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ORIGINAL RESEARCH

Geographic Analysis of the Safety and Efficacy of Filgotinib in Rheumatoid Arthritis

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ABSTRACT

Introduction: Global clinical trials in rheumatoid arthritis (RA) often do not recruit enough patients from diverse racial and ethnic backgrounds to identify any potential differences in treatment outcome across such groups. To overcome this limitation, using data from five previous clinical trials and two ongoing trial extensions, this study aimed to assess the efficacy and safety of filgotinib in patients with RA across geographic regions.

Methods: This was a post hoc, exploratory analysis of data from male and female patients with RA meeting the 2010 RA criteria as defined by the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology. Data were analyzed from phase 2 (DARWIN 1–2) and phase 3 (FINCH 1–3) clinical trials, as well as two long-term extension studies (DARWIN 3, FINCH 4), of filgotinib. Efficacy endpoints included ACR 20%/50%/70% improvement (ACR20/50/70) responses, disease activity score in 28 joints using C-reactive protein [DAS28(CRP)], Clinical Disease Activity Index scores, Boolean remission, and change from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI). Safety data were presented as exposure-adjusted incidence rates per 100 patient-years of exposure of treatment-emergent adverse events.

Results: Compared with placebo, at week 12 a greater proportion of patients receiving filgotinib 200 mg (FIL200) or 100 mg (FIL100) achieved ACR20 ($p < 0.01$), with similar outcomes in most regions. Overall, the reduction in HAQ-DI with FIL200 or FIL100 was greater than with placebo ($p < 0.05$) at week 12. Compared with placebo, at week 24 the proportions of patients achieving DAS28(CRP) ≤ 3.2 were greater for both doses of FIL, as seen in most regions ($p < 0.01$). Safety outcomes did not

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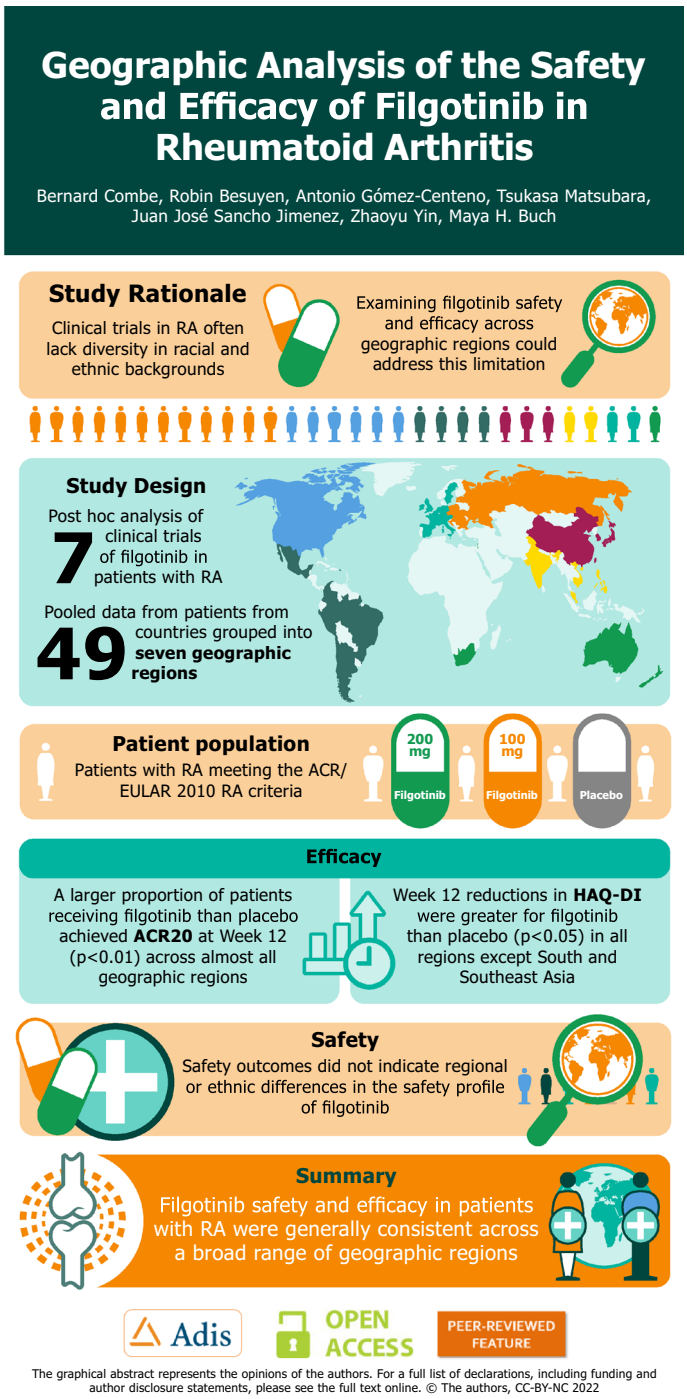
indicate regional or ethnic differences in the safety profile of filgotinib.
Conclusion: Filgotinib efficacy and safety in patients with RA were generally consistent across geographic regions.

ClinicalTrials.gov Trial Registration Numbers: NCT02889796; NCT02873936; NCT02886728; NCT03025308; NCT01888874; NCT01894516; NCT02065700.

Graphical Abstract:



PLAIN LANGUAGE SUMMARY

Clinical trials in rheumatoid arthritis recruit too few patients from diverse ethnic backgrounds to be able to identify differences in treatment outcomes. In adults with moderate-to-severe active rheumatoid arthritis who do not tolerate or have responded poorly to other advanced treatments, the Janus kinase inhibitor filgotinib can be used alone or in combination with the immunosuppressant methotrexate. Using data from 4695 patients with rheumatoid arthritis from five previous clinical trials and two ongoing trial extensions, this paper examined the efficacy and safety of filgotinib in patients with rheumatoid arthritis across geographic locations worldwide.

Patients were grouped by region: North America, South and Central America, Western Europe, Eastern Europe, East Asia, South and Southeast Asia, and Other (South Africa, New Zealand, Australia, and Israel). The efficacy of filgotinib in treating the symptoms of rheumatoid arthritis was assessed using several measures of disease activity, with changes in patient quality of life determined using a health assessment questionnaire. Safety data were reported as the rates of side effects experienced by patients.

Across different geographic regions, no major differences in filgotinib treatment response were observed. Rheumatoid arthritis disease activity levels were consistently lower in patients receiving filgotinib than in patients receiving placebo. Across the regions examined, quality-of-life scores also improved to a greater degree in patients receiving filgotinib compared with placebo. The rates of side effects, including infections, were similar irrespective of region. The number of deaths was low, mostly resulting from cardiovascular events, infections, and malignancies.

This study demonstrates that the efficacy and safety of filgotinib are consistent in patients with rheumatoid arthritis from a broad range of geographic regions and ethnic backgrounds.

Keywords: Adverse effects; Disease-modifying antirheumatic drug; Filgotinib; Outcomes; Rheumatoid arthritis

Key Summary Points

Why carry out this study?

Most clinical trials in rheumatoid arthritis (RA) do not adequately represent the race and ethnicity of RA patient populations.

This study assessed the efficacy and safety of filgotinib in patients with RA across geographic regions.

What was learned from the study?

No major differences in filgotinib treatment response were observed across geographic regions.

Safety profiles were largely consistent across regions, with reported differences in safety outcomes likely the result of small event numbers.

Filgotinib efficacy and safety in patients with RA were therefore generally consistent across geographic regions.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.21108070.

INTRODUCTION

Clinical trials in rheumatoid arthritis (RA) recruit too few patients from diverse ethnic backgrounds to ensure generalizability across ethnic groups and limiting the ability to identify any differences in treatment outcomes. This is important as, while the global prevalence of RA is reported to be between 0.24% [1] and

0.46% [2], prevalence differs between geographic regions [2, 3] and between ethnic groups, including indigenous populations [4–6]. Regional variations in placebo response and adverse-event rates have also been reported in clinical trials [7].

Consequently, some patient populations are overrepresented in clinical trials, partly because of economic factors, which can influence trial access [8]. Importantly, there are also regional inequities in treatment—often linked to national economic factors and healthcare systems—especially with regard to access to biologic disease-modifying antirheumatic drugs (bDMARDs) [9, 10].

Filgotinib is a preferential Janus kinase (JAK)-1 inhibitor approved for use in the European Union and Japan, alone or in combination with methotrexate (MTX), for the treatment of moderate-to-severe RA in adults who are intolerant or who have had an inadequate response to DMARDs [11, 12]. The efficacy and safety of filgotinib have been demonstrated in several clinical trials in RA, including phase 2, phase 3, and ongoing long-term extension (LTE) studies [13–19].

The objective of this study was to assess the efficacy and safety of filgotinib in patients with RA across a range of geographic regions, using pooled data from phase 2 and phase 3 clinical trials and LTE studies to provide a larger population of patients from different racial/ethnic backgrounds.

METHODS

Study Design

This post hoc, exploratory analysis was conducted using data from seven clinical trials of filgotinib in patients with RA. Data were analyzed from patients who met the 2010 RA criteria defined by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology [20], from phase 2 (DARWIN 1–2), phase 3 (FINCH 1–3), and LTE studies (DARWIN 3, FINCH 4) [13–18]. The dates of safety data extraction were 16 July 2019 for DARWIN 3, and 18 December 2019 for FINCH 4. These trials represent the randomized, placebo-controlled data available for filgotinib in patients with RA. For this analysis, patients were grouped by geographic region: North America, South and Central America, Western Europe, Eastern Europe, East Asia, South and Southeast Asia, and Other (Supplementary Table S1). The efficacy and safety of filgotinib 200 mg and filgotinib 100 mg were compared with those of placebo and evaluated across regions.

Detailed methods for each clinical trial are reported elsewhere and summarized in Table 1 [15–18, 21]. All trials were conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. Trials were approved by the institutional review board or ethics committee for each participating study center. Patients provided written informed consent.

Efficacy

Efficacy analyses were conducted on data pooled from three placebo-controlled phase 2 (DARWIN 1) and phase 3 (FINCH 1, FINCH 3) trials, in which filgotinib was administered in addition to MTX. In FINCH 1, patients elicited an inadequate response to MTX, and in FINCH 3, patients were MTX naïve (Supplementary Table S2) [13, 15, 21]. At week 12 in DARWIN 1, patients in the placebo group without at least 20% improvement in swollen and tender joint counts were reassigned to filgotinib (100 mg once daily or 50 mg twice daily). In FINCH 1 and FINCH 3, such patients moved to standard of care at week 14. For analysis of each efficacy endpoint in this post hoc analysis, patients were included as per initial randomization to treatment groups.

Binary efficacy endpoints were analyzed using logistic regression. Subgroup analyses using pooled data were conducted for week 12 ACR 20%/50%/70% improvement (ACR20/ACR50/ACR70) responses, week 24 disease activity score in 28 joints using C-reactive protein [DAS28(CRP)] ≤ 3.2 and < 2.6, week 24 Clinical Disease Activity Index (CDAI) ≤ 10 and ≤ 2.8, and week 24 Boolean

remission. Missing data were imputed using nonresponder imputation. At week 12, change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) was analyzed using a mixed effects model for repeated measures. There was no adjustment for multiplicity.

Safety

Safety analyses were carried out on two sets of pooled data from the seven trials. The first dataset included as-randomized data from the 12-week placebo-controlled period of DARWIN 1–2 and FINCH 1–2. The second dataset included longer-term as-treated data from all seven clinical trials: FINCH 1–3, DARWIN 1–2, and the LTE studies DARWIN 3 and FINCH 4 (Supplementary Table S2).

Uncensored exposure-adjusted incidence rates (EAIRs) per 100 patient-years of exposure (PYE) were calculated for treatment-emergent adverse events (TEAEs). EAIRs and corresponding 95% confidence intervals (CIs) were determined using Poisson regression by treatment, including study and treatment with an offset of the natural log of exposure time. CIs for zero counts were not presented. The Poisson model was not adjusted by study, except when any study had zero events within a treatment.

TEAEs of special interest were assessed. These included infections, cardiovascular events, and malignancies. Treatment-emergent major adverse cardiovascular events (MACE), venous thromboembolisms (VTEs; deep vein thrombosis or pulmonary embolism), and arterial systemic thromboembolism were adjudicated by an independent committee for each trial.

RESULTS

Patients

A total of 4695 patients from seven studies were included in the analyses (as-treated population). The largest number of patients were from Eastern Europe ($n = 1807$; 38.5%), followed by North America ($n = 985$; 21.0%), South and Central America ($n = 748$; 15.9%), East Asia ($n = 432$; 9.2%), South and Southeast Asia ($n = 304$; 6.5%), Western Europe ($n = 274$; 5.8%), and "Other" (i.e., South Africa, New Zealand, Australia, and Israel; $n = 145$; 3.1%). Baseline demographics were generally comparable across geographic regions, except for race. Some regional variability in prior exposure to bDMARDs was observed, the lowest of which was in South and Southeast Asia (Supplementary Tables S3–S9). Trials included in the placebo-controlled safety analysis set ($N = 2346$) and pooled efficacy analysis set ($N = 2135$) are presented in Supplementary Table S2. The regional proportional representation within these analysis sets was broadly similar to that in the as-treated population described above.

Efficacy

In most regions, a larger proportion of patients receiving filgotinib than placebo achieved ACR20 at week 12 ($p < 0.01$). This was true of all regions, except for the category Other, which had a relatively small sample of 69 (Fig. 1, Supplementary Table S10). Similar results were seen for ACR50 and ACR70 at week 12, which were achieved by a greater proportion of patients receiving filgotinib than placebo ($p < 0.05$) in all regions except South and Southeast Asia and Other (Supplementary Table S10). In most regions, numerically greater proportions of patients receiving filgotinib 200 mg achieved ACR20 (exceptions South and Central America and South and Southeast Asia), ACR50 (exceptions were Western Europe and South and Southeast Asia), and ACR70 (exceptions were Western Europe and Other) compared with those receiving filgotinib 100 mg. Week 12 reductions in HAQ-DI were greater for filgotinib than placebo ($p < 0.05$) in all regions except South and Southeast Asia, with numerically greater reductions also apparent for patients receiving filgotinib 200 mg compared with filgotinib 100 mg (with the exception of Other) (Fig. 1, Supplementary Table S11).

At week 24, the proportion of patients achieving DAS28(CRP) ≤ 3.2 was higher for filgotinib than for placebo ($p < 0.01$) in South and

Table 1 Summary of filgotinib RA clinical trials included in pooled data analyses

Trial name and number	Phase	Duration (weeks)	Number of patients treated	RA patient population (background therapy)	Regions	Primary efficacy endpoint	Key secondary efficacy endpoints	Key safety endpoints
FINCH 1 NCT02889796 [13]	3	52	1755	Moderately to severely active RA and inadequate response to MTX (stable MTX)	North America, South and Central America, Eastern Europe, Western Europe, East Asia, South and Southeast Asia, Other	Week 12 ACR20	HAQ-DI[a] DAS28(CRP) < 2.6[a] DAS28(CRP) ≤ 3.2[a] ACR50[b] ACR70[b] CDAI ≤ 10[b] CDAI ≤ 2.8[b]	Laboratory tests AEs MACE Thromboembolic events
FINCH 2 NCT02873936 [14]	3	24	448	Moderately to severely active RA and inadequate response/ intolerance to ≥ 1 DMARD (1–2 protocol-specified csDMARDs)	North America, South and Central America, Eastern Europe, Western Europe, East Asia, Other	Week 12 ACR20	HAQ-DI[a] DAS28(CRP) < 2.6[a] DAS28(CRP) ≤ 3.2[a] ACR50[c] ACR70[c] CDAI ≤ 10[c]	Laboratory tests AEs
FINCH 3 NCT02886728 [21]	3	52	1249	Moderately to severely active RA and MTX naïve (none)	North America, South and Central America, Eastern Europe, Western Europe, East Asia, South and Southeast Asia, Other	Week 24 ACR20	HAQ-DI[d] DAS28(CRP) < 2.6[d] ACR50[b] ACR70[b] CDAI ≤ 2.8[b]	Laboratory tests AEs MACE Thromboembolic events

Table 1 continued

Trial name and number	Phase	Duration (weeks)	Number of patients treated	RA patient population (background therapy)	Regions	Primary efficacy endpoint	Key secondary efficacy endpoints	Key safety endpoints
FINCH 4 NCT03025308 [18]	LTE of FINCH 1, FINCH 2, FINCH 3	Data cutoff Sep 16, 2019	2731	Populations from FINCH 1, FINCH 2, and FINCH 3 (MTX or 1–2 protocol-specified conventional synthetic DMARDs)	North America, South and Central America, Eastern Europe, Western Europe, East Asia, South and Southeast Asia, Other	–	ACR20[e] ACR50[e] ACR70[e]	Laboratory tests AEs
DARWIN 1 NCT01888874 [15]	2b	24	594	Moderately to severely active RA and inadequate response to MTX (stable MTX)	North America, South and Central America, Eastern Europe, Western Europe, Other	Week 12 ACR20	DAS28(CRP), including low activity and remission[f] ACR50[f] ACR70[f] CDAI[f]	Laboratory tests AEs
DARWIN 2 NCT01894516 [16]	2b	24	283	Moderately to severely active RA and inadequate response to MTX (none)	North America, South and Central America, Eastern Europe, Western Europe, Other	Week 12 ACR20	DAS28(CRP), including low activity and remission[f] ACR50[f] ACR70[f] CDAI[f]	Laboratory tests AEs

Table 1 continued

Trial name and number	Phase	Duration (weeks)	Number of patients treated	RA patient population (background therapy)	Regions	Primary efficacy endpoint	Key secondary efficacy endpoints	Key safety endpoints
DARWIN 3 NCT02065700 [17]	LTE of DARWIN 1 and DARWIN 2	Data cutoff Apr 26, 2019	739	Populations from DARWIN 1 and DARWIN 2 (MTX)	North America, South and Central America, Eastern Europe, Western Europe, Other	–	ACR20[g] ACR50[g] ACR70[g] DAS28(CRP) < 2.6[g] DAS28(CRP) ≤ 3.2[g]	AEs EAIR MACE Thromboembolic events

Other = South Africa, New Zealand, Australia, and Israel

ACR20/50/70 American College of Rheumatology 20%/50%/70% improvement, *AE* adverse event, *CDAI* Clinical Disease Activity Index, cs*DMARD* conventional synthetic disease-modifying antirheumatic drug, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *EAIR* exposure-adjusted incidence rate, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *LTE* long-term extension, *MACE* major adverse cardiovascular events, *MTX* methotrexate, *RA* rheumatoid arthritis

[a]Timeframe: baseline, week 12

[b]Timeframe: Weeks 2, 4, 12, and 24

[c]Timeframe: Weeks 4, 12, and 24

[d]Timeframe: baseline, Week 24

[e]Timeframe: up to 6 years

[f]Timeframe: Weeks 1, 2, 4, 8, 12, and 24

[g]Timeframe: up to 96 months

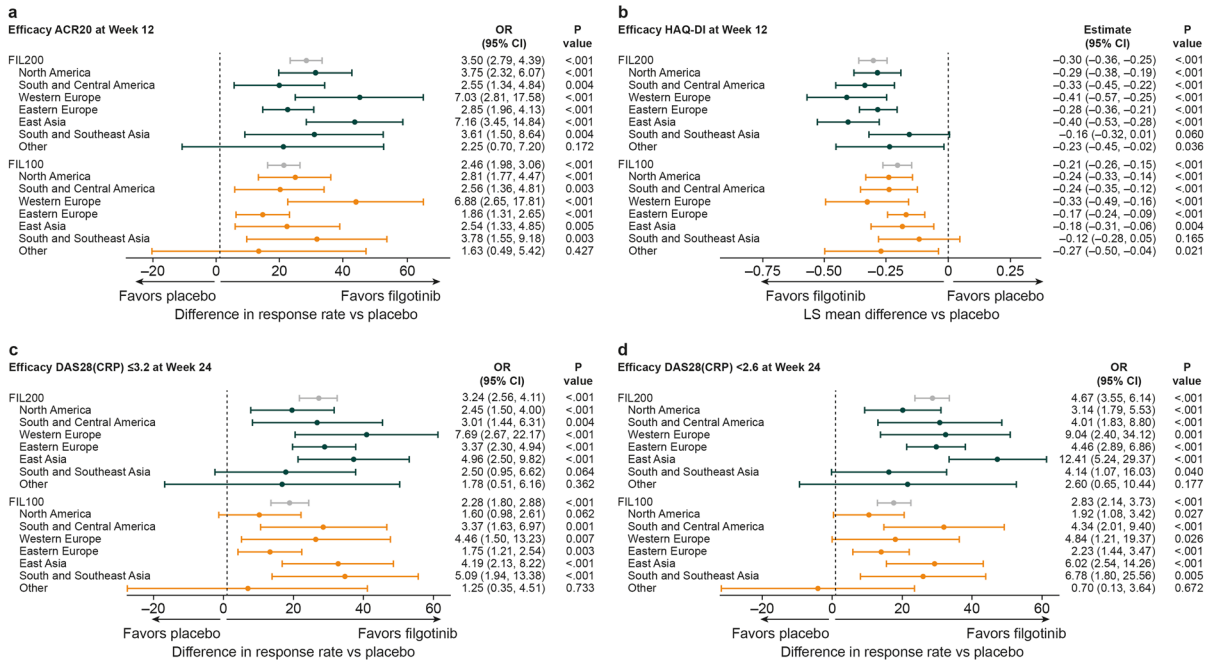


Fig. 1 Pooled efficacy data for **a** ACR20, **b** HAQ-DI, **c** DAS28(CRP) ≤ 3.2, and **d** DAS28(CRP) < 2.6. Other = South Africa, New Zealand, Australia, and Israel. For ACR20 and DAS28(CRP), 95% CIs and *P* values were calculated from the logistic regression with treatment groups, stratification factors, subgroup, study, and treatment by subgroup included in the model. For HAQ-DI, the MMRM included treatment, visit (as categorical variable), subgroup, treatment by visit, treatment by subgroup, baseline value, stratification factors, and study as fixed effects, and patients as the random effect. LS mean, 95% CI, and *P* value were obtained from the MMRM. The common stratification factor is prior exposure to bDMARDs for the analysis through week 12 and includes prior exposure to bDMARDs and presence of anti-cyclic citrullinated peptide or rheumatoid factor for the analysis through week 24. *ACR20* American College of Rheumatology 20% improvement, *bDMARD* biologic disease-modifying antirheumatic drug, *CI* confidence interval, *DAS28(CRP)* disease activity score in 28 joints using C-reactive protein, *FIL100/200* filgotinib 100 mg/200 mg, *HAQ-DI* Health Assessment Questionnaire–Disability Index, *LS* least squares, *MMRM* mixed effects model for repeated measures, *OR* odds ratio

Central America, Western Europe, and Eastern Europe. The proportion achieving DAS28(CRP) < 2.6 was greater for filgotinib than placebo ($p < 0.05$) in all regions except Other (Fig. 1, Supplementary Table S12). For most regions, a numerically greater proportion of patients receiving filgotinib 200 mg compared with filgotinib 100 mg achieved DAS28(CRP) ≤ 3.2 and DAS28(CRP) < 2.6, with the exception of South and Central America and South and Southeast Asia (Supplementary Table S12). For CDAI, the proportion of patients achieving CDAI ≤ 10 was greater for filgotinib than placebo ($p < 0.05$) in South and Central America, Western Europe, and East Asia (Supplementary Table S12). Numerically, a greater proportion of patients in all regions other than South and Southeast Asia achieved CDAI ≤ 10 when receiving filgotinib 200 mg compared with filgotinib 100 mg (Supplementary Table S12). Week 24 Boolean remission rates were higher for filgotinib than placebo ($p < 0.05$) in South and Central America and Eastern Europe (Supplementary Table S13).

Safety

In placebo-controlled as-randomized analyses, EAIRs of all TEAEs were higher for filgotinib than placebo in North America and South and Southeast Asia. In South and Central America,

Table 2 EAIRs of TEAEs to week 12 (placebo-controlled safety analysis set)

	North America (*n* = 481)	South and Central America (*n* = 350)	Western Europe (*n* = 141)	Eastern Europe (*n* = 933)	East Asia (*n* = 236)	South and Southeast Asia (*n* = 135)	Other (*n* = 70)
TEAE							
FIL200[a]	216.9 (162.5, 289.5)	205.6 (155.1, 272.6)	285.0 (188.6, 430.8)	150.3 (119.3, 189.4)	248.9 (180.6, 343.1)	165.1 (104.0, 262.1)	298.4 (150.3, 592.5)
FIL100[b]	182.2 (136.8, 242.7)	159.2 (117.3, 216.1)	285.7 (183.7, 444.3)	146.4 (115.9, 185.0)	246.9 (180.3, 338.1)	153.7 (94.2, 251.0)	263.5 (113.9, 609.2)
PBO[c]	174.5 (130.3, 233.7)	162.1 (118.8, 221.2)	314.9 (200.7, 493.9)	148.4 (117.6, 187.4)	259.0 (188.0, 356.8)	81.6 (40.8, 163.3)	306.0 (142.8, 655.7)
Serious TEAE							
FIL200[a]	14.3 (6.0, 34.4)	11.4 (3.7, 35.5)	8.3 (1.2, 59.0)	12.2 (5.2, 28.7)	5.5 (0.8, 38.9)	0.0 (0.0, ∞)	49.6 (10.2, 144.9)
FIL100[b]	10.6 (4.0, 28.3)	7.2 (1.8, 28.7)	19.9 (5.0, 79.7)	15.1 (6.8, 33.7)	16.2 (5.2, 50.2)	28.8 (9.3, 89.4)	20.5 (0.5, 114.0)
PBO[c]	16.1 (7.2, 35.9)	7.5 (1.9, 30.0)	29.6 (9.5, 91.7)	4.6 (1.3, 15.8)	11.4 (2.8, 45.5)	10.2 (1.4, 72.4)	0.0 (0.0, 69.2)
TEAE leading to discontinuation							
FIL200[a]	8.6 (2.8, 26.6)	3.8 (0.1, 21.2)	16.6 (4.2, 66.5)	12.9 (5.5, 30.5)	0.0 (0.0, 20.2)	9.2 (1.3, 65.1)	16.5 (0.4, 92.1)
FIL100[b]	10.6 (4.0, 28.3)	7.2 (0.9, 26.0)	19.9 (5.0, 79.7)	1.9 (0.2, 13.8)	5.4 (0.1, 30.1)	9.6 (1.4, 68.2)	0.0 (0.0, 75.5)
PBO[c]	5.4 (1.3, 21.5)	0.0 (0.0, 13.8)	9.9 (1.4, 70.0)	12.9 (5.4, 30.7)	17.1 (3.5, 49.9)	20.4 (5.1, 81.6)	0.0 (0.0, 69.2)

Other = South Africa, New Zealand, Australia, and Israel

Data are presented as EAIR (95% CI) per 100 patient-years. The Poisson model was not adjusted by study, except when any study had zero events within a treatment

CI confidence interval, *EAIR* exposure-adjusted incidence rate, *FIL100/200* filgotinib 100 mg/200 mg, *PBO* placebo, *PYE* patient-years of exposure, *TEAE* treatment-emergent adverse event

[a]*N* = 777, 179.8 PYE

[b]*N* = 788, 181.6 PYE

[c]*N* = 781, 178.4 PYE

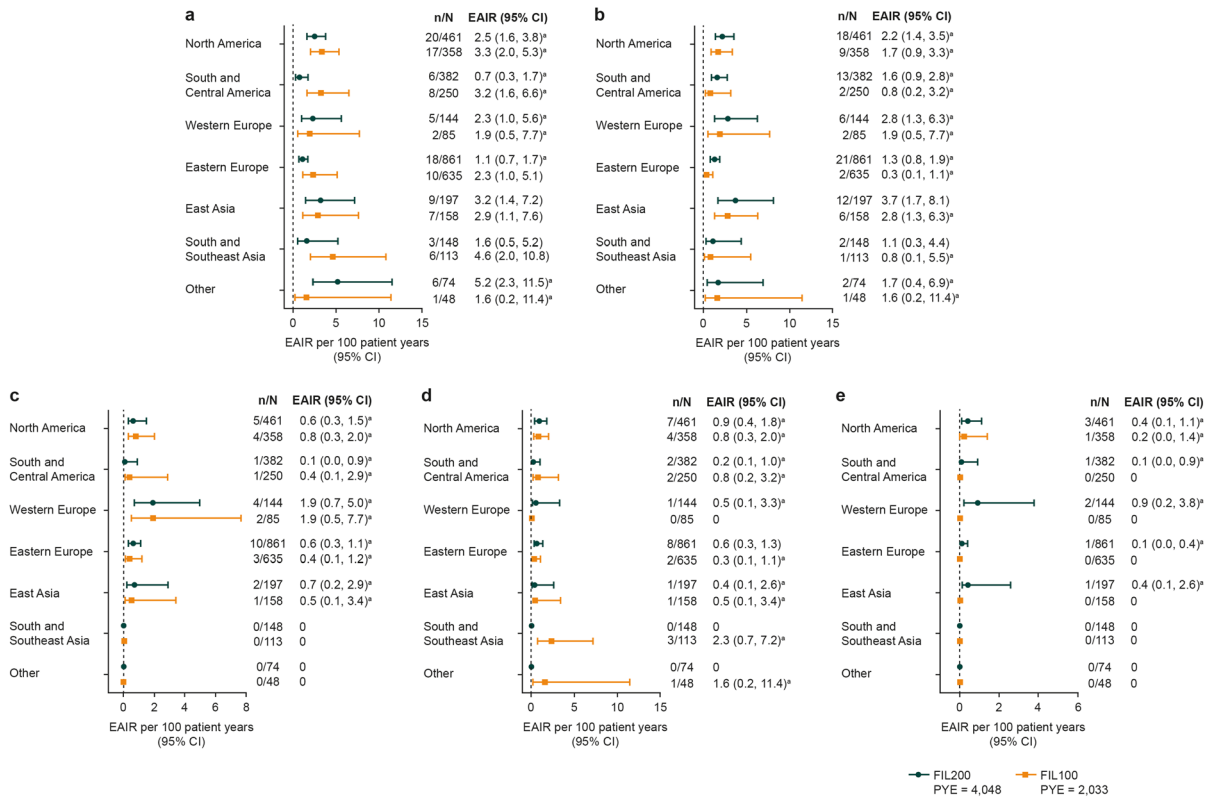


Fig. 2 EAIR of **a** serious infections, **b** herpes zoster[b], **c** malignancy other than NMSC (long-term, as-treated), **d** major adverse cardiovascular events, and **e** venous thromboembolism. Other = South Africa, New Zealand, Australia, and Israel. aThe Poisson model was not adjusted by study, except when any study had zero events within the treatment. [b]Data reported in Winthrop et al. 2022 [19]. *CI* confidence interval, *EAIR* exposure-adjusted incidence rate, *FIL100/200* filgotinib 100 mg/200 mg, *NMSC* non-melanoma skin cancer, *PYE* patient-years of exposure

EAIRs of all TEAEs were higher for placebo than filgotinib 100 mg. In Western Europe, East Asia, and Other, EAIRs of all TEAEs were higher for placebo than filgotinib in some instances. EAIRs of serious TEAEs were higher for filgotinib than placebo in Eastern Europe and Other, and higher for placebo than filgotinib in North America and Western Europe. In South and Central America, EAIRs of serious TEAEs were higher than placebo in the filgotinib 200 mg group, but lower than placebo in the filgotinib 100 mg group. In East Asia and South and Southeast Asia, the opposite pattern was seen. EAIRs of TEAEs leading to study discontinuation were higher for filgotinib 200 mg than for placebo in North America, South and Central America, Western Europe, and Other, and higher for placebo than for either dose of filgotinib in East Asia and South and Southeast Asia (Table 2).

In as-treated analyses of longer-term data, EAIRs of deaths were less than 1.0 per 100 PYE in all regions. In the filgotinib 200 mg group, deaths occurred in North America (n = 5), South and Central America (n = 4), Western Europe (n = 1), Eastern Europe (n = 5), and East Asia (n = 1). Deaths in the filgotinib 100 mg group occurred in South and Central America (n = 2), Eastern Europe (n = 3), and South and Southeast Asia (n = 1) (Supplementary Fig. S1). In all regions, the CIs for EAIRs of deaths overlapped between dose groups (although not presented for zero counts), indicating that EAIRs of deaths did not differ significantly between filgotinib doses. The most common causes of death overall were cardiovascular events (n = 11),

infections (n = 8), and malignancies (n = 6). Cardiovascular events accounted for most of the deaths that occurred in North America, cardiovascular and respiratory events for deaths in Eastern Europe, and infections for deaths in South and Central America and East Asia. Deaths due to malignancies occurred only in Eastern Europe and North America.

EAIRs for infections were comparable across filgotinib doses in most regions (Supplementary Fig. S2). Across regions, the most common infection was not consistently the same. Upper respiratory tract infection (URTI) and urinary tract infection (UTI) were the most common infections in the Americas, whereas nasopharyngitis and URTI were the most common in Europe and Asia. Bronchitis, influenza, and latent tuberculosis were more common in Eastern Europe, East Asia, and South and Southeast Asia than other regions. URTI, UTI, and gastroenteritis were the most common infections in the Other category (data not shown).

Serious infections were also comparable across filgotinib doses in most regions but were more common for filgotinib 100 mg than filgotinib 200 mg in South and Central America and in Eastern Europe (Fig. 2a). Pneumonia was the most common serious infection in all geographic regions except South and Southeast Asia and Other, where the most common serious infections were cellulitis and respiratory tract infections, respectively (data not shown). EAIRs for opportunistic infections were less than 1.0 per 100 PYE for filgotinib in all regions (Supplementary Fig. S3). Rates were highest in East Asia (with filgotinib 200 mg) and in South and Southeast Asia (with filgotinib 100 mg). No active tuberculosis cases were reported with filgotinib 200 mg in any region. Eastern Europe, East Asia, and Southeast Asia each had one case of tuberculosis reported with filgotinib 100 mg.

EAIRs for herpes zoster infection were mostly comparable between filgotinib doses and were highest in East Asia (Fig. 2b).

EAIRs for nonmelanoma skin cancer (NMSC) were highest in the Other category (with filgotinib 200 mg) and were not observed in Western Europe, East Asia, or South and Southeast Asia (Fig. S4). There was no discernible pattern of malignancy occurrences.

EAIRs for malignancies (other than NMSC) were highest in Western Europe and were not observed in filgotinib groups in South and Southeast Asia or Other (Fig. 2c).

EAIRs for MACE were highest in North America for filgotinib 200 mg (n = 7; 1.5%), and in South and Southeast Asia (n = 3; 2.7%) and Other (n = 1; 2.1%) for filgotinib 100 mg (Fig. 2d). EAIRs for VTE were low for filgotinib 200 mg in North America (n = 3; 0.65%), South and Central America (n = 1; 0.26%), Western Europe (n = 2; 1.39%), Eastern Europe (n = 1; 0.12%), and East Asia (n = 1; 0.51%). EAIRs for VTE were generally higher for filgotinib 200 mg versus 100 mg, since EAIRs for VTE for filgotinib 100 mg were recorded only in North America (n = 1; 0.27%). No VTEs were reported in South and Southeast Asia or Other (Fig. 2e).

DISCUSSION

These post hoc analyses of pooled data from phase 2, phase 3, and LTE clinical trials evaluated the efficacy and safety of filgotinib in patients with RA from different racial/ethnic backgrounds and by analyzing across different geographic regions. Efficacy endpoints encompassed measures of disease activity and disease remission. The magnitude of treatment response was broadly consistent across regions. Filgotinib efficacy was higher versus placebo for most endpoints, and the efficacy of filgotinib 200 mg was generally higher than that of filgotinib 100 mg. The evaluation of adverse events included serious infections, opportunistic infections, herpes zoster infections, VTEs, cardiovascular events, malignancies, and deaths [22].

Apart from race, patient demographics and baseline characteristics were broadly comparable across regions. Prior exposure to bDMARDs was subject to regional variation. Body mass index varied to a degree and was highest in North America. Lower proportions of patients in South and Southeast Asia and South and Central America were aged 65 years or over and 75 years or over compared with in other

regions. For South and Central America, this is reflective of the younger age of the general adult population and reports of earlier onset of RA in this region, particularly in indigenous populations [5, 6]. Similarly, India, Malaysia, and Thailand have relatively young adult populations [23–25] and a "sizeable" prevalence of RA has been reported for younger adult patient populations in India [26].

In South and Southeast Asia and Other, the proportion of patients achieving ACR50 or ACR70 at week 12 was not higher in the filgotinib groups than in the placebo group. Similarly, reductions in HAQ-DI were not greater with filgotinib than with placebo in South and Southeast Asia; however, DAS28(CRP) < 2.6 was higher in filgotinib- than placebo-treated patients in all regions, including South and Southeast Asia. As such, although significant differences in all efficacy endpoints were not apparent for filgotinib- versus placebo-treated patients in each region, the data suggest that a similar treatment effect was observed. As the number of patients examined across the regions was small, it cannot be excluded that race- or ethnicity-dependent differences in treatment or placebo effects exist. To this end, a previous publication has reported differences in the response to tumor necrosis factor inhibitors that are dependent on race and ethnicity [27], and a study conducted at a US university hospital suggested that RA disease outcomes differ by race and ethnicity [28].

Safety profiles were largely consistent across regions, with overlapping CIs observed for most EAIRs. Similarly, although differences between the filgotinib dose groups were observed for some EAIRs (e.g., EAIRs for VTE were generally higher for filgotinib 200 mg versus 100 mg), the CIs for the two doses generally overlapped, indicating lack of statistical significance. Any differences in safety outcomes may have been driven by small event numbers and/or regional treatment differences. EAIRs of TEAEs were generally lower, regardless of treatment group, in South and Central America, Eastern Europe, and South and Southeast Asia than in the other regions. A similar pattern was observed in an analysis of seven RA clinical trials [7]. The slightly higher EAIRs for VTE observed in North America and Western Europe, in comparison with other regions, may partly be explained by genetic variation in mutations of Leiden factor V, since carrier frequency has been reported to be higher in Caucasians than in other ethnic groups [29]. It should be noted that VTEs have been reported in studies of other JAK inhibitors in patients with RA and other immune-mediated inflammatory diseases [30]. Rates of herpes zoster infection during filgotinib treatment were highest in East Asia; similar results have been reported for other JAK inhibitors, including baricitinib [31], tofacitinib [32–34], and upadacitinib, for the Asian region [34]. Of note, the rates for herpes zoster infection in this region appear lower for filgotinib than for other JAK inhibitors [31–34].

Substantial variation in the EAIRs of serious TEAEs by treatment group was apparent across different regions, in some cases higher in the filgotinib groups, and in other instances higher in the placebo group. In some regions (e.g., East Asia and South and Southeast Asia), EAIRs of TEAEs were higher with filgotinib 100 mg than with placebo, and lower with filgotinib 200 mg than with placebo. Given the small number of serious TEAEs reported, it is difficult to draw any firm conclusions from these data.

Causes of death are aligned with geographic differences in lifestyle (e.g., diet, physical activity, tobacco use, alcohol use), with the highest risk of cardiovascular disease evident in North America and Eastern Europe [35]. EAIRs of deaths did not differ significantly between filgotinib doses. In South and Central America and East Asia, there is a higher prevalence and risk of infections [36].

Regional variations in safety outcomes were evident with the use of placebo as well as filgotinib, and it is therefore likely that these differences arose, at least in part, from regional and ethnic differences in genetics, lifestyle factors, and access to medical care resulting from socioeconomic factors (as evidenced by regional differences in the use of bDMARDs); for example, the risk of infections was higher in regions less likely to have access to medical care. However, overall, the study's findings did not reveal any particular safety signal(s) to indicate

regional or ethnic differences in the safety profile of filgotinib.

As a non-prespecified, exploratory analysis, these findings are subject to certain limitations. Randomization in the individual clinical trials was not stratified by the geographic regions evaluated in this analysis, and the numbers of patients were not equal in all subgroups. In line with previous reports [7], some regional variation in placebo response was observed, which was reflected in regional variations in the size of the treatment difference between filgotinib and placebo. Analyses of the data based on sex or age were not performed, since this was beyond the scope of the current study. Patient demographics showed that most patients across regions were female, which is in line with the known epidemiology of RA.

CONCLUSION

This post hoc analysis of seven clinical trials showed that filgotinib efficacy and safety in patients with RA were generally consistent across a broad range of geographic regions. Ongoing LTEs, together with data collected from real-world evidence studies, will help to further understand the safety of filgotinib in relation to infrequent adverse events.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available; however, aggregate data will be shared upon request for research purposes dependent upon the nature of the request, the merit of the proposed research, the availability of the data, and its intended use. The full data sharing policy for Gilead Sciences, Inc., can be found at https://www.gilead.com/science-and-medicine/research/clinical-trials-transparency-and-data-sharing-policy.

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