RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Major adverse cardiovascular, thromboembolic and malignancy events in the filgotinib rheumatoid arthritis and ulcerative colitis clinical development programmes

Xavier Mariette ,[1] Sven Borchmann,[2] Sandrine Aspeslagh,[3] Zoltan Szekanecz,[4] Christina Charles-Schoeman ,[5] Stefan Schreiber,[6] Ernest HS Choy ,[7] Laurent Peyrin-Biroulet,[8,9,10] Marc Schmalzing,[11] Yoshiya Tanaka ,[12] Hugo ten Cate,[13] René Westhovens ,[14] C Janneke van der Woude,[15] Edmund V Ekoka Omoruyi,[16] Margaux Faes,[16] Tomasz Masior,[17] Paul Van Hoek,[16] Chris Watson,[18] Christine Rudolph,[19] Andreas Stallmach[20]

To cite: Mariette X, Borchmann S, Aspeslagh S, *et al*. Major adverse cardiovascular, thromboembolic and malignancy events in the filgotinib rheumatoid arthritis and ulcerative colitis clinical development programmes. *RMD Open* Published Online First: [please include Day Month Year]. doi:10.1136/rmdopen-2024-005033

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/rmdopen-2024-005033).

For 'Presented at' see end of article.

Received 23 September 2024
Accepted 5 January 2025

For numbered affiliations see end of article.

Correspondence to
Dr Xavier Mariette;
xavier.mariette@aphp.fr

ABSTRACT

Objectives Long-term safety is fundamental for treatment decision-making. This integrated analysis of filgotinib clinical trials in rheumatoid arthritis (RA) and ulcerative colitis (UC) assessed adverse events of interest (AEI): major adverse cardiovascular events (MACE), venous thromboembolism (VTE) and malignancies.

Methods Data were integrated from all phase II and III trials that have investigated filgotinib 100 mg or 200 mg once daily in RA and UC to date.

Results Analyses represent >12 500 (RA) and >2800 (UC) patient-years of exposure (PYE) to filgotinib. Incidences of AEI in the integrated analysis population were low. Modest numerical increases in incidence rates occurred in patients aged ≥65 years, including MACE (patients with RA), and malignancies (excluding non-melanoma skin cancer (NMSC)) and NMSC (patients with RA or UC). VTE was rare; in patients with RA aged ≥65 years receiving filgotinib 200 mg, exposure-adjusted incidence rate (95% CI) for VTE was 0.3 (0.1, 0.8)/100 PYE; no VTE events occurred in patients with UC aged ≥65 years. In patients with RA aged ≥65 years, MACE incidence rates were identical between filgotinib 100 mg and 200 mg; rates of malignancies and NMSC were numerically higher with 200 mg compared with 100 mg.

Conclusions Data are consistent with previous overall safety analyses demonstrating low rates of AEI in the overall study population. Numerically increased rates of AEI occurred in patients aged ≥65 years; further data are needed to assess the effect of CV risk factors. Overall, in this analysis, there was no consistent filgotinib dose effect on AEI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study reported increased risks of major adverse cardiovascular events (MACE) and malignancies with tofacitinib compared with tumour necrosis factor inhibitors in patients aged ≥50 years with ≥1 cardiovascular risk factor.

⇒ These findings resulted in updated recommendations for all Janus kinase (JAK) inhibitors regarding their use in patients aged ≥65 years or with cardiovascular or malignancy risk factors.

⇒ Filgotinib is a JAK1-preferential inhibitor approved for the treatment of moderate to severe active rheumatoid arthritis (RA) and moderately to severely active ulcerative colitis (UC).

WHAT THIS STUDY ADDS

⇒ This post hoc integrated analysis provides a detailed examination of MACE, VTE and malignancy across both filgotinib indications.

⇒ While rates of malignancy and non-melanoma skin cancer were numerically but not statistically higher with filgotinib 200 mg compared with 100 mg in patients with RA aged ≥65 years, overall, there was no consistent filgotinib dose effect.

⇒ In patients with RA aged ≥65 years, the rates of MACE were the same with filgotinib 100 mg and 200 mg.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These data support the recommendation of filgotinib dose adjustment in patients aged ≥65 years to 100 mg once daily, escalated to 200 mg in case of insufficient RA disease control or UC disease flare.

INTRODUCTION

Safety considerations are particularly important when choosing long-term therapies for

patients with inflammatory diseases. The Food and Drug Administration-mandated postmarketing Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study assessed long-term safety of the Janus kinase (JAK) inhibitor tofacitinib compared with antitumour necrosis factor (TNF) therapy in patients with active rheumatoid arthritis (RA) aged ≥50 years with ≥1 cardiovascular (CV) risk factor.[1] In ORAL Surveillance, the incidences of major adverse CV events (MACE) and malignancies were numerically higher with tofacitinib compared with TNF inhibitors, and did not meet non-inferiority criteria, especially in patients aged ≥65 years. Furthermore, ORAL Surveillance found an increased risk of venous thromboembolism (VTE) with the unapproved 10 mg dose of tofacitinib relative to TNF inhibitors.[1] The ongoing B023 registry and database study in patients with RA receiving baricitinib reported a significant 1.5-fold increased risk of VTE with baricitinib versus TNF inhibitors, and a numerically greater risk of MACE; however, length of follow-up was short (average 9 months), limiting full assessment of risk.[2] Long-term integrated analysis of adverse events (AEs) of interest in clinical trials of baricitinib in RA showed that MACE and malignancy remained stable over a median of 4.6 years.[3]

Based on these findings in RA, the European Medicines Agency updated the product information for all JAK inhibitors, including filgotinib, to state that they should only be used if no suitable treatment alternatives are available in patients who are 65 years of age or older, or in those with a history of atherosclerotic CV disease or other CV risk factors, or with malignancy risk factors. This guidance has been applied to all indications of JAK inhibitors, even though safety analyses of filgotinib, tofacitinib and upadacitinib in ulcerative colitis (UC) have not identified increased risk of MACE or malignancies, and VTE events occurred in low numbers.[4–6] There is currently no equivalent study to ORAL Surveillance in UC, with available safety analyses in this indication performed on populations not selected by age or existing risk factors.[7–9] However, recent large claims database studies in inflammatory bowel disease have shown no increase in MACE, VTE and malignancies with oral small molecule use (including JAK inhibitors),[10 11] and specifically no increase in malignancy rates after 4 years of follow-up in patients aged >50 years who received tofacitinib or upadacitinib compared with patients who had not received JAK inhibitors.[11]

Filgotinib is a JAK1-preferential inhibitor approved in the European Union, UK and Japan[12 13] for the treatment of RA and UC. A recently updated long-term integrated safety analysis of filgotinib in patients with RA over a median (maximum) treatment duration of 3.8 (8.3) years reported that, with the exception of herpes zoster, rates of AEs of interest (MACE, VTE, non-melanoma skin cancer (NMSC), malignancies excluding NMSC, serious infections and all-cause mortality) were similar between filgotinib 200 mg and 100 mg dose groups, and remained stable over time.[14] In an integrated safety analysis of filgotinib in patients with UC, incidence rates of MACE and VTE were comparable with placebo and generally similar across filgotinib doses.[6]

The aim of this post hoc analysis was to perform a detailed analysis of integrated clinical study data to assess the risk of key AEs, MACE, VTE and malignancies in patients with RA or UC treated with filgotinib, and to investigate risk factors associated with these AEs of interest.

METHODS

Study design and patients

RA data were integrated from seven clinical trials: the phase II DARWIN 1 (NCT01888874) and DARWIN 2 (NCT01894516) trials; phase III FINCH 1 (NCT02889796), FINCH 2 (NCT02873936) and FINCH 3 (NCT02886728) trials and DARWIN 3 (NCT02065700) and FINCH 4 (NCT03025308) long-term extension (LTE) trials. Eligible patients were aged ≥18 years with a diagnosis of RA per EULAR/American College of Rheumatology 2010 criteria. UC data were integrated from the phase IIb/III SELECTION (NCT02914522) and SELECTIONLTE (NCT02914535) trials.

Assessments

Duration of exposure to filgotinib (in years) was calculated as (last dosing date−first dosing date+1)/365.25. Time to first event and exposure-adjusted incidence rates (EAIRs) per 100 patient-years of exposure (PYE) with corresponding 95% CIs were assessed for AEs of interest, and also for treatment-related AEs (TEAEs) leading to death (for CV and malignancy events). AEs of interest were adjudicated MACE, adjudicated VTE, arterial systemic thromboembolism (ASTE), malignancies excluding NMSC and NMSC. Adjudicated MACE were defined as CV events leading to death, myocardial infarction (MI; fatal or non-fatal) and non-fatal stroke. Adjudicated VTE events were defined as deep vein thrombosis (DVT; both distal and proximal), pulmonary embolism (PE) and other.

Analysis sets

The long-term, as-treated analysis sets for RA and UC included all available data for patients who received ≥1 dose of once-daily filgotinib 200 mg or 100 mg. Patient data were included from both the original treatment received in the parent studies and after re-randomisation to filgotinib in LTE studies; as such, patients' exposure time may contribute to more than one treatment group. Post hoc analyses were performed on patients aged <65 years and ≥65 years; patients aged <65 years without CV risk factors and ≥65 years or with ≥1 CV risk factor and patients aged <50 years or with no CV risk factor and ≥50 years and with ≥1 CV risk factor. CV risk factors were defined as family history of CV disease; history of dyslipidaemia, diabetes mellitus or CV disease; hypertension, ischaemic vascular conditions, peripheral vascular disease or extra-articular manifestations of RA; or having ever smoked. AEs were coded according to MedDRA V.25.0. Grade of AEs were reported using the Common Terminology Criteria for

Adverse Events V.4.03 (grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening; grade 5, death related to AE).

Statistical analyses

Data from the ongoing RA LTE trials were included through 2 May 2022 for DARWIN 3, and 6 May 2022 for FINCH 4. Data for MACE and VTE only include events positively adjudicated by an independent committee (adjudicated data cut-off: 3 April 2022). Data from the ongoing UC SELECTIONLTE trial were included through 24 February 2022. Data for MACE and VTE only included events positively adjudicated by an independent committee (adjudicated data cut-off: 31 December 2021).

Baseline demographics, disease characteristics and TEAEs were summarised using descriptive statistics. EAIRs per 100 PYE, censored at the time of the first event, were determined for TEAEs of interest. Analysis used censored PYE, which is the PYE until onset of the first event if the patient has the event of interest or the total PYE for patients without the event. For patients without an event, exposure was censored at the data cut-off date for ongoing studies or last patient contact for patients who completed or discontinued the study. Exact 95% CIs of the EAIRs were calculated based on the Poisson distribution.[15]

RESULTS

Patient population and exposure

In RA, 3691 patients were included in the integrated as-treated population with a total exposure of 12 541.0 PYE to filgotinib (median exposure 3.8 years). Filgotinib 200 mg was received by 2267 patients (8008.6 PYE, median (maximum) exposure 3.8 (8.3) years) and filgotinib 100 mg was received by 1647 patients (4532.4 PYE, median (maximum) exposure 3.3 (7.8) years). In UC, the integrated as-treated population comprised 1253 patients with 2866.9 PYE to filgotinib (median exposure 2.8 years). Filgotinib 200 mg and 100 mg were received by 971 patients (2318.6 PYE) and 583 patients (548.3 PYE), with median (maximum) exposure of 3.0 (5) years and 0.2 (5) years, respectively.

Of the patients with RA, approximately 19% were aged ≥65 years; adverse CV medical history was frequent, including ~34% with hypertension (table 1). Of the patients with UC, approximately 7% were aged ≥65 years, ~16% had hypertension and around 5% were current smokers (table 2).

More patients with RA aged ≥65 years had an adverse CV medical history than those aged <65 years. The number of current smokers was similar between age groups and doses and mean creatinine clearance was lower in patients aged ≥65 years versus aged <65 years, as expected (online supplemental table S1). Adverse CV medical history also occurred more frequently in patients with UC aged ≥65 years than in those aged <65 years, while smoking status and creatinine clearance were similar between age groups in the UC population (online supplemental table S2).

MACE and VTE

Incidence rates of MACE and VTE were low across filgotinib-treated patients with RA or UC in the parent studies and integrated analyses; EAIRs (95% CI)/100 PYE for MACE and VTE ranged from 0.1 (0.0, 0.3) to 0.5 (0.3, 0.7) in the long-term, as-treated populations (figures 1 and 2). In patients with RA, the EAIRs (95% CI)/100 PYE for MACE were higher in patients aged ≥65 years compared with <65 years: 1.0 (0.5, 1.7) and 0.2 (0.1, 0.4) for filgotinib 200 mg and 1.0 (0.5, 1.9) and 0.4 (0.2, 0.6) for filgotinib 100 mg, respectively (figure 1A). The EAIRs for VTE were 0.3 (0.1, 0.8) and 0.2 (0.1, 0.3) for patients with RA aged ≥65 and <65 years, respectively, receiving filgotinib 200 mg (figure 1B).

For patients with UC, the EAIR of MACE was higher in patients aged ≥65 years compared with <65 years: EAIRs (95% CI)/100 PYE: 1.7 (0.4, 5.0) and 0.2 (0.1, 0.5), respectively (figure 2A). No VTE events occurred in patients with UC aged ≥65 years, and in patients aged <65 years, the EAIRs (95% CI)/100 PYE for VTE were 0.1 (0.0, 0.3) and 0.2 (0.0, 1.0) for filgotinib 200 mg and 100 mg, respectively (figure 2B). EAIRs for MACE and VTE in patients with UC were similar for filgotinib 200 mg and 100 mg, except for an EAIR of 3.6 (0.1, 19.9)/100 PYE attributed to one patient aged ≥65 years having a MACE while receiving filgotinib 100 mg.

In time to event analyses in RA and UC, MACE and VTE events generally occurred evenly over time, and time to onset was similar between filgotinib 200 mg and 100 mg dose groups in patients aged <65 years and in those ≥65 years (figures 3–6).

ASTE events were reported in two patients with RA: one patient had peripheral artery thrombosis (grade 4) and one patient had cerebral infarction (grade 2), subclavian artery occlusion and PE (both grade 3). The patients recovered, or were recovering, at the time of the analysis. There were no ASTE events in patients with UC.

Additional analysis in both RA and UC by age and CV risk showed similar EAIRs for MACE and VTE in the group of patients who were aged <50 years or ≥50 years but with no CV risk factor, compared with the group of patients who were aged ≥50 years and had ≥1 CV risk factor. The difference in EAIR between these patient groups was small with overlapping CIs, although values were numerically higher in those aged ≥50 years with a CV risk factor (online supplemental figures S1 and S2).

The severity of MACE and VTE, relationship to treatment, and outcome are shown in online supplemental tables S3 and S4. The most frequently occurring MACE in patients with RA were acute MI, MI, ischaemic stroke, cerebrovascular accident and transient ischaemic attack. Most other types of MACE occurred in individual patients in each dose group. PE was the most frequent VTE event in patients with RA, followed by DVT (online supplemental figure S3). One case of PE had a fatal outcome

Table 1 Baseline demographics and disease characteristics in patients with RA

	Filgotinib 200 mg once daily (n=2267)	Filgotinib 100 mg once daily (n=1647)
Age, years, mean (SD)	52.6 (12.8)	53.2 (12.8)
≥65 years	407 (18.0)	326 (19.8)
Sex, female	1828 (80.6)	1319 (80.1)
Weight, kg, mean (SD)	73.2 (18.3)	73.4 (18.6)
Body mass index, kg/m^2, mean (SD)	27.6 (6.2)	27.6 (6.2)
Race		
Asian	372 (16.4)	286 (17.4)
Black or African American	63 (2.8)	53 (3.2)
Native American or Alaska Native	117 (5.2)	87 (5.3)
Native Hawaiian or other Pacific Islander	5 (0.2)	1 (<0.1)
White	1568 (69.2)	1137 (69.0)
Other/Not permitted	142 (6.3)	83 (5.0)
Duration of RA from diagnosis, years, mean (SD)*	6.3 (7.6)	7.4 (7.8)
Creatinine clearance, mL/min, mean (SD)	115.1 (38.3)	114.7 (38.9)
CRP, mg/L, mean (SD)	18.9 (24.5)	18.6 (25.6)
DAS28-CRP, mean (SD)	5.8 (0.9)	5.8 (1.0)
Concurrent oral glucocorticoids*	782 (34.5)	632 (38.4)
Concurrent csDMARDs*	1327 (58.5)	1183 (71.8)
Concurrent methotrexate*	1219 (53.8)	1100 (66.8)
Prior exposure to bDMARDs†	276 (12.2)	255 (15.5)
Smoking status*‡		
Current smoker	244 (13.7), n=1776	193 (14.1), n=1370
Former smoker	236 (13.3), n=1776	174 (12.7), n=1370
Never smoked	1296 (73.0), n=1776	1003 (73.2), n=1370
CV family history‡	53 (3.0), n=1773	59 (4.3), n=1370
CV medical history		
Hypertension	766 (33.8)	560 (34.0)
Dyslipidaemia	335 (14.8)	280 (17.0)
Diabetes mellitus	221 (9.7)	158 (9.6)
CV disease	111 (4.9)	69 (4.2)
Ischaemic CNS vascular disorder	51 (2.2)	34 (2.1)
Extra-articular disease	9 (0.4)	11 (0.7)
Peripheral vascular disease	5 (0.2)	6 (0.4)

Data are n (%) unless otherwise indicated. As the trials were not designed to capture CV risk at baseline, data should be interpreted with caution.
Table used with permission of Elsevier Science & Technology Journals, from Winthrop *et al*[40]. Copyright © 2022; permission conveyed through Copyright Clearance Center, Inc.
*On the first dosing date in the parent study.
†Up to the first dosing date in the parent study.
‡Not available for the DARWIN studies.
b/csDMARD, biologic/conventional synthetic disease-modifying antirheumatic drug; CNS, central nervous system; CRP, C-reactive protein; CV, cardiovascular; DAS28-CRP, Disease Activity Score in 28 joints using C-reactive protein; RA, rheumatoid arthritis.

in a woman aged 65 years with CV risk factors who died following a DVT and subsequent PE in the filgotinib 200 mg group. There was no clustering of MACE or VTE event types in patients with UC (online supplemental figure S4), and the incidence of MACE or VTE did not increase with increasing exposure to study drug in patients with RA or UC.

In total, 17 patients with RA experienced CV TEAEs leading to death, out of a total of 83 deaths (2.2%) in the integrated safety cohort.[14] The most frequent

Table 2 Baseline demographics and disease characteristics in patients with UC

	Filgotinib 200 mg once daily (n=971)	Filgotinib 100 mg once daily (n=583)
Age, years, mean (SD)	42.8 (13.7)	42.8 (13.8)
≥65 years	65 (6.7)	39 (6.7)
Sex, female	413 (42.5)	219 (37.6)
Weight, kg, mean (SD)	71.6 (17.2)	72.6 (17.5)
Body mass index, kg/m^2, mean (SD)	24.6 (5.3), n=971	24.7 (4.9), n=582
Race*		
Asian	222 (22.9)	132 (22.6)
Black or African American	8 (0.8)	12 (2.1)
Native American or Alaska Native	1 (0.1)	0
White	693 (71.4)	419 (71.9)
Other/Not permitted	47 (4.8)	20 (3.4)
Duration of UC from diagnosis, years, mean (SD)†	8.4 (7.3)	8.3 (7.5)
Mayo Clinic Score, mean (SD)	9.0 (1.4)	9.0 (1.4)
Creatinine clearance, mL/min, mean (SD)	113.1 (28.5)	112.4 (28.0)
Faecal calprotectin, µg/g, mean (SD)	2367.5 (3406.5), n=941	2143.1 (3266.8), n=570
Concurrent oral or systemic glucocorticoids at induction baseline	427 (44.0)	240 (41.2)
Concurrent immunomodulator at induction baseline†	253 (26.2)	147 (25.2)
Smoking status†		
Current smoker	46 (4.7), n=971	33 (5.7), n=582
Former smoker	258 (26.6), n=971	153 (26.2), n=582
Never smoked	667 (68.7), n=971	397 (68.1), n=582
CV medical history		
Hypertension	146 (15.0)	100 (17.2)
Dyslipidaemia	90 (9.3)	72 (12.3)
Diabetes mellitus	48 (4.9)	29 (5.0)
CV disease	23 (2.4)	23 (3.9)
Ischaemic CNS vascular disorder	11 (1.1)	3 (0.5)
Extra-articular disease	0	0
Peripheral vascular disease	1 (0.1)	2 (0.3)

Data are n (%) unless otherwise indicated. As the trials were not designed to capture CV risk at baseline, data should be interpreted with caution. CV family history was not collected in SELECTION.
*Hawaiian/Pacific Islander not included as a group in UC studies.
†On the first dosing date in the parent study.
CNS, central nervous system; CV, cardiovascular; UC, ulcerative colitis.

MACE-related causes of death were MI and acute MI, occurring in four and three patients, respectively. There was no difference in the EAIR for CV-related deaths between filgotinib 200 mg and 100 mg in the overall RA cohort or in subgroups by age (online supplemental figure S5). Two MACE-related deaths occurred in patients with UC: one patient had a fatal MI and cerebrovascular accident (ischaemic stroke) and one patient had left ventricular heart failure; both patients were receiving filgotinib 200 mg.

Malignancies and NMSC

EAIRs (95% CI)/100 PYE of malignancies (excluding NMSC) and NMSC were low (0.0 (0.0, 1.2) to 1.8 (0.2, 6.7)) across filgotinib-treated patients with RA or UC in the parent studies and integrated analyses (figures 1 and 2). In subgroup analyses by age, the EAIRs (95% CI)/100 PYE of malignancies were higher in patients with RA aged ≥65 years than in younger patients: 2.0 (1.3, 2.9) and 0.5 (0.3, 0.7), respectively, for filgotinib 200 mg (figure 1C). For patients with UC, the corresponding EAIRs (95%

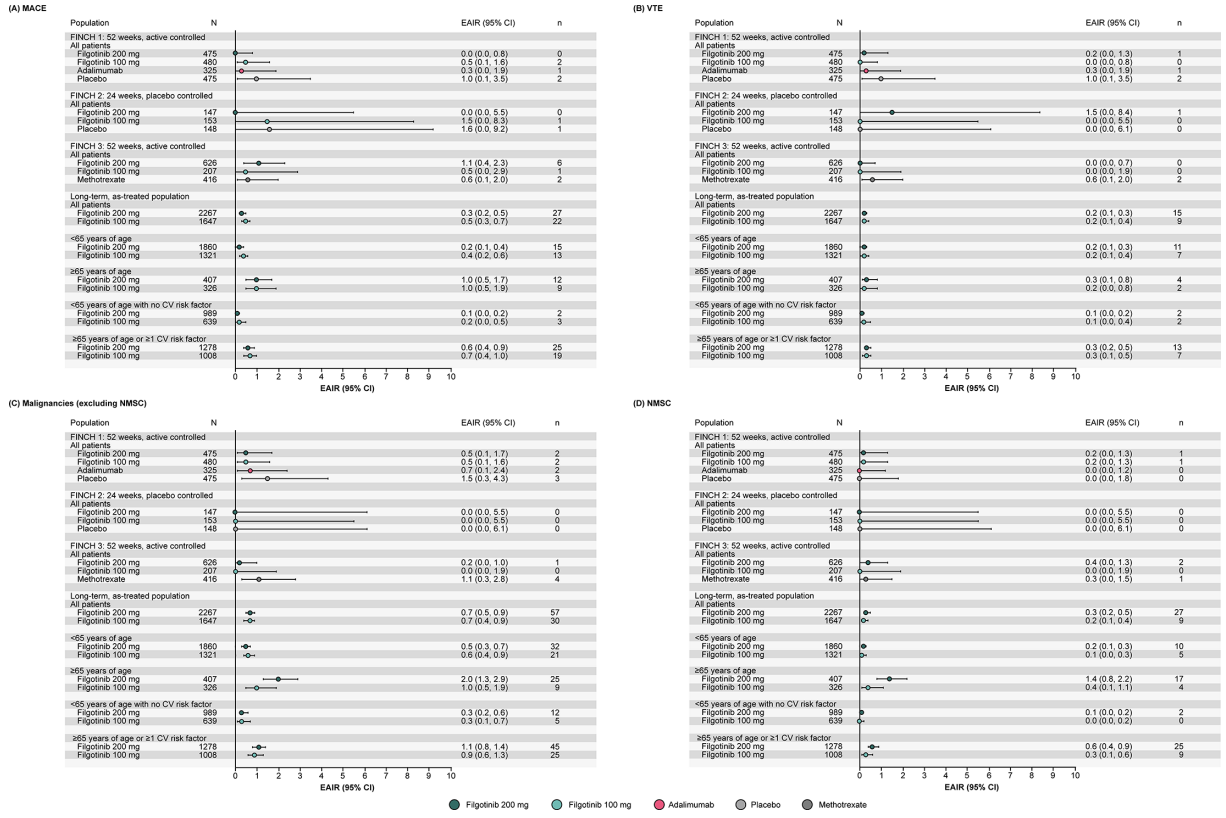

Figure 1 EAIRs of MACE (A), VTE (B), malignancies (excluding NMSC) (C) and NMSC (D) in patients with RA. CV, cardiovascular; EAIR, exposure-adjusted incidence rate; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; RA, rheumatoid arthritis; VTE, venous thromboembolism.

CI)/100 PYE for malignancies were 2.3 (0.6, 5.8) and 0.4 (0.2, 0.7) (figure 2C). The pattern was similar for NMSC, with numerically lower EAIRs observed in patients aged <65 years than in older patients for both RA and UC (figures 1D, 2D).

Malignancy rates in patients with RA aged ≥65 years were numerically higher with filgotinib 200 mg compared with filgotinib 100 mg, but with overlapping 95% CIs (figure 1). In younger patients, malignancy rates were similar between filgotinib doses in both RA and UC, except for the rate of malignancy (excluding NMSC) in patients with UC, which was higher with filgotinib 100 mg.

Time to event analyses showed that occurrence of malignancy and NMSC events was generally even over time and did not increase with longer exposure to treatment (figures 3–6).

In patients with RA, the EAIR for malignancies and NMSC was numerically higher in those aged ≥50 years with a CV risk factor compared with those aged <50 years or with no CV risk factors (online supplemental figure S1). In patients with UC, the difference in EAIR between these patient groups for both malignancies and NMSC was small with overlapping CIs, although numerically higher in those aged ≥50 years with a CV risk factor (online supplemental figure S2).

No pattern was seen in the types of malignancies recorded in patients with RA or in patients with UC, and incidence remained low during long exposure to filgotinib (online supplemental figure S3 and S4). In patients with RA, there were 11 malignancy-related deaths (online supplemental table S3): two patients had the same malignancy by preferred term (non-Hodgkin lymphoma) and the other nine patients each had a different type of malignancy. There were no malignancy-related deaths in patients with UC.

Risk factors for AEs of interest

Although no formal statistical analysis was performed, in the populations of patients with RA or UC who had MACE, there was a higher proportion of male patients, patients ≥65 years of age and those who had a history of hypertension or dyslipidaemia, compared with patients who did not have MACE, irrespective of filgotinib dose (online supplemental table S5 and S6). In the FINCH studies, a higher proportion of patients with RA receiving filgotinib 200 mg who had MACE were current smokers at baseline. In contrast, the proportion of current smokers was higher in patients who did not have MACE in the filgotinib 100 mg group (online supplemental table S5). Mean body mass index (BMI) was higher in patients with UC who had MACE compared with patients who did not have MACE (online supplemental table S6). Patients with RA who developed MACE were also more likely to be receiving concurrent oral glucocorticoids at baseline.

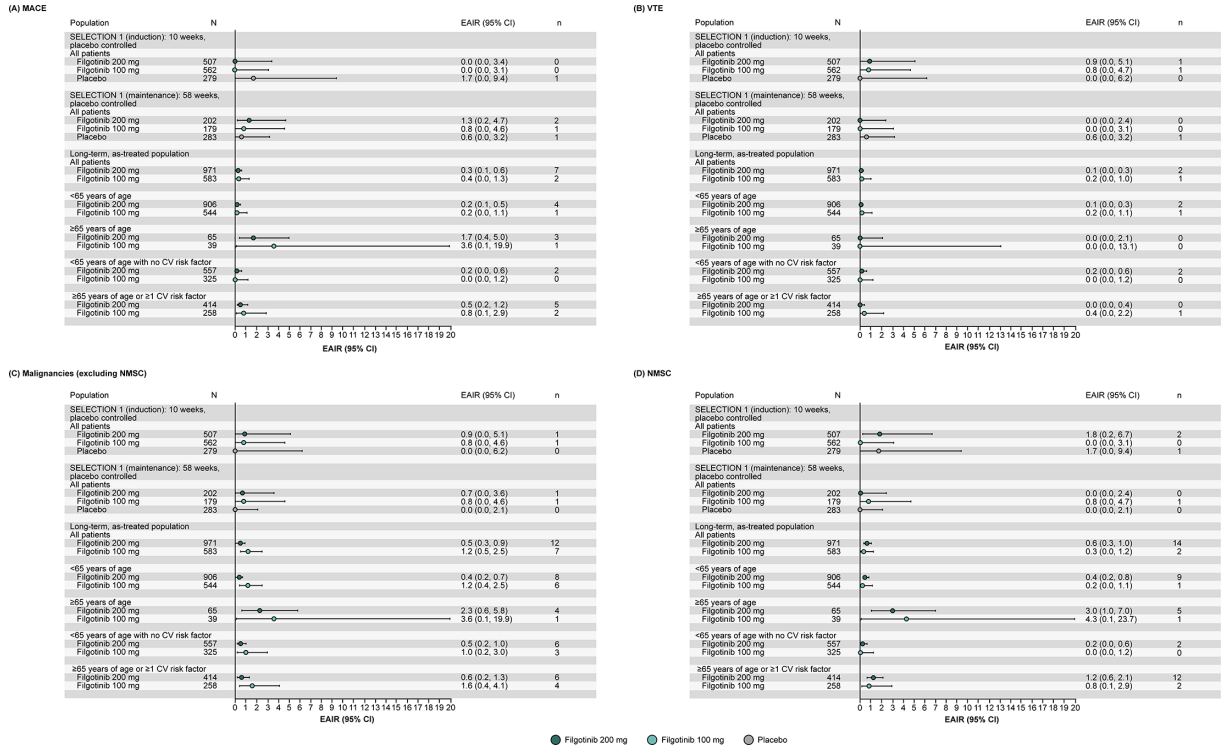

Figure 2 EAIRs of MACE (A), VTE (B), malignancies (excluding NMSC) (C) and NMSC (D) in patients with UC (SELECTION placebo-controlled and long-term analysis sets). Data for long-term 'SELECTION 1', 'all patients', '<65 years of age' and '≥65 years of age' have been reported previously[6] but are included here for context. CV, cardiovascular; EAIR, exposure-adjusted incidence rate; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; UC, ulcerative colitis; VTE, venous thromboembolism.

Patients with RA who developed VTE events were older, with a longer disease duration and higher BMI (filgotinib 200 mg group only), and were more likely to be receiving concurrent conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or methotrexate but less likely to be receiving concurrent oral glucocorticoids. For patients with UC, there were only two VTE events reported in the filgotinib 200 mg group and one in the filgotinib 100 mg group.

In the FINCH studies, a higher proportion of patients with RA receiving filgotinib 200 mg who developed MACE were current smokers at baseline. Smoking status did not appear to be a risk factor for MACE in patients receiving filgotinib 100 mg or for VTE in patients receiving filgotinib 100 mg or 200 mg. For both MACE and VTE, there were too few events among current smokers at baseline in patients with UC to interpret.

Patients with RA or UC who had malignancy (excluding NMSC) events were more likely to be ≥65 years of age or to have a history of hypertension, irrespective of filgotinib dose. Patients with RA who developed malignancy were also more likely to be male, and patients with UC were more likely to have a higher mean faecal calprotectin level or a history of diabetes mellitus, although small event numbers limit interpretation. Similar characteristics were also seen for patients with RA who developed NMSC events, who also had lower creatinine clearance, were less likely to be receiving concurrent oral glucocorticoids and were also more likely to have diabetes mellitus or dyslipidaemia at baseline. Patients with UC who developed NMSC were more likely to be ≥65 years of age or have a history of hypertension or dyslipidaemia at baseline.

In the FINCH studies, a higher proportion of patients with RA receiving filgotinib 200 mg who developed malignancy were current smokers at baseline. In contrast, the proportion of current smokers was higher in patients who did not develop malignancy in the filgotinib 100 mg group. Only three cases of NMSC in patients with RA were reported, and there were no events of malignancy or NMSC among current smokers at baseline in patients with UC.

DISCUSSION

After the ORAL Surveillance trial, long-term safety of the different JAK inhibitors is a key area that needs to be explored. This paper combines long-term safety data from all phase II and phase III studies of filgotinib in both RA and UC. In the current analysis, the incidence of MACE and VTE was low in patients with RA or UC treated with filgotinib. The highest EAIR for MACE or VTE in the overall long-term, as-treated population, unselected by age or risk factors, was 0.5 (0.3, 0.7)/100 PYE for MACE in patients with RA receiving filgotinib 100 mg/day. This incidence rate is similar to the overall

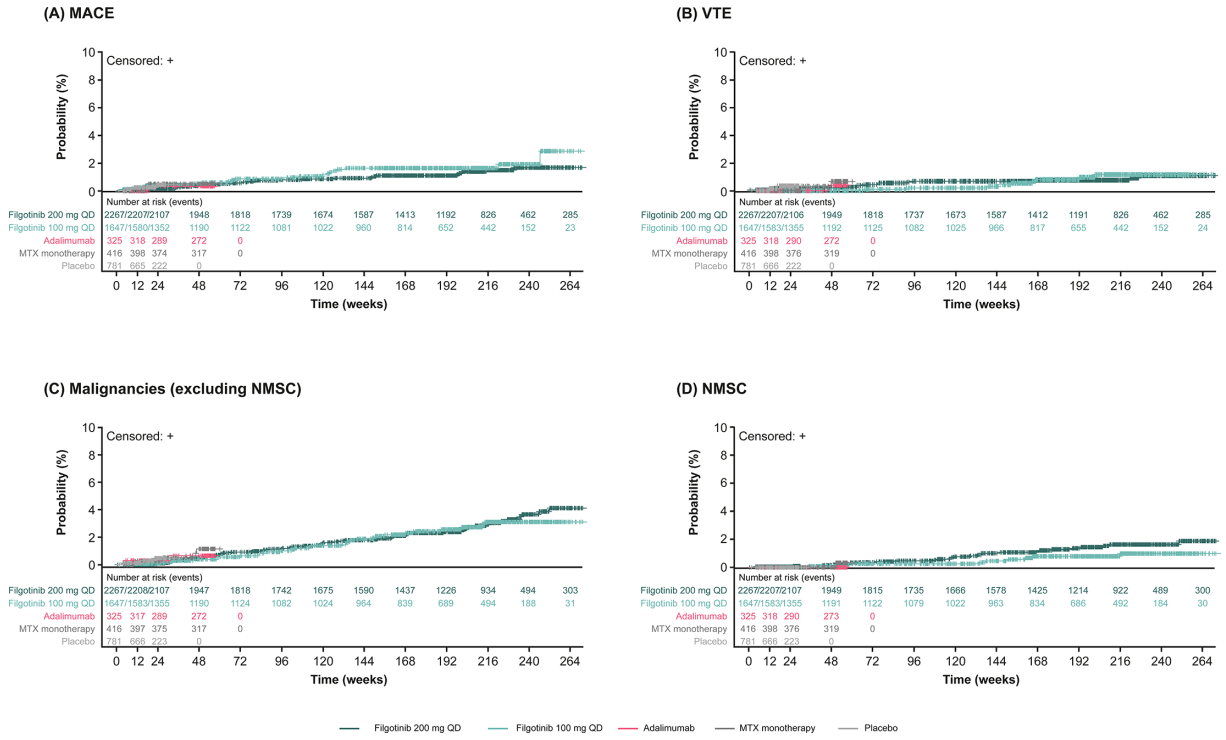

Figure 3 Time to first event for MACE (A), VTE (B), malignancies (excluding NMSC) (C) and NMSC (D) in patients with RA (long-term, as-treated population). MACE only include positively adjudicated events. For MACE subcategories 'stroke' and 'myocardial infarction', both fatal and non-fatal events are considered. VTE only includes positively adjudicated events. For VTE, subcategories 'pulmonary embolism', 'deep vein thrombosis' and 'other' are considered. As-treated population includes patients who received ≥1 dose of any study drug in the individual study. A patient may contribute to more than one treatment group summary if the patient received more than one treatment of interest. The time to event was calculated as (onset date of first event–first dose date+1). MACE, major adverse cardiovascular events; MTX, methotrexate; NMSC, non-melanoma skin cancer; QD, once daily; RA, rheumatoid arthritis; VTE, venous thromboembolism.

incidence rate of MACE reported in a large observational study (0.73 (0.61, 0.85)/100 PY) in patients with RA receiving JAK inhibitors, TNF inhibitors, other biologic disease-modifying antirheumatic drugs (bDMARDs) or csDMARDs.[16] However, higher rates of MACE have been reported; for example, a large case-control study from Taiwan reported a MACE incidence rate of 1.5 (1.4, 1.5)/100 PY in patients with newly diagnosed RA, increasing to 2.6 (2.6, 2.7)/100 PY in patients aged ≥65 years.[17] The probability of MACE in our study was modestly increased in patients with RA or UC aged ≥65 years, but there was no apparent dose relationship. The prevalence of MACE and VTE was comparable between patients with RA aged <65 years and with UC aged <65 years, irrespective of filgotinib dose, suggesting that the risk of these events is driven by a combination of an underlying inflammatory disease state and age, with little evidence of a filgotinib treatment effect. Consistent with the overall MACE rates, CV-related deaths occurred more frequently in older patients, but filgotinib dose did not affect CV-related mortality in either of the age subgroups studied here. The ability to assess patterns of VTE events was limited in this study by their infrequency, particularly in the cohort of patients with UC. However, the probability of VTE in patients with RA appeared to be similar between patients aged ≥65 years and <65 years, and no effect of filgotinib dose was observed in subgroups by age or by age and CV risk factors. In contrast, the ORAL Surveillance study demonstrated higher rates of VTE and PE at a higher dose level of tofacitinib, although in an older population selected for increased CV risk.

Patients with RA and UC have a greater risk of malignancies compared with the general population. Malignancy risk is estimated to be approximately 10% higher in patients with RA,[18] particularly due to increased incidence of lymphoma, lung cancer and melanoma compared with the general population.[18 19] Similarly, patients with UC have an estimated 5%–15% increased risk of malignancy compared with the general population, including both intestinal and extra-intestinal cancers.[20–22] A Danish cohort study of incident UC cases estimated the rate of all cancers (including NMSC) as 1.20/100 PY in patients with UC compared with 1.1/100 PY in the general population.[23] In the present study, the EAIR for all malignancies (excluding NMSC) was only 0.5 (0.3, 0.9)/100 PYE in patients with UC who received filgotinib 200 mg and 1.2 (0.5, 2.5) with filgotinib 100 mg. As in the general population, age is a key driver of the risk of developing malignancies among patients with RA and UC.[24–26] Moreover, uncontrolled or greater disease activity is associated with an increased risk of malignancies for patients with RA (lymphoma only) and UC.[27–29] The total incidences of

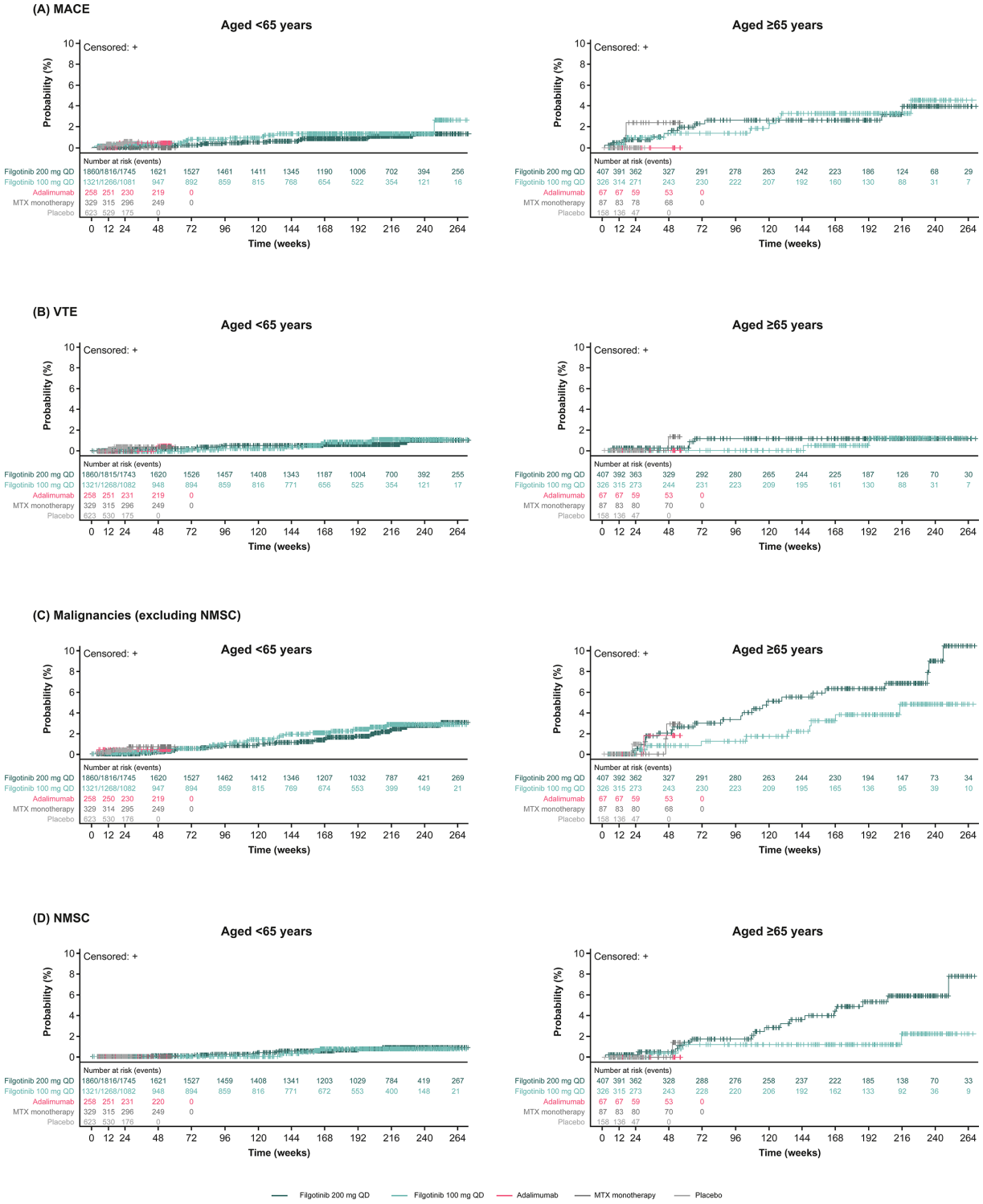

Figure 4 Time to first event for MACE (A), VTE (B), malignancies (excluding NMSC) (C) and NMSC (D) by age <65 years and ≥65 years in patients with RA. MACE only include positively adjudicated events. For MACE subcategories 'stroke' and 'myocardial infarction', both fatal and non-fatal events are considered. VTE only includes positively adjudicated events. For VTE, subcategories 'pulmonary embolism', 'deep vein thrombosis' and 'other' are considered. As-treated population includes patients who received ≥1 dose of any study drug in the individual study. A patient may contribute to more than one treatment group summary if the patient received more than one treatment of interest. The time to event was calculated as (onset date of first event–first dose date+1). MACE, major adverse cardiovascular events; MTX, methotrexate; NMSC, non-melanoma skin cancer; QD, once daily; RA, rheumatoid arthritis; VTE, venous thromboembolism.

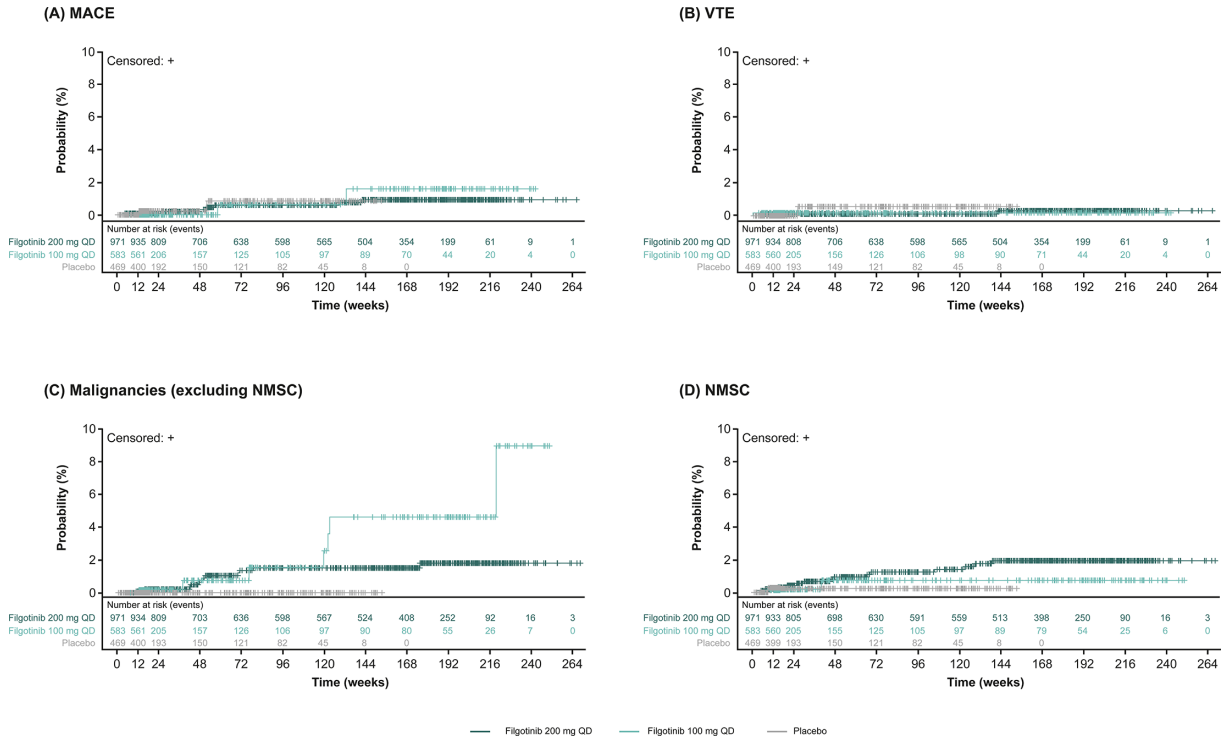

Figure 5 Time to first event for MACE (A), VTE (B), malignancies (excluding NMSC) (C) and NMSC (D) in patients with UC (long-term, as-treated population). MACE only include positively adjudicated events. For MACE subcategories 'stroke' and 'myocardial infarction', both fatal and non-fatal events are considered. VTE only includes positively adjudicated events. For VTE, subcategories 'pulmonary embolism', 'deep vein thrombosis' and 'other' are considered. As-treated population includes patients who received ≥1 dose of any study drug in the individual study. A patient may contribute to more than one treatment group summary if the patient received more than one treatment of interest. The time to event was calculated as (onset date of first event–first dose date+1). MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; QD, once daily; UC, ulcerative colitis; VTE, venous thromboembolism.

malignancies and NMSC were slightly higher in patients aged ≥65 years compared with younger patients, but rates of individual malignancy types remained low when considered in isolation. Patients with RA aged ≥65 years had a numerically higher rate of malignancies and NMSC when treated with filgotinib 200 mg compared with filgotinib 100 mg. This difference, with overlapping CIs, might be due to increased risk, but could also reflect a defect in tumour immunosurveillance, as indicated by in vitro studies of reduced natural killer cell function with tofacitinib.[30] This may be particularly important to consider in older patients treated with the high dose. Some differences in patient demographics were observed between the RA and UC cohorts. Patients with RA were on average older (53 years) than those with UC (43 years), and the proportion of female patients was much higher in the RA (80%) than in the UC (~40%) cohort. These differences were expected based on the known increased prevalence of RA in women and peak incidence by age for both conditions in the general population. Age-associated and sex-associated differences in risk factors may have influenced the types and frequencies of AEs; however, comparison between disease cohorts was not an objective of the analysis.

CV medical history at baseline was associated with AEs of interest in patients with RA for both CV events and malignancies. As expected, traditional risk factors associated with endothelial dysfunction such as hypertension and dyslipidaemia occurred more frequently in patients with RA who had MACE or VTE and in patients with UC experiencing MACE. It has been proposed that only a proportion of the increased CV risk in patients with RA can be attributed to these traditional CV risk factors and that the chronic inflammatory state, sedentary lifestyle and even treatment side effects may confer additional CV risk.[31 32] BMI was not included in the risk stratification here; however, another recent post hoc analysis of the FINCH and DARWIN studies in RA by BMI at baseline showed that filgotinib efficacy was not affected by BMI, but the rates of serious TEAEs, VTEs and MACE were numerically higher in patients with a BMI ≥30 kg/m^2 than in patients with a BMI of 25 to <30 or <25 kg/m^2, although the absolute numbers of patients with VTE events or MACE were low overall.[33]

In our analysis, patients with RA who had MACE were more likely to be receiving concurrent oral glucocorticoids and have had prior exposure to bDMARDs. Similarly, concurrent csDMARDs, specifically methotrexate, and prior bDMARD use were also associated with VTE incidence. In addition to the duration of RA and disease activity at baseline, high background treatment and use of prior treatments may indicate severe disease and higher

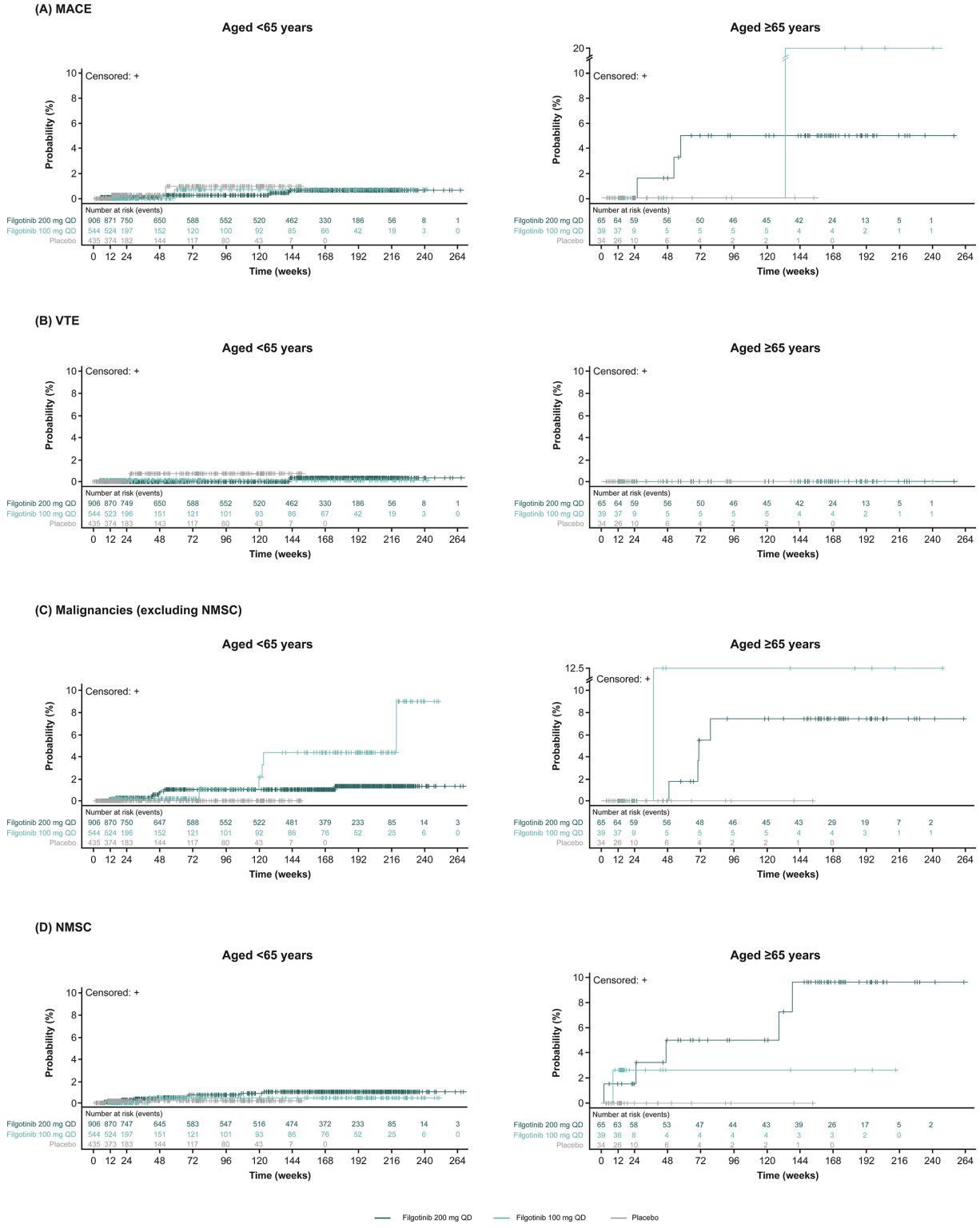

Figure 6 Time to first event for MACE (A), VTE (B), malignancies (excluding NMSC) (C) and NMSC (D) by age <65 years and ≥65 years in patients with UC. MACE only include positively adjudicated events. For MACE subcategories 'stroke' and 'myocardial infarction', both fatal and non-fatal events are considered. VTE only includes positively adjudicated events. For VTE, subcategories 'pulmonary embolism', 'deep vein thrombosis' and 'other' are considered. As-treated population includes patients who received ≥1 dose of any study drug in the individual study. A patient may contribute to more than one treatment group summary if the patient received more than one treatment of interest. The time to event was calculated as (onset date of first event– first dose date+1). MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer; QD, once daily; UC, ulcerative colitis; VTE, venous thromboembolism.

inflammatory burden associated with more frequent AEs of interest in this study. The observed higher incidence of malignancy in patients with CV medical history may reflect presence of shared mechanisms of CV disease and cancer, including inflammation, oxidative stress and microbial dysbiosis.[34]

A key strength of this study is the duration of exposure to filgotinib, with patients with RA studied for a median of 3.8 years and patients with UC for a median of 2.8 years, and a maximum of 8.3 and 7.8 years, respectively. Although a large study, the power to assess these relatively rare events, particularly VTE, would be improved with a further increased sample size. Also, as the number of patients in the ≥65 years age group was relatively low, especially for UC, this resulted in lower precision of point estimates and CIs in this subgroup. Absence of a placebo arm in the LTE studies is a limitation for interpretation of the extent of filgotinib treatment effects on event rates. The impact of smoking as a risk factor for AEs of interest could not be fully assessed; none of the studies collected data on smoking duration or pack-years of tobacco exposure, and data on smoking status were not collected in the DARWIN studies. In addition, information on patients with a medical history of atherosclerotic CV disease, an important subgroup of patients who may be particularly vulnerable to adverse CV events, was not collected at baseline; however, it is expected that these data will have been captured under the broader category of CV disease medical history. A history of malignancy (with some exceptions) within the past 5 years was an exclusion criterion in both the RA and UC studies; therefore, malignancy risk in the study population may have been lower than in the general population. Similarly, history of malignancy, MACE or VTE was only collected as part of the general medical history profile, and family CV history was not collected in the DARWIN studies in RA, or in the UC studies in this analysis; therefore, the risk factor profile of the study population may have been incomplete. Skin was not routinely assessed prior to starting filgotinib; therefore, the underlying risk of NMSC was unknown. Furthermore, the effects of concurrent medications, including glucocorticoids and csDMARDs, on AEs could not be excluded, as background therapy was reported only at the start of the parent studies and could be altered during the studies based on investigators' clinical judgement.

CONCLUSIONS

The data reported here add to the overall proven safety profile of filgotinib in clinical trials—although with a higher degree of granularity—showing a low overall incidence of MACE, VTE and malignancies in patients with RA or UC. No consistent effects of filgotinib dose on CV events were observed in this analysis. However, mirroring age-related increases in risk factors in the general population, age ≥65 years was associated with numeric increases in MACE and malignancies. In patients with RA ≥65 years of age, incidence rates for malignancy and NMSC were numerically higher with filgotinib 200 mg compared with 100 mg, with overlapping CIs. It is recommended that patients with RA ≥65 years of age, or those at increased risk of VTE, MACE and malignancy, are treated with filgotinib 100 mg. In patients with UC who have underlying risk factors, the recommended dose of filgotinib is 200 mg once daily for induction treatment and 100 mg once daily for maintenance treatment. Escalation from the recommended dose of 100 mg once daily to 200 mg once daily can be considered in the case of insufficient RA disease control or UC disease flare.[12] However, given the relationship between MACE, VTE, malignancies and underlying disease activity, it is important to balance benefits and risks in individual patients and tailor the dose accordingly. Studies are continuing, which will assess safety and tolerability of long-term treatment with filgotinib in RA and UC.[35 36] In addition, real-world studies will be valuable to investigate long-term safety in populations not limited by clinical trial selection criteria.[35–39]

Author affiliations
[1]Department of Rheumatology, Université Paris-Saclay, AP-HP-Hôpital Bicêtre, Paris, France
[2]Department of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, University of Cologne, Cologne, Germany
[3]Department of Oncology, UZ Brussel, Brussels, Belgium
[4]Department of Rheumatology, University of Debrecen, Debrecen, Hungary
[5]Division of Rheumatology, University of California Los Angeles, Los Angeles, California, USA
[6]Department of Internal Medicine, University Hospital Schleswig Holstein, Kiel, Germany
[7]Section of Rheumatology, Division of Infection and Immunity, Cardiff University School of Medicine, Cardiff University, Cardiff, UK
[8]Department of Gastroenterology, INFINY Institute, FHU-CURE, INSERM NGERE, Nancy University Hospital, Vandoeuvre-Les-Nancy, France
[9]Groupe Hospitalier privé Ambroise Paré – Hartmann, Neuilly sur Seine, France
[10]Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal, Quebec, Canada
[11]Department of Internal Medicine II, Rheumatology/Clinical Immunology, University Hospital Würzburg, Würzburg, Germany
[12]The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan
[13]Departments of Internal Medicine and Biochemistry and CARIM School for Cardiovascular Diseases, Maastricht University Medical Center, Maastricht, The Netherlands
[14]Department of Development and Regeneration, Skeletal Biology and Engineering Research Center, KU Leuven, Leuven, Belgium
[15]Department of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands
[16]Galapagos NV, Mechelen, Belgium
[17]Galapagos GmbH, Basel, Switzerland
[18]Galapagos Biotech, Cambridge, UK
[19]Galapagos Biopharma GmbH, Munich, Germany
[20]Department of Internal Medicine IV, Jena University Hospital, Jena, Germany

Presented at
Selected data from this analysis were presented as posters at the American College of Rheumatology Convergence 2022 (Mariette X, Aspeslagh S, Moriggl R, et al. Malignancy events in the filgotinib rheumatoid arthritis and ulcerative colitis clinical development programs. Arthritis Rheumatol 2022;74[Suppl 9]:0277), the 18th Congress of the European Crohn's and Colitis Organisation 2023 (van der Woude CJ, Schreiber S, Peyrin-Biroulet L, et al. P520 Thromboembolic and major adverse cardiovascular events among patients in the filgotinib clinical trial programme. J Crohn's Colitis 2023;17[Suppl 1]:i646–9) and the EULAR European Congress of Rheumatology 2023 (Mariette X, Borchmann S, Aspeslagh S, et

al. POS0824 Cardiovascular (CV) and malignancy events in the filgotinib (FIL) rheumatoid arthritis (RA) clinical development programme up to 8.3 years. Ann Rheum Dis 2023;82[Suppl 1]:707–8).

Acknowledgements We thank the physicians and patients who participated in these studies. We thank Jaime Calvo-Alen, Angela de Haas, Francesco De Leonardis, Pieter-Jan Stiers, Richard Moriggl, Vijay Rajendran, Katrien Van Beneden and Nadia Verbruggen for support with data interpretation and review of the associated presentations. Medical writing support was provided by Stephanie Rippon, MBio, and Matthew deSchoolmeester, PhD (Aspire Scientific, Bollington, UK), and funded by Alfasigma S.p.A. Publication coordination was provided by Jo-Ann Elicia West, MSc (SARL KerWestPen Consulting, Cartigny l'Épinay, France), and funded by Alfasigma S.p.A.

Contributors XM, SB, SA, ZS, CC-S, SS, EHSC, LP-B, MS, YT, HtC, RW, CJvdW and AS contributed to data acquisition. All authors contributed to conception and analysis design. EVEO and MF contributed to data analysis and validation. All authors contributed to data interpretation, reviewed and critically revised the manuscript, approved the final version and agreed to be accountable for the accuracy and integrity of the work. The study sponsors, Gilead Sciences and Galapagos, were responsible for the study design, data collection and analysis and consulted in the decision to publish and the preparation of the manuscript. XM is responsible for the overall content as the guarantor.

Funding The FINCH 1–3 and SELECTION studies were funded by Gilead Sciences, Inc. (Foster City, CA, USA). The FINCH 4, DARWIN 1–3 and SELECTIONLTE studies were funded by Galapagos NV (Mechelen, Belgium). This analysis was funded by Galapagos NV.

Competing interests XM has received consultancy fees from BMS, Galapagos, GSK, Janssen, Novartis and Pfizer. SB has received consultancy fees from Galapagos; and is a founder of, and shareholder in, Liqomics. SA has received consultancy fees (paid to institution) from MSD; honoraria (paid to institution) from BMS, Ipsen, Roche; has participated on a data safety monitoring board or advisory board for Astellas; has a leadership role in BITOX network (www.BSMO.bbe/BITOX) and received grants or contracts (paid to BITOX) from AstraZeneca, BMS, Ipsen, MSD, Roche and Sanofi. ZS has received consultancy fees and honoraria from AbbVie, Eli Lilly, Gedeon Richter, Novartis, Pfizer and Sobi; and meeting attendance support from AbbVie, Pfizer and Sobi. CC-S has received consultancy fees from AbbVie, BMS, Boehringer Ingelheim, Octapharma, Pfizer, Recludix and Sana Biotechnology; and grant/research support from AbbVie, Alexion, BMS, CSL Behring, Janssen, Octapharma, Pfizer and Priovant. SS has received honoraria and meeting attendance support from AbbVie, Amgen, Arena, Biogen, BMS, Celgene, Celltrion, Eli Lilly, Falk, Ferring, Fresenius Kabi, Galapagos, Gilead, Hikma, IMAB, Janssen, MSD, Pfizer, Protagonist, Proventin Bio and Sandoz/Hexal; and has participated in an advisory board for Takeda. EHSC has received speaker fees from AbbVie, Amgen, BMS, Chugai, Eli Lilly, Fresenius Kabi, Galapagos, Gilead, Novartis, Pfizer, Regeneron, Roche and Sanofi-Aventis; consultancy fees from AbbVie, Amgen, Biogen Therapeutics, Chugai, Eli Lilly, Fresenius Kabi, Galapagos, Gilead, GSK, Janssen, Novartis, R-Pharm, Roche, Sanofi-Genzyme, SynAct Pharma and UCB and grant/research support from Bio-Cancer, Biogen, Novartis, Pfizer, Roche and Sanofi. LP-B has received grants from Celltrion, Fresenius Kabi, Medac, MSD and Takeda; consultancy fees from AbbVie, Abivax, Adacyte, Alimentiv, Amgen, Applied Molecular Transport, Arena, Banook, Biogen, BMS, Celltrion, Connect Biopharm, Cytoki Pharma, Eli Lilly, Enthera, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead, Gossamer Bio, GSK, IAC Image Analysis, Index Pharmaceuticals, Inotrem, Janssen, Medac, Mopac, Morphic, MSD, Nordic Pharma, Novartis, Oncodesign Precision Medicine, ONO Pharma, OSE Immunotherapeuthics, Pandion Therapeuthics, Par' Immune, Pfizer, Prometheus, Protagonist, Roche, Samsung, Sandoz, Sanofi, Satisfay, Takeda, Telavant, Theravance, Thermo Fischer, Tigenix, Tillots, Vectivbio, Ventyx, Viatris and Ysopia; honoraria from AbbVie, Alfasigma S.p.A., Amgen, Arena, Biogen, Celltrion, Eli Lilly, Ferring, Galapagos, Genentech, Gilead, Janssen, Kern Pharma, Medac, MSD, Nordic Pharma, Pfizer, Sandoz, Takeda, Tillots and Viatris; meeting attendance support from AbbVie, Alfasigma S.p.A., Amgen, Celltrion, Connect Biopharm, Eli Lilly, Ferring, Galapagos, Genentech, Gilead, Gossamer Bio, Janssen, Medac, Morphic, MSD, Pfizer, Sandoz, Takeda, Thermo Fischer and Tillots and participated in data safety monitoring or advisory boards for AbbVie, Alfasigma S.p.A., Amgen, Arena, Biogen, Celltrion, Eli Lilly, Ferring, Galapagos, Genentech, Gilead, Janssen, Kern Pharma, Medac, MSD, Nordic Pharma, Pfizer, Sandoz, Takeda, Tillots and Viatris. MS has received grants from Chugai and Novartis; honoraria from AbbVie, Alfasigma S.p.A., AstraZeneca, Boehringer Ingelheim, BMS, Chugai, EUSA-Pharma, Galapagos, Gilead, Janssen-Cilag, Mylan, Novartis, Onkowissen.de and Roche; meeting attendance support from Boehringer Ingelheim, Celgene, Chugai, Galapagos, Medac, Mylan, Roche and UCB and participated in data safety monitoring or advisory boards for AbbVie, Alfasigma S.p.A., Amgen, AstraZeneca, Boehringer Ingelheim, Chugai, Eli Lilly, EUSA-Pharma, Galapagos, Gilead, Hexal/Sandoz, Janssen-Cilag, Novartis, Onkowissen.de, Roche and UCB. YT has received honoraria from AbbVie, AstraZeneca, BMS, Boehringer Ingelheim, Chugai, Eisai, Eli Lilly, Gilead, GSK, Pfizer and Taisho and research grants from Chugai, Eisai, Mitsubishi Tanabe and Taisho. HtC received consultancy fees from Alveron, AstraZeneca, Galapagos, Novostia and Viatris and research funding from Bayer and Synapse. All revenues are deposited at the CARIM Institute for Research. He is a shareholder in Coagulation Profile. RW has received consultancy fees and honoraria from Celltrion and Galapagos. CJvdW has received research grants from Benelux, Falk, Ferring, Janssen and Pfizer; consultancy fees from Celltrion and Galapagos and speaker fees from AbbVie and UCB. EVEO received consultancy fees from Alfasigma S.p.A., Galapagos and Janssen; and is a shareholder in UCB. MF is an employee of, and holds stock options in, Galapagos. TM is a former employee of Galapagos. PVH has received consultancy fees from AOP Health, Aspen and Galapagos. CW is a former employee of Alfasigma S.p.A. and Galapagos and holds stock options in Galapagos. CR is a former employee of Galapagos and a current employee of Alfasigma S.p.A. AS has received consultancy fees from AbbVie, BMS and Johnson & Johnson; honoraria from AbbVie, BMS, Galapagos, Johnson & Johnson and Takeda and payments to institute from AbbVie, BMS, Galapagos and Takeda.

Patient consent for publication Not applicable.

Ethics approval The protocols were approved by the institutional review board or ethics committee at each site. The trials were conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation guidelines. As there were numerous sites across multiple countries, it is not practical to include the name and reference number for each site. The primary manuscripts reporting results from the studies included in this manuscript have been previously published and contain more details on the ethics committees/institutional review boards. These manuscripts are cited in the current manuscript. Participants provided informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Anonymised individual patient data will be shared on request (beginning 6 months and ending 5 years following manuscript publication) for research purposes, dependent on 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-glpg.com/us/en/data-transparency.html and https://www.gileadclinicaltrials.com/en/transparency-policy#, respectively.

ORCID iDs
Xavier Mariette http://orcid.org/0000-0002-4244-5417
Christina Charles-Schoeman http://orcid.org/0000-0002-1768-7019
Ernest HS Choy http://orcid.org/0000-0003-4459-8609
Yoshiya Tanaka http://orcid.org/0000-0002-0807-7139
René Westhovens http://orcid.org/0000-0002-3432-3073

REFERENCES

1 Ytterberg SR, Bhatt DL, Mikuls TR, *et al*. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022;386:316–26.
2 Salinas CA, Louder A, Polinski J, *et al*. Evaluation of VTE, MACE, and serious infections among patients with RA treated with baricitinib compared to TNFi: a multi-database study of patients in routine care using disease registries and claims database. *Rheumatol Ther* 2023;10:201–23.
3 Taylor PC, Takeuchi T, Burmester GR, *et al*. Safety of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. *Ann Rheum Dis* 2022;81:335–43.

4 Sandborn WJ, Lawendy N, Danese S, *et al*. Safety and efficacy of tofacitinib for treatment of ulcerative colitis: final analysis of OCTAVE Open, an open-label, long-term extension study with up to 7.0 years of treatment. *Aliment Pharmacol Ther* 2022;55:464–78.
5 Panaccione R, Danese S, Zhou W, *et al*. Efficacy and safety of upadacitinib for 16-week extended induction and 52-week maintenance therapy in patients with moderately to severely active ulcerative colitis. *Aliment Pharmacol Ther* 2024;59:393–408.
6 Schreiber S, Rogler G, Watanabe M, *et al*. Integrated safety analysis of filgotinib for ulcerative colitis: results from SELECTION and SELECTIONLTE. *Aliment Pharmacol Ther* 2023;58:874–87.
7 Núñez P, Quera R, Yarur AJ. Safety of Janus kinase inhibitors in inflammatory bowel diseases. *Drugs* 2023;83:299–314.
8 Agrawal M, Kim ES, Colombel JF. JAK inhibitors safety in ulcerative colitis: practical implications. *J Crohns Colitis* 2020;14:S755–60.
9 Honap S, Agorogianni A, Colwill MJ, *et al*. JAK inhibitors for inflammatory bowel disease: recent advances. *Frontline Gastroenterol* 2024;15:59–69.
10 Qapaja T, Alchirazi KA, Naser A, *et al*. S839 Biologic and small molecule therapies are not associated with increased major adverse cardiovascular events (MACE) in IBD: a propensity matched cohort study. *Am J Gastroenterol* 2023;118:S620.
11 Qapaja T, Alchirazi KA, Qapaja M, *et al*. 720 Oral small molecules are not associted with increased cancer rates in IBD patients. *Gastroenterology* 2024;166:S–173.
12 European Medicines Agency. Jyseleca: EPAR - product information. 2023. Available: https://www.ema.europa.eu/en/documents/product-information/jyseleca-epar-product-information_en.pdf [Accessed 8 Feb 2024].
13 Tanaka Y, Kavanaugh A, Wicklund J, *et al*. Filgotinib, a novel JAK1-preferential inhibitor for the treatment of rheumatoid arthritis: an overview from clinical trials. *Mod Rheumatol* 2022;32:1–11.
14 Burmester GR, Gottenberg JE, Caporali R, *et al*. Integrated safety analysis of filgotinib in patients with moderate-to-severe rheumatoid arthritis over a treatment duration of up to 8.3 years. *Ann Rheum Dis* 2024;83:1110–7.
15 Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). *Am J Epidemiol* 1990;131:373–5.
16 Meissner Y, Schäfer M, Albrecht K, *et al*. Risk of major adverse cardiovascular events in patients with rheumatoid arthritis treated with conventional synthetic, biologic and targeted synthetic disease-modifying antirheumatic drugs: observational data from the German RABBIT register. *RMD Open* 2023;9:e003489.
17 Chen YJ, Liu SC, Lai KL, *et al*. Factors associated with risk of major adverse cardiovascular events in patients with rheumatoid arthritis: a nationwide, population-based, case-control study. *Ther Adv Musculoskelet Dis* 2021;13:1759720X211030809.
18 Simon TA, Thompson A, Gandhi KK, *et al*. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. *Arthritis Res Ther* 2015;17:212.
19 Mercer LK, Askling J, Raaschou P, *et al*. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. *Ann Rheum Dis* 2017;76:386–91.
20 Taborelli M, Sozzi M, Del Zotto S, *et al*. Risk of intestinal and extra-intestinal cancers in patients with inflammatory bowel diseases: a population-based cohort study in northeastern Italy. *PLOS One* 2020;15:e0235142.
21 Lo B, Zhao M, Vind I, *et al*. The risk of extraintestinal cancer in inflammatory bowel disease: a systematic review and meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol* 2021;19:1117–38.e19.
22 Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;48:526–35.
23 Burisch J, Lophaven S, Munkholm P, *et al*. Surgery, cancer and mortality among patients with ulcerative colitis diagnosed 1962-1987 and followed until 2017 in a Danish population-based inception cohort. *Aliment Pharmacol Ther* 2022;55:339–49.
24 Carmona L, Abasolo L, Descalzo MA, *et al*. Cancer in patients with rheumatic diseases exposed to TNF antagonists. *Semin Arthritis Rheum* 2011;41:71–80.
25 Khan N, Vallarino C, Lissoos T, *et al*. Risk of malignancy in a nationwide cohort of elderly inflammatory bowel disease patients. *Drugs Aging* 2017;34:859–68.
26 Scharl S, Barthel C, Rossel JB, *et al*. Malignancies in inflammatory bowel disease: frequency, incidence and risk factors-results from the Swiss IBD cohort study. *Am J Gastroenterol* 2019;114:116–26.
27 Baecklund E, Ekbom A, Sparén P, *et al*. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. *BMJ* 1998;317:180–1.
28 Lakatos PL, Lakatos L. Risk for colorectal cancer in ulcerative colitis: changes, causes and management strategies. *World J Gastroenterol* 2008;14:3937–47.
29 Poullenot F, Laharie D. Management of inflammatory bowel disease in patients with current or past malignancy. *Cancers* 2023;15:1083.
30 Nocturne G, Pascaud J, Ly B, *et al*. JAK inhibitors alter NK cell functions and may impair immunosurveillance against lymphomagenesis. *Cell Mol Immunol* 2020;17:552–3.
31 Zegkos T, Kitas G, Dimitroulas T. Cardiovascular risk in rheumatoid arthritis: assessment, management and next steps. *Ther Adv Musculoskelet Dis* 2016;8:86–101.
32 So H, Lam TO, Meng H, *et al*. Time and dose-dependent effect of systemic glucocorticoids on major adverse cardiovascular event in patients with rheumatoid arthritis: a population-based study. *Ann Rheum Dis* 2023;82:1387–93.
33 Balsa A, Wassenberg S, Tanaka Y, *et al*. Effect of filgotinib on body mass index (BMI) and effect of baseline bmi on the efficacy and safety of filgotinib in rheumatoid arthritis. *Rheumatol Ther* 2023;10:1555–74.
34 Wilcox NS, Amit U, Reibel JB, *et al*. Cardiovascular disease and cancer: shared risk factors and mechanisms. *Nat Rev Cardiol* 2024;21:617–31.
35 US National Library of Medicine. Long term extension study to assess the safety and efficacy of filgotinib in adults with rheumatoid arthritis (FINCH 4). 2017. Available: https://clinicaltrials.gov/study/NCT03025308 [Accessed 27 Feb 2024].
36 US National Library of Medicine. Filgotinib in long-term extension study of adults with ulcerative colitis (SELECTIONLTE). 2016. Available: https://classic.clinicaltrials.gov/ct2/show/NCT02914535 [Accessed 27 Feb 2024].
37 US National Library of Medicine. Long-term follow-up study of GLPG0634 in active rheumatoid arthritis patients (DARWIN 3). 2014. Available: https://classic.clinicaltrials.gov/ct2/show/NCT02065700 [Accessed 27 Feb 2024].
38 US National Library of Medicine. Prospective observational study of filgotinib in subjects with rheumatoid arthritis (FILOSOPHY). 2021. Available: https://classic.clinicaltrials.gov/ct2/show/NCT04871919 [Accessed 27 Feb 2024].
39 US National Library of Medicine. Prospective observational study of effectiveness and safety of filgotinib in participants with ulcerative colitis (UC) (GALOCEAN). 2023. Available: https://clinicaltrials.gov/study/NCT05817942 [Accessed 27 Feb 2024].
40 Winthrop KL, Tanaka Y, Takeuchi T, *et al*. Integrated safety analysis of filgotinib in patients with moderately to severely active rheumatoid arthritis receiving treatment over a median of 1.6 years. *Ann Rheum Dis* 2022;81:184–92.