) | -0.633 (0.0795)** | -0.783 (0.0761)** | -0.818 (0.0675)** | -0.618 (0.0660)** | -0.659 (0.0702)** | -0.903 (0.0813)** |
| **Change from baseline in DAS28 (CRP)‡** |                |              |              |              |              |              |                   |
| Week 12, mean (SE) decrease | -1.19 (0.148) | -1.75 (0.152)** | -2.23 (0.151)** | -2.47 (0.136)** | -1.88 (0.145)** | -2.10 (0.161)** | -2.84 (0.146)**    |
| Week 24, mean (SE) decrease | -1.18 (0.163) | -1.98 (0.179)** | -2.70 (0.156)** | -2.80 (0.139)** | -2.19 (0.157)** | -2.40 (0.175)** | -3.23 (0.138)**    |
| **DAS28 (CRP) LDA‡**    |                |              |              |              |              |              |                   |
| Week 12, n (%)         | 6 (7.0)        | 10 (12.2)    | 10 (11.8)    | 13 (15.1)    | 11 (12.8)    | 9 (10.6)     | 12 (14.3)        |
| Week 24, n (%)         | 8 (9.3)        | 10 (12.2)    | 12 (14.1)    | 22 (25.6)    | 14 (16.3)    | 12 (14.1)    | 20 (23.8)        |
| **DAS28 (CRP) remission‡** |                |              |              |              |              |              |                   |
| Week 12, n (%)         | 6 (7.0)        | 10 (12.2)    | 19 (22.4)*   | 19 (22.1)*   | 13 (15.1)    | 15 (17.6)    | 30 (35.7)**       |
| Week 24, n (%)         | 8 (9.3)        | 17 (20.7)*   | 31 (36.5)**  | 22 (25.6)*   | 20 (23.3)*   | 20 (23.5)*   | 34 (40.5)**       |
| **DAS28 (CRP) remission/LDA‡** |                |              |              |              |              |              |                   |
| Week 12, n (%)         | 12 (14.0)      | 20 (24.4)    | 29 (34.1)**  | 32 (37.2)**  | 24 (27.9)    | 24 (28.2)*    | 41 (50.0)**       |
| Week 24, n (%)         | 16 (18.6)      | 27 (32.9)*   | 43 (50.6)**  | 44 (51.2)**  | 34 (39.5)**  | 32 (37.6)*    | 54 (64.3)**       |
| **DAS 28 (CRP) EULAR response‡** |                |              |              |              |              |              |                   |
| Week 12, n (%)         |                |              |              |              |              |              |                   |
| Week 24, n (%)         |                |              |              |              |              |              |                   |

Continued
| Time point | Filgotinib once-daily dose groups | Filgotinib twice-daily dose groups |
|------------|----------------------------------|-----------------------------------|
|            | Placebo (N=86)                   | 50 mg (N=82)                      |
|            |                                  | 100 mg (N=85)                     |
|            |                                  | 200 mg (N=86)                     |
|            |                                  | 2×25 mg (N=86)                    |
|            |                                  | 2×50 mg (N=85)                    |
|            |                                  | 2×100 mg (N=84)                   |
| Week 12, n (%) | Moderate                        | 39 (45)                           |
|            |                                  | Good                              | 41 (48)                           |
|            |                                  | 47 (55)                           |
| Week 24, n (%) | Moderate                        | 29 (34)**                         |
|            |                                  | Good                              | 44 (51)**                         |
|            |                                  | 51 (65)                           |
| Week 12, n (%) | Moderate                        | 12 (14)                           |
|            |                                  | Good                              | 19 (23)                           |
|            |                                  | 29 (34)**                         |
| Week 24, n (%) | Moderate                        | 29 (35)                           |
|            |                                  | Good                              | 32 (38)                           |
|            |                                  | 33 (38)                           |
| Week 12, n (%) | Moderate                        | 6 (7.3)                           |
|            |                                  | Good                              | 15 (18.3)*                        |
|            |                                  | 15 (18.3)*                        |
| Week 24, n (%) | Moderate                        | 2 (2.3)                           |
|            |                                  | Good                              | 6 (7.3)                           |
|            |                                  | 7 (8.2)                           |
| ACR/EULAR remission† | Week 12, n (%) | 12 (14)                           |
|            |                                  | Good                              | 19 (23)                           |
|            |                                  | 29 (34)**                         |
| Week 12, n (%) | Moderate                        | 29 (35)                           |
|            |                                  | Good                              | 32 (38)                           |
|            |                                  | 33 (38)                           |
| Week 24, n (%) | Moderate                        | 6 (7.3)                           |
|            |                                  | Good                              | 15 (18.3)*                        |
|            |                                  | 15 (18.3)*                        |
| Week 24, n (%) | Moderate                        | 2 (2.3)                           |
|            |                                  | Good                              | 6 (7.3)                           |
|            |                                  | 7 (8.2)                           |
| Change from baseline in SDAI‡ | Week 12, mean (SE) decrease | −16.3 (1.84)                      |
|            |                                  | −21.0 (1.84)*                     |
|            |                                  | −25.2 (1.69)***                   |
| Week 24, mean (SE) decrease | −15.8 (2.00)**                   |
|            |                                  | −22.8 (2.07)**                    |
|            |                                  | −30.1 (1.66)***                   |
| SDAI LDA‡ | Week 12, n (%) | 8 (9.3)                           |
|            |                                  | 19 (23.2)                         |
|            |                                  | 22 (25.9)                         |
| Week 24, n (%) | Moderate                        | 1 (1.2)                           |
|            |                                  | 9 (11.0)                          |
|            |                                  | 7 (8.2)                           |
| SDAI remission† | Week 12, n (%) | 4 (4.7)                           |
|            |                                  | 9 (11.0)                          |
|            |                                  | 7 (8.2)                           |
| Week 24, n (%) | Moderate                        | 1 (1.2)                           |
|            |                                  | 13 (15.9)*                        |
|            |                                  | 13 (15.3)*                        |
| Change from baseline in CDAI‡ | Week 12, mean (SE) decrease | −16.6 (1.84)                      |
|            |                                  | −19.7 (1.77)                      |
|            |                                  | −23.8 (1.66)**                    |
| Week 24, mean (SE) decrease | −16.0 (1.95)**                   |
|            |                                  | −21.3 (1.97)**                    |
|            |                                  | −28.6 (1.63)***                   |
| CDAI LDA‡ | Week 12, n (%) | 13 (15.1)                         |
|            |                                  | 20 (24.4)                         |
|            |                                  | 20 (23.5)                         |
| Week 24, n (%) | Moderate                        | 16 (18.6)                         |
|            |                                  | 18 (21.2)                         |
| CDAI remission† | Week 12, n (%) | 2 (2.3)                           |
|            |                                  | 6 (7.3)                           |
|            |                                  | 7 (8.2)                           |
| Week 24, n (%) | Moderate                        | 2 (2.3)                           |
|            |                                  | 15 (18.3)*                        |
|            |                                  | 18 (21.2)**                       |

*p<0.05; **p<0.01; ***p<0.001.

NRI (ITT population).

ACR, American College of Rheumatology; ACR-N, American College of Rheumatology N% improvement; CDAI, Clinical Disease Activity Index; DAS28 (CRP), Disease Activity Score based on 28 joints and C reactive protein value; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, intent-to-treat; LDA, low-disease activity; LOCF, last observation carried forward; N, number of patients per group; n, number of patients with response/change; NRI, non-responder imputation; SDAI, Simplified Disease Activity Index; SJC66, swollen joint count based on 66 joints; TJC68, tender joint count based on 68 joints.
Table 3  Summary of absolute numbers and proportions of patients in each treatment group who experienced TEAEs and laboratory abnormalities over the course of the study

| Patients with | Continued placebo (N=56) | Continued once-daily groups | Continued twice-daily groups | Non-responders* switching to 100 mg/day | Placebo to 100 mg (N=56) | Placebo to 2×50 mg (N=85) | 50–100 mg (N=84) | 2×25 mg to 2×50 mg (N=84) |
|--------------------------------|--------------------------|-----------------------------|-----------------------------|---------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| TEAE, n (%)                  | 32 (57.1)                | 33 (52.4)                   | 37 (43.5)                   | 50 (58.1)                             | 37 (53.6)                | 46 (54.1)                | 45 (53.6)                | 7 (46.7)                 |
| Serious TEAE, n (%)          | 4 (7.1)                  | 0 (0)                       | 4 (4.7)                     | 2 (2.3)                               | 1 (1.4)                  | 0 (0)                    | 3 (3.6)                  | 0 (0)                    |
| SAE leading to death, n (%)  | 0 (0)                    | 0 (0)                       | 0 (0)                       | 0 (0)                                 | 0 (0)                    | 0 (0)                    | 1 (1.2)                  | 0 (0)                    |
| Serious TE infection, n (%)  | 1 (1.8)                  | 0 (0)                       | 3 (3.5)                     | 1 (1.2)                               | 0 (0)                    | 0 (0)                    | 1 (1.2)                  | 0 (0)                    |
| Related TEAE, n (%)          | 6 (10.7)                 | 13 (20.6)                   | 11 (12.9)                   | 21 (24.4)                             | 14 (20.3)                | 19 (22.4)                | 21 (25.0)                | 2 (13.3)                 |
| Related TE infection, n (%)  | 1 (1.8)                  | 4 (6.3)                     | 4 (4.7)                     | 7 (8.1)                               | 5 (7.2)                  | 7 (8.2)                  | 7 (8.3)                  | 0 (0)                    |
| TEAE leading to permanent discontinuation of study treatment, n (%) | 2 (3.6) | 2 (3.2) | 5 (6.9)** | 3 (3.5) | 3 (3.6) | 3 (3.6) | 3 (3.6) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Decreased haemoglobin, g/dL  |                          |                             |                             |                                       |                          |                          |                          |                          |
| Grade 1 (10, LLN)            | 11 (19.36)               | 13 (20.6)                   | 10 (11.8)                   | 11 (12.8)                             | 11 (15.9)                | 13 (15.3)                | 13 (15.5)                | 6 (40.0)                 |
| Grade 2 (<10–8)              | 4 (7.1)                  | 2 (3.2)                     | 7 (8.3)                     | 2 (2.3)                               | 2 (2.3)                  | 4 (4.7)                  | 1 (1.2)                  | 0 (0)                    |
| Grade 3 (<8.0–6.5)           | 0 (0)                    | 0 (0)                       | 0 (0)                       | 0 (0)                                 | 0 (0)                    | 0 (0)                    | 1 (1.2)                  | 0 (0)                    |
| Grade 4 (<6.5)               | 0 (0)                    | 0 (0)                       | 0 (0)                       | 0 (0)                                 | 0 (0)                    | 0 (0)                    | 0 (0)                    | 0 (0)                    |
| Decreased lymphocytes, ×10⁹/L |                          |                             |                             |                                       |                          |                          |                          |                          |
| Grade 1 (0.8, LLN)           | 1 (1.8)                  | 2 (3.2)                     | 3 (3.5)                     | 1 (1.2)                               | 2 (2.4)                  | 0 (0)                    | 1 (1.2)                  | 0 (0)                    |
| Grade 2 (<0.8–0.5)           | 3 (5.4)                  | 6 (9.5)                     | 4 (4.7)                     | 5 (5.8)                               | 2 (2.9)                  | 4 (4.7)                  | 4 (4.87)                 | 0 (0)                    |
| Grade 3 (<0.5–0.2)           | 1 (1.8)                  | 1 (1.6)                     | 2 (2.4)                     | 0 (0)                                 | 1 (1.4)                  | 1 (1.2)                  | 0 (0)                    | 0 (0)                    |
| Grade 4 (<0.2)               | 0 (0)                    | 0 (0)                       | 1 (1.2)                     | 0 (0)                                 | 0 (0)                    | 0 (0)                    | 0 (0)                    | 0 (0)                    |
| Decreased neutrophils, ×10⁹/L |                          |                             |                             |                                       |                          |                          |                          |                          |
| Grade 1 (1.5, LLN)           | 1 (1.8)                  | 1 (1.6)                     | 1 (1.2)                     | 4 (4.7)                               | 3 (4.3)                  | 1 (1.2)                  | 1 (1.2)                  | 0 (0)                    |
| Grade 2 (<1.5–1.0)           | 3 (5.4)                  | 0 (0)                       | 0 (0)                       | 3 (3.5)                               | 2 (2.9)                  | 1 (1.2)                  | 0 (0)                    | 0 (0)                    |
| Grade 3 (<1.0–0.5)           | 0 (0)                    | 0 (0)                       | 0 (0)                       | 1 (1.2)                               | 0 (0)                    | 0 (0)                    | 0 (0)                    | 1 (6.7)                  |
| Grade 4 (<0.5)               | 0 (0)                    | 0 (0)                       | 1 (1.2)                     | 0 (0)                                 | 0 (0)                    | 0 (0)                    | 0 (0)                    | 0 (0)                    |
| Decreased platelets, ×10⁹/L   |                          |                             |                             |                                       |                          |                          |                          |                          |
| Grade 1 (75, LLN)            | 1 (1.8)                  | 0 (0)                       | 2 (2.4)                     | 3 (3.5)                               | 0 (0)                    | 1 (1.2)                  | 2 (2.4)                  | 0 (0)                    |
| Grade 2 (<75–50)             | 0 (0)                    | 0 (0)                       | 0 (0)                       | 0 (0)                                 | 0 (0)                    | 0 (0)                    | 0 (0)                    | 0 (0)                    |
| Grade 3 (<50–25)             | 0 (0)                    | 0 (0)                       | 0 (0)                       | 0 (0)                                 | 0 (0)                    | 0 (0)                    | 0 (0)                    | 0 (0)                    |
| Grade 4 (<25)                | 0 (0)                    | 0 (0)                       | 1 (1.2)                     | 0 (0)                                 | 0 (0)                    | 0 (0)                    | 0 (0)                    | 0 (0)                    |
| Decrease to <LLN              | 3 (5.4)                  | 5 (7.9)                     | 5 (5.9)                     | 12 (14.0)                             | 7 (10.1)                 | 5 (5.9)                  | 6 (7.1)                  | 2 (13.3)                 |
| Increase to >ULN             | 2 (3.6)                  | 0 (0)                       | 3 (3.5)                     | 3 (3.5)                               | 1 (1.4)                  | 0 (0)                    | 2 (2.4)                  | 0 (0)                    |
| Elevated creatinine µmol/L   |                          |                             |                             |                                       |                          |                          |                          |                          |
| Grade 1 (1–1.5×ULN)          | 0 (0)                    | 1 (1.6)                     | 2 (2.4)                     | 1 (1.2)                               | 0 (0)                    | 2 (2.4)                  | 1 (1.2)                  | 0 (0)                    |
| Grade 2 (1.5–3×ULN)          | 0 (0)                    | 0 (0)                       | 0 (0)                       | 0 (0)                                 | 0 (0)                    | 0 (0)                    | 0 (0)                    | 0 (0)                    |
| Grade 3 (3–6×ULN)            | 0 (0)                    | 0 (0)                       | 0 (0)                       | 0 (0)                                 | 0 (0)                    | 0 (0)                    | 0 (0)                    | 0 (0)                    |
| Grade 4 (6–9×ULN)            | 0 (0)                    | 0 (0)                       | 0 (0)                       | 0 (0)                                 | 0 (0)                    | 0 (0)                    | 0 (0)                    | 0 (0)                    |
| Elevated ALT                |                          |                             |                             |                                       |                          |                          |                          |                          |
| Grade 1 (1–2.5×ULN)          | 3 (5.4)                  | 6 (9.5)                     | 9 (10.6)                    | 10 (11.6)                             | 10 (14.5)                | 7 (8.2)                  | 7 (8.3)                  | 0 (0)                    |
| Grade 2 (2.5–5×ULN)          | 1 (1.8)                  | 0 (0)                       | 1 (1.2)                     | 2 (2.4)                               | 0 (0)                    | 0 (0)                    | 1 (1.2)                  | 0 (0)                    |

Continued
70 and DAS28 (CRP) responses, along with improvements in HRQoL (HAQ-DI); in addition to the convenience of oral administration, rapid action may facilitate effective treat-to-target strategies without the need for bridging glucocorticoids. The flogitinib doses studied and the similar efficacy noted between the once-daily and twice-daily dosing regimens Table 3 Continued

Table 3

| Patients with 100 mg once daily | Patients with 50 mg twice daily | Patients with 25 mg twice daily | Placebo |
|--------------------------------|--------------------------------|--------------------------------|---------|
| Continued placebo (N=56)       | Continued once-daily group (N=63) | Continued twice-daily group (N=85) | Non-responders* switching to 100 mg/day |
| 50 mg (N=19)                   | 100 mg (N=19)                   | 200 mg (N=19)                   | 2×25 mg (N=19) |
| 2×25 mg to 2×50 mg (N=17)      | Grade 3 (5–20×ULN)              | 2×100 mg (N=19)                 | Placebo to 100 mg (N=19) |
| 2×50 mg (N=19)                 | Grade 4 (>20×ULN)               | 2×50 mg (N=19)                  | Placebo to 2×50 mg (N=19) |
| 2×100 mg (N=19)                | Grade 1 (1–2.5×ULN)             | 2×100 mg (N=19)                 | 50–100 mg |
| (N=19)                         | Grade 2 (2.5–5×ULN)             | (N=19)                         | 2×50 mg to 2×50 mg (N=19) |

Elevated AST

Grade 1 (1–2.5×ULN) 1 (1.8) 5 (7.9) 8 (9.4) 10 (11.6) 6 (8.7) 9 (10.6) 9 (10.7) 1 (6.7) 0 (0) 1 (5.3) 3 (17.6)

Grade 2 (2.5–5×ULN) 0 (0) 0 (0) 0 (0) 2 (2.3) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0)

Grade 3 (5–20×ULN) 0 (0) 0 (0) 1 (1.2) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0)

Grade 4 (>20×ULN) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0)

Pneumonia, diabetic gangrene, subcutaneous abscess.

†Appendicitis.

§Erysipelas.

¶Intervertebral discitis+pneumonia+septic shock.*Non-responders defined as patients who had not achieved a 20% improvement in swollen joint count based on 66 joints and tender joint count based on 68 joints and who continued on the same treatment throughout the study. Focal events or serious adverse events occurring after completion of study drug treatment were not included in the analysis. TIDAE, treatment-emergent adverse event; ULN, upper limit of normal.

Figures

Figure 3

Mean (SE) change from baseline over time in patients considered to be responders (achieved a 20% improvement in swollen joint count based on 66 joints and tender joint count based on 68 joints) and who continued on the same treatment throughout the study for (A) haemoglobin (g/dL), (B) neutrophils (×10⁹/L) and (C) platelets (×10⁹/L). b.i.d., twice daily; N, number of subjects per group; q.d., once daily.

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are in line with the previously reported pharmacokinetic and pharmacodynamic effects of filgotinib and its major metabolite, both of which selectively inhibit JAK1. Although there was a numerical trend towards better efficacy results with the 200 mg dose given as 100 mg twice daily versus 200 mg once daily, this trend did not extend to the next (lower) dose level of 100 mg, where the reverse trend was observed, such that the once-daily schedule generally performed better than the split dose. In terms of safety, there were no major differences in terms of AEs between the once-daily and twice-daily regimens.

Harmful complications would be expected if any member of the JAK family is completely inhibited, as exemplified by the relationship between JAK3 deficiency and severe combined immunodeficiency. However, with small-molecule inhibitors selective for particular JAK enzymes, the heterodimeric pairing of enzymes and the unique pharmacological profile of a given small molecule makes AEs difficult to predict. In the current study, filgotinib was well tolerated at all doses evaluated. Although infections were the most frequent AE, few serious AEs and overall were infrequent; few AEs led to discontinuation. Importantly, no cases of TB or opportunistic infections were reported. Careful monitoring and management of infections will be required in future studies of filgotinib. Small, dose-dependent changes in mean laboratory values were observed, including increases in mean haemoglobin and decreases in mean neutrophil counts; however, the latter were without clinical consequence. No reductions in absolute lymphocyte counts were observed, and there were no dose-dependent changes in mean NK cell counts. The dose-dependent increase in mean haemoglobin can be attributed to the decrease in inflammation resulting from a therapeutic effect and the lack of any associated JAK2 inhibitory effect. A dose-dependent decline in platelet counts was observed; however, platelet counts plateaued at week 4 and remained relatively stable thereafter. This observation contrasts with the dose-dependent platelet count increase seen in the 24-week phase IIb study of the JAK1/2 inhibitor baricitinib in patients receiving MTX. Small increases in mean creatinine concentration were not associated with clinical consequences and the effect of filgotinib co-administered with MTX on liver parameters was minimal. Although dose-dependent increases in both HDL and LDL cholesterol were observed in all filgotinib groups, the LDL: HDL ratio fell. This is in contrast to results seen with some RA treatments that preferentially increase LDL, thereby worsening the atherogenic index.

The chief limitation of the study was its short (24 weeks) duration, hampering definite judgement of longer maintenance of efficacy and eventual side effects. Furthermore, radiographic assessments were not included in the study design, so the impact of filgotinib on the structure of bones and joints could not be evaluated.

In conclusion, the results of this phase IIb study of filgotinib, added to a stable background dose of MTX, demonstrate clinically relevant dose-dependent improvements in the signs and symptoms of active RA. At a daily dose of 200 mg filgotinib, these improvements were initiated rapidly and were sustained throughout 24 weeks of treatment, regardless of whether a once-daily or twice-daily dosing regimen was used. These robust data support the future development of filgotinib for the treatment of active RA in patients receiving MTX treatment.

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