














ORIGINAL RESEARCH

Safety and efficacy of filgotinib in patients with rheumatoid arthritis: final results of the DARWIN 3 long-term extension study

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ABSTRACT

Objectives DARWIN 3 (ClinicalTrials.gov: NCT02065700) assessed the safety and efficacy of filgotinib in a long-term extension (LTE) of two phase II randomised controlled rheumatoid arthritis (RA) trials.

Methods Eligible patients completing the 24-week DARWIN 1 (filgotinib plus methotrexate) and DARWIN 2 (filgotinib monotherapy) trials could enrol. Patients received filgotinib 100 mg/day, except 15 men who received filgotinib 100 mg/day. The primary endpoints were safety and tolerability, which were assessed by the incidence of treatment-emergent adverse events (TEAEs). Safety and efficacy analyses included all enrolled patients who received ≥ 1 dose of filgotinib in DARWIN 3.

Results 739 patients entered the LTE. The total patient-years of exposure (PYE) to filgotinib was 3706.3 years; the mean exposure duration was 259.8 weeks. 497 patients (67.3%) discontinued prematurely (including 266 TEAEs and 172 withdrawals due to the patient's decision or 'sponsor request'). Overall exposure-adjusted incidence rate (EAIR) was 67 (95% CI 62 to 72.2)/100 PYE for TEAEs and 3.8 (95% CI 3.2 to 4.5)/100 PYE for serious TEAEs. EAIR of infections was 23.3 (95% CI 21.2 to 25.6)/100 PYE, 1.3 (95% CI 0.9 to 1.7)/100 PYE for serious infections and 1.3 (95% CI 0.9 to 1.7)/100 PYE for herpes zoster. EAIRs of major adverse cardiovascular events (0.19 (95% CI 0.8 to 0.39)/100 PYE) and malignancies (0.6 (95% CI 0.4 to 0.9)/100 PYE) were low. Disease response assessed using non-responder imputation plateaued at LTE week 12 before slowly declining over time, with overall American College of Rheumatology (ACR)20/50/70 response rates of 26.9%/20.2%/14.7% at week 396.

Conclusion Filgotinib was well tolerated in patients with RA for up to 8 years. Safety and efficacy profiles were maintained in patients previously receiving either filgotinib plus methotrexate or filgotinib monotherapy.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disease that can lead to functional impairment,

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

⇒ Filgotinib is an oral Janus kinase inhibitor approved for the treatment of rheumatoid arthritis (RA) and ulcerative colitis.

WHAT DOES THIS STUDY ADD

⇒ During up to 8 years of treatment in a long-term extension of the phase IIb DARWIN clinical trials, no new safety signals were observed and the rates of adverse events of interest, including malignancies and cardiovascular events, were low.
 ⇒ Patients who responded to filgotinib and continued treatment had sustained low disease activity and improvements in function and patient-reported outcomes.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE

⇒ These results show that long-term filgotinib treatment is well tolerated by patients with RA and is associated with durable responses.

loss of mobility and reduced quality of life (QoL).^{1 2} The main treatment goals for RA are to reduce joint inflammation and pain, maximise joint function and prevent joint destruction and deformity while maintaining long-term patient safety.²⁻⁴ Additionally, patient-experienced symptoms and QoL (eg, fatigue and mental health) are important considerations in an overall holistic approach to RA disease management.⁴

Janus kinase (JAK) inhibitors are the latest class of targeted, disease-modifying therapies used to treat patients with moderate to severe RA, with tofacitinib, baricitinib, peficitinib, upadacitinib and filgotinib approved in various regions.⁵ Filgotinib

is a JAK1-preferential inhibitor that has been extensively studied for the treatment of RA in a series of phase IIb (DARWIN) and phase III (FINCH) trials.^{6–10} DARWIN 1 (NCT01888874) investigated filgotinib in combination with methotrexate (MTX) and DARWIN 2 (NCT01894516) investigated filgotinib monotherapy^{6,7}; these were followed by DARWIN 3 (NCT02065700), an open-label long-term extension (LTE) of the phase IIb parent studies. An interim analysis of DARWIN 3 reported that the safety profile of filgotinib was consistent with that in the parent studies and that filgotinib efficacy was sustained over the 4-year follow-up period.¹¹

Here, we report the final data from DARWIN 3 up to a maximum of 8 years' follow-up. The primary objective was to evaluate the long-term safety and tolerability of filgotinib for the treatment of RA. The secondary objectives were to assess the long-term efficacy of filgotinib and its effects on patients' fatigue and QoL.

PATIENTS AND METHODS

Study design

DARWIN 3 methodology has been detailed previously.¹¹ Briefly, the study was a phase II open-label LTE of the phase IIb randomised controlled DARWIN 1⁶ and DARWIN 2⁷ trials of filgotinib in RA. DARWIN 1 was a 24-week study in which patients with an inadequate response to MTX received a placebo twice daily or filgotinib (50, 100 or 200 mg/day, administered once or twice daily) plus MTX (15–25 mg/week). At week 12, patients in the placebo and filgotinib 50 mg/day arms who had not achieved a $\geq 20\%$ improvement from baseline in swollen joint count based on 66 joints (SJC66) and tender joint count based on 68 joints (TJC68) were reassigned to filgotinib 100 mg/day through week 24.⁶ Patients in the other dose groups maintained their randomised treatment until week 24. DARWIN 2 was a 24-week study in which patients with an inadequate response to MTX received placebo or filgotinib monotherapy (50, 100 or 200 mg once daily). At week 12, all patients in the placebo arm and those in the filgotinib 50 mg/day arm who had not achieved $\geq 20\%$ improvement in SJC66 and TJC68 were reassigned to filgotinib 100 mg/day through week 24.⁷ Patients in the other dose groups maintained their randomised treatment until week 24.

In the LTE, all patients received filgotinib 200 mg, either as 200 mg once daily or 100 mg two times per day (the same administration regimen as during the parent study), for up to 8 years, except for 15 men in the USA who received 100 mg once daily due to a requirement by the US Food and Drug Administration. A dose adjustment between 200 and 100 mg daily was allowed for safety/tolerability. MTX was allowed for patients enrolled in DARWIN 2 at the investigator's discretion, and patients in both groups could discontinue or start MTX according to the investigator's clinical judgement. The concurrent use and dose of glucocorticoids could be changed at the investigator's discretion.

Patients

The population included in DARWIN 3 has been described previously.¹¹ Eligible patients were men and women aged ≥ 18 years who met the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) criteria¹² and completed the DARWIN 1 and DARWIN 2 parent studies. Patients from DARWIN 1 had been receiving MTX for ≥ 6 months and were on a stable dose (15–25 mg/week, oral or parenteral) 4 weeks prior to screening.⁶ Patients from DARWIN 2 had shown an inadequate response to MTX (in the opinion of the treating physician) and had a washout period from MTX for ≥ 4 weeks before or during screening.⁷ It was recommended that patients' vaccinations were up to date according to local standards prior to study participation. All patients provided written informed consent for inclusion in the study.

Endpoints and assessments

Details of the assessments for DARWIN 3 have been reported.¹¹ The primary endpoint was the safety and tolerability of long-term dosing of filgotinib 200 mg/day, as assessed by the incidence of adverse events (AEs). AEs coded according to the Medical Dictionary for Regulatory Activities (MedDRA) V.25.0 were recorded. AEs of interest were identified by either standardised MedDRA queries, sponsor-defined medical search terms or a combination of these methods. AEs of interest included malignancy (including lymphoma but excluding non-melanoma skin cancer (NMSC)), NMSC, venous thromboembolism (VTE), arterial systemic thromboembolism (ASTE), major adverse cardiovascular events (MACE), infections, serious infections, infections of interest (herpes zoster, active tuberculosis, opportunistic infections and evidence of active hepatitis B or C), gastrointestinal perforations and fractures. Clinical laboratory analyses included haematology, serum chemistry, hormone tests (in male patients only) and urinalysis. Tuberculosis testing was performed using QuantiFERON-TB Gold every 48 weeks. Positive or confirmed indeterminate tuberculosis results were reported as AEs, and all newly positive tuberculosis test results led to study discontinuation until March 2018, after which patients with latent tuberculosis could remain in the study with initiation and completion of appropriate latent tuberculosis treatment. Grades 3 and 4 laboratory abnormalities were reported and graded using the Common Terminology Criteria for Adverse Events V.4.03. Safety data were reviewed periodically by an independent data monitoring board; all potential MACE and thromboembolic events were independently adjudicated.

Secondary endpoints included the proportion of patients achieving a 20%/50%/70% improvement in ACR criteria (ACR20/50/70),¹³ Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP) < 2.6 and ≤ 3.2 ,¹⁴ EULAR response¹⁵ and ACR/EULAR remission. Individual components of ACR response (including serum CRP level, Health Assessment

Questionnaire-Disability Index (HAQ-DI), subject's pain assessment and Subject's and Physician's Global Assessment of Disease Activity), actual value and change from parent study baseline (CFB) for the following measures were also recorded: DAS28-CRP, Clinical Disease Activity Index (CDAI), Simple Disease Activity Index (SDAI),¹⁶ 36-Item Short-Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores,¹⁷ pain on a visual analogue scale and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue).¹⁸ Efficacy endpoints were assessed every 12 weeks up to week 396, except for SF-36 PCS/MCS and FACIT-Fatigue scores, which were assessed every 48 weeks. Except in cases of treatment discontinuation or patient withdrawal, patients remained on study until study completion (local regulatory approval of filgotinib), at which time they returned for their next scheduled visit (final visit) and a follow-up visit 2 weeks later.

Statistical analyses

The safety and efficacy analyses included the data from both the DARWIN 1 and DARWIN 2 parent studies and the DARWIN 3 LTE. The primary analysis set for safety (safety analysis set) and efficacy (full analysis set) analyses included all enrolled patients who received ≥ 1 dose of filgotinib in DARWIN 3. Data are grouped by populations of DARWIN 1 (filgotinib plus MTX), DARWIN 2 (filgotinib monotherapy) and DARWIN 3 (filgotinib overall); however, MTX treatment was at the investigator's discretion for all patients throughout the LTE. Observed data and non-responder imputation (NRI) analyses were used in this study. Observed data (complete case) analysis did not include missing data and, therefore, reflect the outcomes of patients who remained on study treatment. NRI coded patients with missing information relevant to the study endpoints as treatment failures; thus, it reflects the outcomes of all patients, including those who discontinued for any reason. A sensitivity analysis of NRI data, modified NRI (mNRI), excluded patients who left the study due to 'sponsor request' (due to study termination in some countries), while other patients with missing outcomes remained imputed as treatment failures. All statistical analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient population and exposure

The study period (incorporating the duration of the parent studies) ran from February 2014 to January 2023. Overall, 739 patients (497 from DARWIN 1 (including 47 from the placebo arm) and 242 from DARWIN 2) entered the LTE and received ≥ 1 dose of filgotinib. On entry to DARWIN 3, 271 patients from DARWIN 1 and 120 from DARWIN 2 increased their filgotinib dose. Patient demographics and baseline characteristics at entry into DARWIN 1 or DARWIN 2 are summarised in [table 1](#). The mean (SD) age was 53 (11.9) years, and most patients (81.6%) were women. A higher proportion of

patients in DARWIN 2 than in DARWIN 1 were receiving concurrent glucocorticoids on the first filgotinib dosing date (59.1% vs 48.1%; [table 1](#)).

The total patient-years of exposure (PYE) to filgotinib was 3706.3 (2504.3 and 1201.9 PYE for patients from DARWIN 1 and DARWIN 2, respectively). The mean (SD) total duration of exposure to filgotinib was 259.8 (149.51) weeks (261 and 257.1 weeks for patients from DARWIN 1 and DARWIN 2, respectively), with a maximum exposure of 433 weeks ([table 2](#)).

Overall, 99% of patients received ≥ 1 concomitant medication during the study, most commonly MTX (70.2%), folic acid (63.9%), paracetamol (27.2%) and omeprazole (25.8%). During the study, 101 patients (13.6%) were reported to have received an influenza vaccine, 98 (13.2%) received a COVID-19 vaccine and 20 (2.6%) received a pneumonia vaccine. One patient (0.1%) was reported to have received a recombinant zoster vaccine during the study.

Overall, 242 patients (32.7%) completed the LTE ([figure 1](#)). A total of 497 patients (67.3%) discontinued the LTE prematurely: 336 patients (67.6%) from DARWIN 1 and 161 patients (66.5%) from DARWIN 2 ([figure 1](#)). The most common reasons for premature discontinuation were AEs (n=266, 36%), patient withdrawal (n=119, 16.1%) and sponsor request (n=53, 7.2%).

Safety

Treatment-emergent AEs (TEAEs) are summarised in [table 2](#). Overall, 453 patients in the filgotinib DARWIN 1 group (exposure-adjusted incidence rate (EAIR) 68.3 (95% CI 62.2 to 74.9)/100 PYE) and 223 patients in the filgotinib DARWIN 2 group (EAIR 64.3 (95% CI 56.2 to 73.4)/100 PYE) experienced TEAEs during exposure to filgotinib. Serious TEAEs were experienced by 84 patients (EAIR 3.6 (95% CI 2.9 to 4.4)/100 PYE) in the filgotinib DARWIN 1 group and 48 patients (EAIR 4.3 (95% CI 3.2 to 5.7)/100 PYE) in the filgotinib DARWIN 2 group. Serious TEAEs are detailed in online supplemental table 1. The most common serious TEAEs were osteoarthritis and pneumonia, each reported in 10 patients (1.4%). Most osteoarthritis TEAEs were hospitalisation for joint replacement due to osteoarthritis (n=7); for the remainder, no further information was available. The most common TEAE that led to premature study discontinuation was a positive tuberculosis test result (n=82, 11.1%); however, no cases of active tuberculosis were reported during the study. 34 patients (4.6%) discontinued due to lymphopenia (online supplemental table 2). Overall, 208 patients (28.1%) temporarily stopped their study treatment owing to a TEAE, most frequently COVID-19 (4.1%) and herpes zoster (2.6%). TEAEs leading to dose reduction occurred in 28 patients (3.8%). A total of 16 TEAE-related deaths (EAIR 0.4 (95% CI 0.3 to 0.7)/100 PYE) occurred during the study; the most common cause of death was COVID-19 pneumonia (n=4) ([table 2](#)).

TEAEs of interest are summarised in [table 3](#). Malignancies (excluding NMSC) were reported in 21 patients overall (EAIR

Table 1 Patient demographic and baseline characteristics at entry into parent studies (DARWIN 1 or DARWIN 2)

Characteristic	Filgotinib (DARWIN 1), n=497	Filgotinib (DARWIN 2), n=242	Filgotinib overall, n=739
Age, years, mean (SD)	53 (11.7)	52 (12.2)	53 (11.9)
Female sex, n (%)	405 (81.5)	198 (81.8)	603 (81.6)
Race, n (%)			
Asian	1 (0.2)	1 (0.4)	2 (0.3)
Black or African American	3 (0.6)	3 (1.2)	6 (0.8)
Native Hawaiian or Pacific Islander	0	1 (0.4)	1 (0.1)
White	374 (75.3)	181 (74.8)	555 (75.1)
Other	119 (23.9)	56 (23.1)	175 (23.7)
Ethnicity, n (%)			
Hispanic or Latino	208 (41.9)	85 (35.1)	293 (39.6)
Not Hispanic or Latino	289 (58.1)	157 (64.9)	446 (60.4)
Body mass index, kg/m ² , mean (SD)	28.3 (5.7)	27.6 (5.6)	28.1 (5.7)
Geographical region, n (%)			
Central and Eastern Europe, EU	136 (27.4)	53 (21.9)	189 (25.6)
Central and Eastern Europe, non-EU	79 (15.9)	73 (30.2)	152 (20.6)
Latin America	186 (37.4)	75 (31.0)	261 (35.3)
West and Asia Pacific	96 (19.3)	41 (16.9)	137 (18.5)
Duration of RA from diagnosis, years,* mean (SD)	8.3 (7.1)	8.9 (7.1)	8.5 (7.1)
Rheumatoid factor positive, n (%)	382 (76.9)	180 (74.4)	562 (76.0)
Anti-cyclic citrullinated peptide positive, n (%)	402 (80.9)	192 (79.3)	594 (80.4)
Prior exposure to biologic disease-modifying antirheumatic drugs, n (%)	41 (8.2)	17 (7.0)	58 (7.8)
Concurrent glucocorticoid use on first dosing date, n (%)	239 (48.1)	143 (59.1)	382 (51.7)
Concurrent MTX on first dosing date, n (%)	496 (99.8)	0	496 (67.1)
Concurrent MTX dose on first dosing date, mg/week, mean (SD)	16.8 (4.22†)	NA	16.8 (4.22†)

*Duration of RA (years)=(first dose date in parent studies–date of initial diagnosis+1)/365.25.
†Data are for 493 patients.
EU, European Union; MTX, methotrexate; NA, not applicable; RA, rheumatoid arthritis.

0.6 (95% CI 0.4 to 0.9)/100 PYE). Details of malignancies are shown in online supplemental table 3. The most frequently reported malignancies (excluding NMSC) were lymphomas, which occurred in six patients (0.8%), including four patients with non-Hodgkin lymphoma. NMSC was reported in eight patients (EAIR 0.2 (95% CI 0.1 to 0.4)/100 PYE), including four cases of basal cell carcinoma and three of squamous cell carcinoma. Independent adjudicated MACE was confirmed in seven patients (0.9%; EAIR 0.2 (95% CI 0.1 to 0.4)/100 PYE), including two MACE-related deaths (one due to acute myocardial infarction and the other due to pulmonary embolism, both in female patients aged 68 and 55 years, respectively) and five non-fatal cases of stroke (online supplemental table 4). VTE events were reported in five patients (0.7%) (EAIR 0.1 (95% CI 0.0 to 0.3)/100 PYE). The female 55-year-old patient who died of a pulmonary embolism (above; adjudicated MACE) also had a moderate event of deep vein thrombosis. One patient (0.1%) experienced an ASTE event of severe peripheral artery thrombosis.

Treatment-emergent infections occurred in 459 patients (62.1%) (EAIR 23.3 (95% CI 21.2 to 25.6)/100 PYE). The most common infections were urinary tract infections, nasopharyngitis and upper respiratory tract infections (14.1%, 12.7% and 12.7% of patients, respectively)

(online supplemental table 5). Serious infections were reported in 47 patients (6.4%) (EAIR 1.3 (95% CI 0.9 to 1.7)/100 PYE) and are summarised in online supplemental table 6. Overall, 45 patients (6.1%) had herpes zoster infection (EAIR 1.3 (95% CI 0.9 to 1.7)/100 PYE). There were two cases of serious herpes zoster infection (one was of moderate intensity and the other was severe), both of which were considered possibly related to filgotinib treatment by the investigator, and both resolved within 12 days. One patient had an opportunistic infection (oesophageal candidiasis); there were no cases of hepatitis B or C infection. One patient in the filgotinib plus MTX group had a treatment-emergent serious AE of procedural intestinal perforation in the small bowel that was considered mild and unrelated to filgotinib treatment by the investigator. Fractures were reported in 63 of 739 patients (8.5%), with most moderate in severity. The incidence and EAIRs of TEAEs and TEAEs of interest were similar between female and male patients, although more male patients had TEAEs leading to dose reduction (online supplemental table 7).

Grade 3 or 4 laboratory abnormalities were reported in 280 of 738 patients (37.9%) overall. Decreased

Table 2 Continued

	Filgotinib (DARWIN 1), n=497 (PYE=2504.3)	Filgotinib (DARWIN 2), n=242 (PYE=1201.9)	Filgotinib overall, n=739 (PYE=3706.3)
Lymphocyte count decreased	20 (4.0)	18 (7.4)	38 (5.1)
Blood cholesterol increased	13 (2.6)	23 (9.5)	36 (4.9)
Blood creatinine increased	13 (2.6)	20 (8.3)	33 (4.5)
Musculoskeletal and connective tissue disorders	148 (29.8)	60 (24.8)	208 (28.1)
Rheumatoid arthritis	41 (8.2)	15 (6.2)	56 (7.6)
Back pain	37 (7.4)	11 (4.5)	48 (6.5)
Gastrointestinal disorders	143 (28.8)	54 (22.3)	197 (26.7)
Diarrhoea	33 (6.6)	12 (5.0)	45 (6.1)
Metabolism and nutrition disorders	118 (23.7)	60 (24.8)	178 (24.1)
Hypercholesterolaemia	39 (7.8)	30 (12.4)	69 (9.3)
Dyslipidaemia	39 (7.8)	17 (7.0)	56 (7.6)
Hypertriglyceridaemia	18 (3.6)	13 (5.4)	31 (4.2)
Vascular disorders	91 (18.3)	33 (13.6)	124 (16.8)
Hypertension	75 (15.1)	28 (11.6)	103 (13.9)
Nervous system disorders	83 (16.7)	41 (16.9)	124 (16.8)
Headache	34 (6.8)	26 (10.7)	60 (8.1)
Blood and lymphatic system disorders	80 (16.1)	43 (17.8)	123 (16.6)
Lymphopenia	45 (9.1)	23 (9.5)	68 (9.2)

PYE was adjusted to include up to 30 days after the last dose of study drug. EAIR, 95% CIs were estimated using the Exact Poisson distribution method.

*COVID-19 pneumonia (n=4), Hodgkin lymphoma (n=2), pneumonia (n=2), acute leukaemia (n=1), acute myocardial infarction (n=1), COVID-19 (n=1), meningococcal meningitis (n=1), metastatic leiomyosarcoma (n=1), malignant lung neoplasm (n=1), pulmonary embolism (n=1) and urosepsis (n=1).

†29 patients reported with herpes zoster, 1 with herpes zoster oticus and 1 with both herpes zoster and ophthalmic herpes zoster.

EAIR, exposure-adjusted incidence rate per 100 PYE; MTX, methotrexate; PYE, patient-years of exposure; RA, rheumatoid arthritis; TEAE, treatment-emergent adverse event.

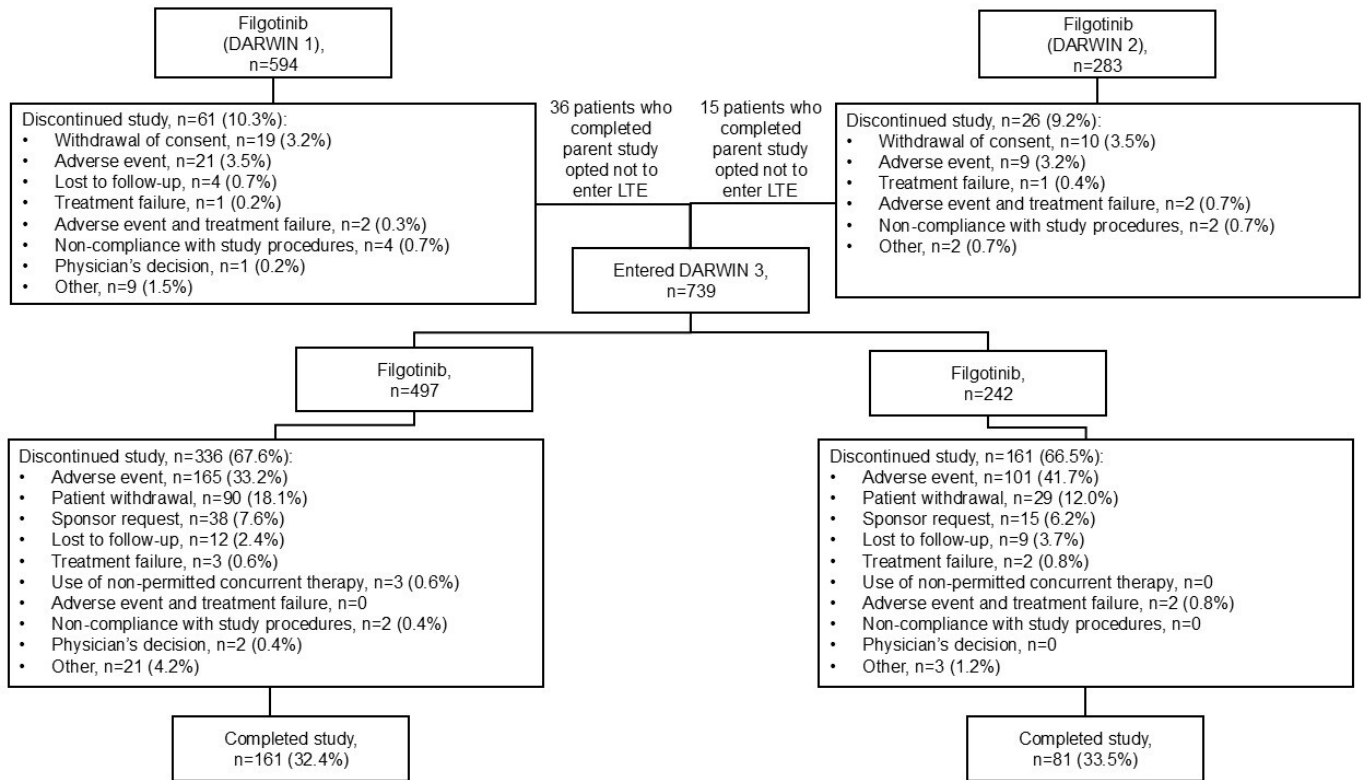


Figure 1 Patient disposition. LTE, long-term extension; MTX, methotrexate.

lymphocyte levels were the most frequently reported treatment-emergent grade 3 or 4 laboratory abnormality (table 4) but were not associated with increased incidence of severe infections; one patient who had severe lymphopenia also had severe COVID-19, which developed 1 year after resolution of lymphopenia. Changes in laboratory parameters were generally minor and transient. There were no clinically relevant changes from baseline in median values for haematology, clinical chemistry, lipid levels or hormonal parameters over time other than the known haematological effects of filgotinib (decreased neutrophil, lymphocyte and platelet counts). Mean haemoglobin values showed a slight increase from the start of filgotinib dosing to week 60 (mean increase of 0.6 g/dL) and thereafter remained relatively stable throughout the study. There were no notable observations in mean/median actual values or CFB over time in vital sign parameters (systolic blood pressure, diastolic blood pressure and pulse rate). No patients had clinically significant changes in ECG evaluation over time; prolonged QT interval (mild intensity) was reported for two patients, which did not prompt a change of filgotinib dosing.

Efficacy

ACR response rates were sustained through week 396 in both treatment groups. Based on the observed case analysis, at week 396, ACR 20/50/70 response rates were 85.0%/65.6%/49.0%, 92.0%/64.9%/45.5% and 87.3%/65.4%/47.8% in the filgotinib DARWIN 1, filgotinib DARWIN 2 and filgotinib overall group, respectively

(figure 2). Responses increased from LTE baseline to week 12 and remained stable thereafter. NRI ACR 20/50/70 response data showed a small increase from the LTE baseline (76.7%/47.4%/27.7%) to week 12 (83.6%/60.9%/36.7%), followed by a slow decline over time to 26.9%/20.2%/14.7% at week 396 as a result of early discontinuations in the study. mNRI analyses supported the NRI results.

Reduction in disease activity with filgotinib treatment, as measured by DAS28-CRP, was sustained through week 396. The overall proportion of patients achieving DAS28-CRP <2.6 increased from 28.6% at LTE baseline to 53.4% at week 84 and 62.8% at week 396 (observed case analysis) (figure 3). NRI data showed an increase in rates of DAS28-CRP remission from LTE baseline (28.0%) to week 12 (39.2%); remission rates were maintained until week 84 and then slowly declined through to week 396 (16.6%) as a result of early discontinuations (figure 3). Patterns similar to those reported for DAS28-CRP 2.6 were seen for change over time based on the observed case and NRI analyses for DAS28-CRP <3.2 response rates, and mNRI analyses supported the NRI results. Overall, mean (SD) DAS28-CRP improved from 6.1 (0.8) at parent study baseline to 3.5 (1.3) at LTE baseline (mean (SD) CFB, -2.6 (1.4)), plateauing at week 72 (DAS28-CRP 2.7; CFB, -3.4 (1.2)) and remaining at this level through to week 396 (DAS28-CRP 2.6 (1.1); CFB, -3.6 (1.3)) (figure 3).

Improvements in other efficacy endpoints, including function and patient-reported outcomes, were observed through week 396. Changes in individual components of

Table 3 Summary of TEAEs of interest

TEAEs, n (%)	Filgotinib (DARWIN 1), n=497 (PYE=2504.3)		Filgotinib (DARWIN 2), n=242 (PYE=1201.9)		Filgotinib overall, n=739 (PYE=3706.3)	
	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)
MACE (adjudicated)	4 (0.8)	0.2 (0.0 to 0.4)	3 (1.2)	0.3 (0.1 to 0.7)	7 (0.9)	0.2 (0.1 to 0.4)
All VTE (adjudicated)	5 (1.0)	0.2 (0.1 to 0.5)	0	0.0 (0.0 to 0.3)	5 (0.7)	0.1 (0.0 to 0.3)
Venous thrombotic and embolic events	3 (0.6)	0.1 (0.0 to 0.4)	0	0.0 (0.0 to 0.3)	3 (0.4)	0.1 (0.0 to 0.2)
Other VTE	2 (0.4)	0.1 (0.0 to 0.3)	0	0.0 (0.0 to 0.3)	2 (0.3)	0.1 (0.0 to 0.2)
ASTE (adjudicated)	1 (0.2)	0.0 (0.0 to 0.2)	0	0.0 (0.0 to 0.3)	1 (0.1)	0 (0.0 to 0.2)
Infections	319 (64.2)	24.6 (22.0 to 27.5)	140 (57.9)	20.8 (17.5 to 24.5)	459 (62.1)	23.3 (21.2 to 25.6)
Serious infections	28 (5.6)	1.1 (0.8 to 1.6)	19 (7.9)	1.6 (1.0 to 2.5)	47 (6.4)	1.3 (0.9 to 1.7)
Herpes zoster	31 (6.2)*	1.3 (0.9 to 1.8)	14 (5.8)	1.2 (0.7 to 2.0)	45 (6.1)	1.3 (0.9 to 1.7)
Malignancies (excluding NMSC)	12 (2.4)	0.5 (0.3 to 0.8)	9 (3.7)	0.8 (0.3 to 1.4)	21 (2.8)	0.6 (0.4 to 0.9)
NMSC	6 (1.2)	0.2 (0.1 to 0.5)	2 (0.8)	0.2 (0.0 to 0.6)	8 (1.1)	0.2 (0.1 to 0.4)
Gastrointestinal perforations	1 (0.2)	0.0 (0.0 to 0.2)	0	0.0 (0.0 to 0.3)	1 (0.1)	0.0 (0.0 to 0.2)
Fractures	46 (9.3)	2.0 (1.4 to 2.6)	17 (7.0)	1.5 (0.9 to 2.4)	63 (8.5)	1.8 (1.4 to 2.3)

PYE was adjusted to include up to 30 days after the last dose of study drug. EAIR 95% CIs were estimated using the Exact Poisson distribution method.
 *29 patients reported with herpes zoster, 1 with herpes zoster ophthalmicus and 1 with both herpes zoster and ophthalmic herpes zoster.
 ASTE, arterial systemic thromboembolism; EAIR, exposure-adjusted incidence rate per 100 PYE; MACE, major cardiovascular adverse events; MTX, methotrexate; NMSC, non-melanoma skin cancer; PYE, patient-years of exposure; TEAE, treatment-emergent adverse event; VTE, venous thromboembolism.

Table 4 Treatment-emergent laboratory abnormalities (safety analysis set)

	Filgotinib (DARWIN 1), n=497	Filgotinib (DARWIN 2), n=242	Filgotinib overall, n=739
Patients with postbaseline data	n=496	n=242	n=738
Treatment-emergent laboratory abnormalities, n (%)			
Grade 3 or 4	190 (38.3)	90 (37.2)	280 (37.9)
Grade 3	142 (28.6)	69 (28.5)	211 (28.6)
Grade 4	48 (9.7)	21 (8.7)	69 (9.3)
Flow cytometry, n (%)			
Lymphocytes (decreased)*			
Grade 3 or 4	58 (11.7)	31 (12.8)	89 (12.1)
Grade 3	35 (7.1)	21 (8.7)	56 (7.6)
Grade 4	23 (4.6)	10 (4.1)	33 (4.5)
Haematology, n (%)			
Lymphocytes (decreased)			
Grade 3 or 4	34 (6.9)	13 (5.4)	47 (6.4)
Grade 3	32 (6.5)	13 (5.4)	45 (6.1)
Grade 4	2 (0.4)	0	2 (0.3)
Prothrombin international normalised ratio (increased)			
Grade 3 or 4	23 (4.6)	6 (2.5)	29 (3.9)
Grade 3	23 (4.6)	6 (2.5)	29 (3.9)
Grade 4	0	0	0
Neutrophils (decreased)			
Grade 3 or 4	11 (2.2)	7 (2.9)	18 (2.4)
Grade 3	7 (1.4)	5 (2.1)	12 (1.6)
Grade 4	4 (0.8)	2 (0.8)	6 (0.8)
Leucocytes (decreased)			
Grade 3 or 4	4 (0.8)	4 (1.7)	8 (1.1)
Grade 3	4 (0.8)	4 (1.7)	8 (1.1)
Grade 4	0	0	0
Platelets (decreased)			
Grade 3 or 4	2 (0.4)	0	2 (0.3)
Grade 3	1 (0.2)	0	1 (0.1)
Grade 4	1 (0.2)	0	1 (0.1)
Chemistry, n (%)			
Lipase (increased)			
Grade 3 or 4	43 (8.7)	20 (8.3)	63 (8.5)
Grade 3	34 (6.9)	15 (6.2)	49 (6.6)
Grade 4	9 (1.8)	5 (2.1)	14 (1.9)
Triglycerides (increased)			
Grade 3 or 4	17 (3.4)	9 (3.7)	26 (3.5)
Grade 3	14 (2.8)	9 (3.7)	23 (3.1)
Grade 4	3 (0.6)	0	3 (0.4)
Gamma glutamyl transferase (increased)			
Grade 3 or 4	17 (3.4)	6 (2.5)	23 (3.1)
Grade 3	16 (3.2)	6 (2.5)	22 (3.0)
Grade 4	1 (0.2)	0	1 (0.1)

Continued

Table 4 Continued

	Filgotinib (DARWIN 1), n=497	Filgotinib (DARWIN 2), n=242	Filgotinib overall, n=739
Glucose (increased)			
Grade 3 or 4	19 (3.8)	4 (1.7)	23 (3.1)
Grade 3	19 (3.8)	4 (1.7)	23 (3.1)
Grade 4	0	0	0
Triglycerides, fasting (increased)†			
Grade 3 or 4	11 (2.4)	7 (3.3)	18 (2.7)
Grade 3	8 (1.7)	7 (3.3)	15 (2.2)
Grade 4	3 (0.7)	0	3 (0.4)

*Differential lymphocyte count measuring CD3, CD19, CD4, CD8, CD3-/CD16+ and CD56+ subsets.
†Filgotinib (DARWIN 1), n=459; Filgotinib (DARWIN 2), n=214; Filgotinib overall, n=673. Data are shown for grade ≥3 laboratory abnormalities that were reported in ≥2% of patients overall.

ACR response were observed over time (online supplemental table 8). Mean (SD) HAQ-DI scores improved from 0.98 (0.65) at LTE baseline to 0.88 (0.64) at week 12; thereafter, scores remained stable until the end of the study (mean CFB, -0.89) (observed case analysis) (figure 4). Patient's pain assessment improved during DARWIN 1 and 2, from a mean (SD) of 68.1 (19.7) mm to 33.6 (23.4) mm at the start of the LTE (n=730). A further improvement was seen in DARWIN 3 to LTE week 12 (mean (SD), 27.7 (20.9) mm, n=724), with an overall CFB of -40.2mm (n=720). Pain assessment then remained relatively stable throughout the LTE, with a mean (SD) of 28.5 (24.2) mm (n=236; mean CFB, -40.2mm (n=235)) at week 396. Other ACR components (tender joint count, swollen joint count, Subject's and Physician's Global Assessment of Disease Activity and serum CRP level) remained stable from baseline through week 396 (observed case analysis) (online supplemental table 8). The overall proportion of patients with an EULAR response increased from 89.9% (45.2% moderate and 44.7% good response) at LTE baseline to 96.4% (20.9% moderate and 75.5% good response) at week 396 (observed case analysis) (online supplemental table 9). Overall rates of ACR/EULAR remission increased steadily over time from 9.3% at LTE baseline to 22.1% at week 396 (observed case analysis) (online supplemental table 9).

Data for CDAI, SDAI, SF-36 PCS/MCS and FACIT-Fatigue over time are shown in online supplemental table 10. CDAI scores (observed case analysis) showed an improvement from the parent study baseline (overall mean (SD), 42.2 (11.6)) to the LTE baseline (13.6 (11.9); CFB, -28.5 (14.3)), reaching 7.1 (8.3) at week 396 (CFB, -34.5 (13)). SDAI values (observed case analysis) showed a similar pattern of improvement to that of the CDAI, demonstrating decreases from the parent study baseline (overall mean (SD), 44.7 (12.4)) to the LTE baseline (14.6 (12.4); CFB, -30.1 (15.1)), reaching 7.3 (8.8) at week 396 (CFB, -37.2 (14.1)). Overall, mean (SD) SF-36 PCS scores in the observed case analysis increased from 31.7 (6.7) at parent study baseline to 41.0 (8.7) at LTE baseline (mean (SD) CFB, 9.3 (9)), plateauing at week 48 (43.1

(8.7); CFB, 11.3 (9.2)) and remaining at this level through to the final observation at week 384 (43.1 (8.8); CFB, 11.5 (9.3)). Similarly, the overall mean (SD) SF-36 MCS scores improved from 42.9 (11) at the parent study baseline to 49.4 (10.3) at the LTE baseline (mean (SD) CFB, 6.4 (9.8)) and remained stable throughout the study to week 384 (49.2 (9.8); CFB, 6.9 (11.5)) (observed case analysis). FACIT-Fatigue total scores in the observed case analysis showed an improvement from the parent study baseline (overall mean (SD), 25.9 (10.4)) to the LTE baseline (37.1 (9.5); CFB, 11.1 (11)) and remained stable through to week 384 (38 (9.7); CFB, 13 (12.5)).

DISCUSSION

The data from the DARWIN 3 LTE demonstrate filgotinib's long-term safety, tolerability and efficacy in patients with moderate to severe RA. This analysis includes the longest observational data on filgotinib to date, with an average follow-up of 5 years and a maximum follow-up of 8 years.

Long-term treatment with filgotinib was well tolerated, with no new safety signals identified versus previous studies.^{11 19 20} Approximately 10% of patients discontinued the study prematurely owing to a positive *Mycobacterium tuberculosis* test result (a mandated study criterion for discontinuation); however, no active tuberculosis was reported in any patient. Positive test results in patients who initially had negative screening tests may be attributable to new exposure during the study in some regions of high tuberculosis prevalence. A proportion of screening tests may have been falsely negative due to variability in QuantiFERON test results known to occur with fluctuating immunocompetency, immunosuppression or advanced age.²¹ In addition, false-positive results have been reported in patients with RA due to high background interferon levels²² and may account for some positive test findings during the study. It should also be noted that some safety events, such as infections and thrombotic events, may have been influenced by the concurrent use

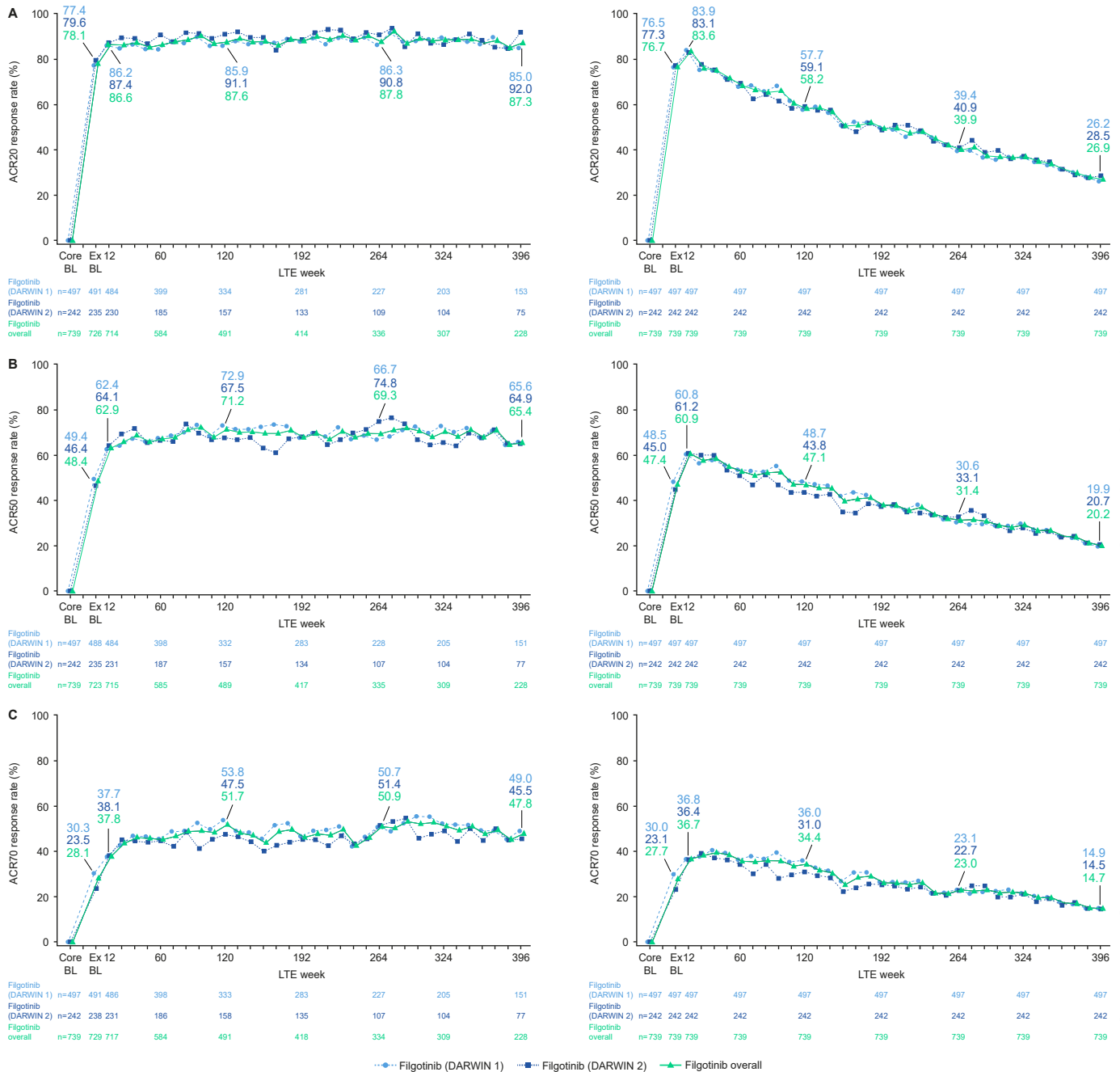


Figure 2 Observed case (left) and NRI (right) analyses for ACR20 (A), ACR50 (B) and ACR70 (C) response rates by LTE visit. Parent study BL value was the last available value collected on or before the first dose of the study drug in the parent studies. The Ex BL value was the last available value collected on or before the first dose of the study drug in the LTE study. ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; BL, baseline; Ex, extension; LTE, long-term extension; NRI, non-responder imputation.

of MTX and/or glucocorticoids. The incidence of herpes zoster is reportedly increased in patients treated with JAK inhibitors.^{23–25} In DARWIN 3, the EAIR/100 PYE was 1.3, which is consistent with previously reported data for filgotinib.^{19, 20} The risk of infections associated with immunosuppressive therapy can be mitigated by the use of vaccinations, and the study protocol recommended that vaccinations were up-to-date according to local vaccination standards. However, we were not able to assess the vaccination status of patients who had infection AEs. The

number of influenza or pneumococcal vaccines received during the study was substantially lower than expected based on treatment recommendations and observational data in patients with RA²⁶; therefore, it is possible that vaccinations were under-reported.

The reported rate of malignancies was comparable to the incidence rate in the general RA population.^{23, 27–29} The most frequently reported malignancy was lymphoma, although it should be noted that the risk of malignancies, including lymphoma, is known to be higher among

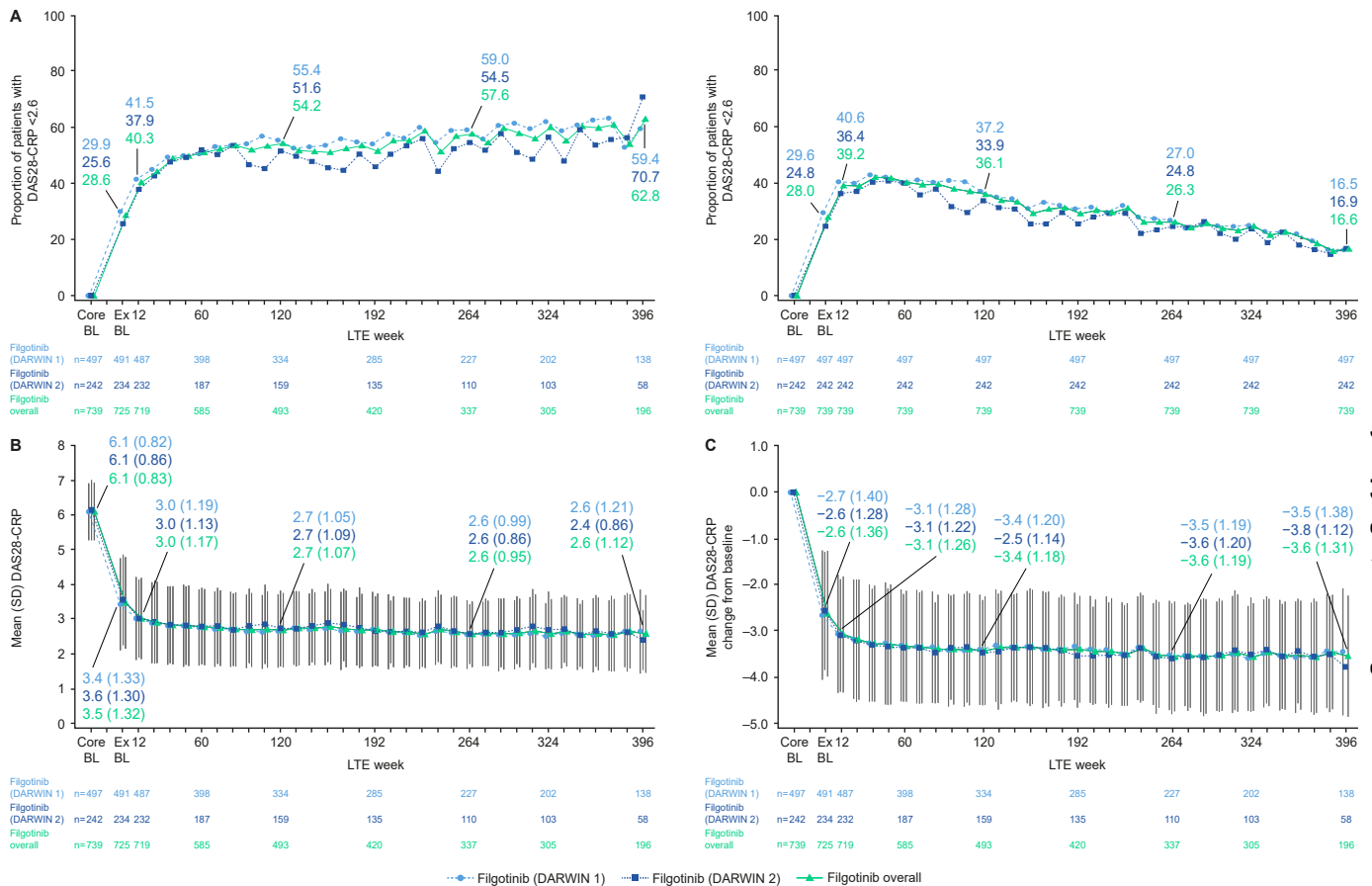


Figure 3 Observed case (left) and NRI (right) analyses for proportions of patients with DAS28-CRP<2.6 (A) and observed case analyses for mean DAS28-CRP (B) and mean DAS28-CRP change from parent study baseline (C) by LTE visit. Parent BL value was the last available value collected on or before the first dose of the study drug in the parent studies. The Ex BL value was the last available value collected on or before the first dose of the study drug in the LTE study. BL, baseline; DAS28-CRP, Disease Activity Score in 28 joints using C-reactive protein; Ex, extension; LTE, long-term extension; NRI, non-responder imputation.

patients with RA than in the general population.³⁰ The risk of cardiovascular events is also higher among patients with RA compared with the general population.

Moreover, a randomised safety study, ORAL Surveillance, showed a higher risk of MACE with the JAK inhibitor tofacitinib compared with tumour necrosis factor

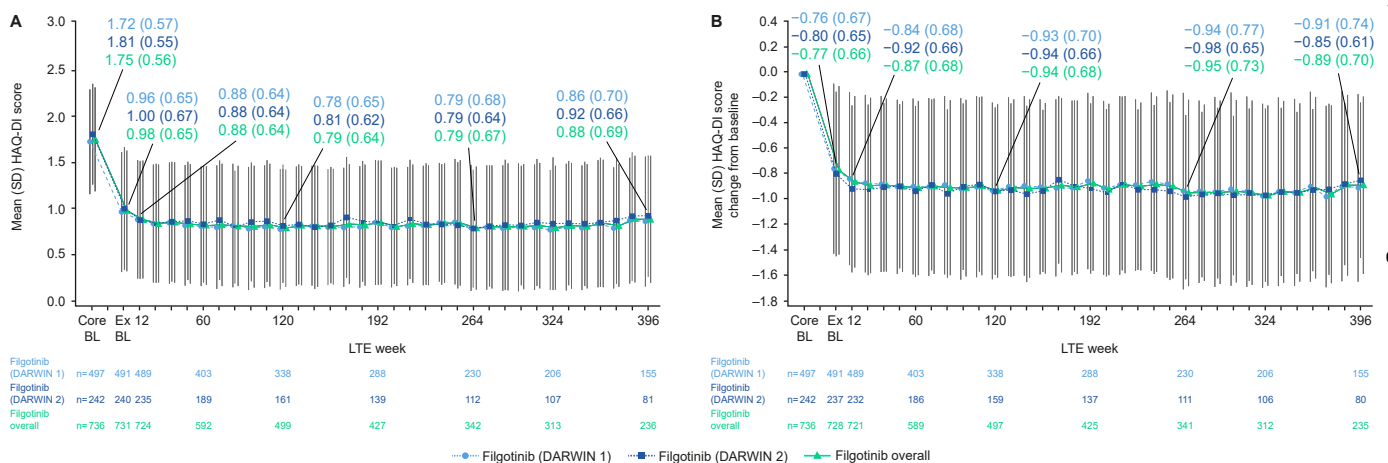


Figure 4 Mean HAQ-DI score by visit (A) and mean change from parent study baseline in HAQ-DI score (B). Parent BL value was the last available value collected on or before the first dose of the study drug in the parent studies. Ex BL value was the last available value collected on or before the first dose of the study drug in the LTE study. BL, baseline; Ex, extension; HAQ-DI, Health Assessment Questionnaire–Disability Index; LTE, long-term extension.

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inhibitors among patients aged over 50 years with at least one cardiovascular risk factor.³¹ As such, an independent adjudication committee was formed to periodically review and adjudicate all potential MACE and thromboembolic events in DARWIN 3 in a blinded manner. The numbers of adjudicated MACE, VTE and ASTE events were low in DARWIN 3 (overall EAIRs 0.2 (95% CI 0.1 to 0.4), 0.1 (95% CI 0.0 to 0.3) and 0.0 (95% CI 0.0 to 0.2), respectively); however, the patient population was not selected by age or cardiovascular risk. Vital signs, including ECG results, remained stable throughout the LTE, and there were no significant changes from baseline over time in any laboratory parameters; only minor shifts or normal variations were observed beyond the known haematological effects of filgotinib (decreased neutrophil, lymphocyte and platelet counts). Observed changes in laboratory parameters were generally transient and most were not confirmed at either unscheduled or next visits.

The efficacy of filgotinib demonstrated in the parent studies was maintained in the LTE, with an ACR 20/50/70 rate of approximately 90%/65%/50% at week 396 overall (observed cases). Initial improvements were seen from the LTE baseline in DAS28-CRP and other study endpoints, likely due to patients transitioning from placebo to filgotinib or an increased filgotinib dose when moving from the parent study to the LTE. Declines over time in efficacy outcomes were observed with NRI, an analysis that codes patients with missing information as treatment failures. The findings of the NRI analyses therefore reflect the increasing number of patients discontinuing the study over time (including those with a positive tuberculosis test result or those who stopped treatment due to administrative decisions). Furthermore, the results of a sensitivity analysis, which classified the 53 patients who left the study due to sponsor requests as missing data rather than non-responders, were almost identical to those of the NRI analysis.

Limitations of this LTE include the open-label design and potential bias from the continued inclusion of patients who are more likely to respond to and tolerate filgotinib well. However, the majority of patients from the parent studies (83% in DARWIN 1 and 85% in DARWIN 2) entered the LTE and continued in the study with a median of >5 years of filgotinib exposure. In addition, a high number of discontinuations occurred because of positive tuberculosis test results and due to patient withdrawal, reducing the number of patients who completed the study. Notably, high discontinuation rates are common in LTE studies.^{29,32} The absence of radiological assessment of disease progression in the DARWIN studies is a further limitation. In addition, data on concurrent glucocorticoid use throughout the study were inadequate to assess if a reduction in average glucocorticoid dose occurred during filgotinib treatment. The potential steroid-sparing effects of filgotinib are being assessed in ongoing real-world studies (eg, FILOSOPHY; ClinicalTrials.gov: NCT04871919).

CONCLUSIONS

This analysis through 8 years of filgotinib exposure demonstrated a safety profile consistent with previously published data for filgotinib in patients with RA.^{11 19 20} Patients who remained on continued filgotinib treatment, either alone or in combination with MTX, in the LTE experienced continued and durable responses through week 396. Together, these results show that long-term filgotinib treatment is both well tolerated and associated with durable responses in patients with RA.

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Competing interests RW reports consultancy fees and speaker fees from Celltrion, Galapagos and Gilead. KLW reports consultancy fees from AbbVie, AstraZeneca, BMS, Galapagos, Gilead, GSK, Lilly, Novartis, Pfizer, Regeneron, Roche, Sanofi and UCB; and grant/research support from BMS and Pfizer. AK reports consultancy fees from Amgen, AbbVie, BMS, Janssen, Novartis, Pfizer and UCB. MG reports grant/research support from AbbVie, Aclaris, Galapagos, Janssen, Lilly and Nimbus. LD reports consultancy fees from AbbVie, Amgen, AstraZeneca, Biogen, Boehringer Ingelheim, BMS, Celltrion, Galapagos, GSK, Janssen, Kiniksa Pharmaceuticals, Lilly, Novartis, Pfizer, Roche, Sanofi-Genzyme, Sobi and Takeda; and grant/research support from AbbVie, BMS, Celgene, GSK, Janssen, Kiniksa Pharmaceuticals, MSD, Mundipharma, Novartis, Pfizer, Roche, Sanofi-Genzyme and Sobi. RC none declared. RB and DdV were employees of, and shareholders in, Galapagos at the time of the study. VM is an employee of, and shareholder in, Galapagos. LHL is an employee of AlfaSigma S.p.A. MCG was an employee of, and shareholder in, Gilead at the time of the analysis. PE reports consultancy fees from

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Anonymized individual patient data will be shared upon request (beginning 6 months and ending 5 years following manuscript publication) for research purposes, dependent upon the nature of the request, the merit of the proposed research, the availability of the data and their intended use. Scientifically sound proposals should be directed to evidencegenerationcommittee@alfasigma.com. The full data sharing policies for Galapagos and Gilead Sciences can be found at <https://www.clinicaltrials-glp.com/us/en/data-transparency.html> and <https://www.gileadclinicaltrials.com/en/transparency-policy#DataSharing>, respectively.

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