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Integrated Safety Analysis of Filgotinib Treatment for Rheumatoid Arthritis from 7 Clinical Trials

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Introduction

- Filgotinib, an oral, potent, selective Janus kinase (JAK) 1 inhibitor, provided statistically significant and clinically meaningful improvement in rheumatoid arthritis (RA) signs and symptoms, physical function, radiographic progression and quality of life in a comprehensive clinical programme[1–6]
- In this analysis, we assessed the long-term safety of filgotinib using integrated data from three Phase 3 (FINCH 1–3), two Phase 2 (DARWIN 1, 2) and two long-term extension (LTE) (FINCH 4, DARWIN 3) trials in patients with early to biologic-refractory RA

Methods

- Treatment-emergent adverse events (TEAEs) from the filgotinib clinical programme were integrated and presented for patients receiving filgotinib 200 mg or 100 mg once daily (QD) as well as patients receiving placebo, active comparator methotrexate (MTX) and active comparator adalimumab across all 7 studies (**Table 1**)
- All data for filgotinib 200 mg QD and 100 mg QD were included for DARWIN 1 and 2 and for FINCH 1, 2 and 3
- For long-term extension studies, data through May 2018 were included for DARWIN 3 and through March 2019 for FINCH 4

Table 1. Key features of filgotinib clinical trials

	Required background medication			Control		Rescue treatment		Protocol-defined rerandomisation to FIL
	None	MTX	csDMARD(s)	PBO	Active comparator	FIL	Standard of care[a]	
Phase 3 studies								
FINCH 1		X		24 weeks	52 weeks (ADA)		X	PBO subjects at Week 24
FINCH 2			X	24 weeks			X	
FINCH 3	X				52 weeks (MTX)		X	
FINCH 4	X[b]							At study entry[c]
Phase 2 studies								
DARWIN 1		X		24 weeks		X		Non-responders at Week 12
DARWIN 2	X			12 weeks		X		PBO subjects and non-responders at Week 12
DARWIN 3	X[d]							At study entry[e]

[a] Patients who met protocol-defined inadequate response criteria discontinued study drug and received standard of care; [b] Patients continued to receive parent-study protocol-approved background medication. Patients from FINCH 3 stopped MTX or MTX placebo to match upon entry into FINCH 4; [c] All patients who received FIL at the time of completion of parent study continued to receive blinded FIL dose (100 mg QD or 200 mg QD). Patients who received ADA, PBO or MTX monotherapy, or who completed FINCH 2 on standard of care, were rerandomised at LTE entry to receive either FIL 100 mg or FIL 200 mg. Patients from FINCH 1 and FINCH 3 who completed parent study on standard of care were not eligible; [d] Patients were permitted to restart background MTX therapy if deemed necessary by the investigator; [e] Patients who received FIL 200 mg QD or FIL 100 mg BID at the time of completion of parent study continued to receive the same FIL dose in the LTE study. Patients who received FIL 25 mg BID, FIL 50 mg QD, FIL 50 mg BID or FIL 100 mg at the time of completion of parent study were assigned either FIL 200 mg QD or FIL 100 mg BID at LTE entry. Patients who received PBO at the time of completion of parent study were rerandomised at LTE entry to receive either FIL 200 mg QD or FIL 100 mg BID. In the US, dosing in male subjects was restricted to FIL 100 mg QD
ADA: adalimumab; BID: twice daily; csDMARD: conventional synthetic disease-modifying antirheumatic drug; FIL: filgotinib; LTE: long-term extension; MTX: methotrexate; PBO: placebo; QD: once daily

Analysis data sets

- Patients who received ≥1 dose of study drug were included in the analysis
- Data are presented for 4 different analysis sets
  - **Placebo-controlled analysis set** includes data from patients randomised to filgotinib or placebo for up to 12 weeks in 4 studies (DARWIN 1, DARWIN 2, FINCH 1, FINCH 2) and allows comparisons of filgotinib with placebo. Data were included from a patient's original assigned study treatment, but data were censored after Week 12
  - **Adalimumab-controlled analysis set** includes data from patients randomised to filgotinib or adalimumab for up to 52 weeks in FINCH 1 and allows comparisons of filgotinib with adalimumab. Data through Week 52 were included from a patient's original assigned study treatment
  - **MTX-controlled analysis set** includes data from patients randomised to filgotinib or MTX for up to 52 weeks in FINCH 3 and allows comparison of filgotinib with MTX. Data through Week 52 were included from a patient's original assigned study treatment
  - **Long term safety data set (as-treated)** includes data from patients receiving filgotinib 100 or 200 mg QD in all 7 studies and includes data from patients after rerandomisation or assignment to a different treatment group. Therefore, a single patient may have contributed data to >1 treatment group if they switched to filgotinib from adalimumab, MTX, standard of care or a different dose of filgotinib

Statistical methods

- Key safety events were presented by number and proportion of patients (raw incidence rate; n [%]) for the placebo-controlled period up to Week 12, given the short exposure time
- For the active-controlled and long-term (as-treated) safety analysis sets, exposure-adjusted incidence rates (EAIRs) of key safety events are presented
- EAIRs per 100 patient-years (PY) and 95% confidence intervals were estimated for adverse events (AEs) of interest using a Poisson regression model including study and treatment with an offset of natural log of exposure time. Patient-years exposure (PYE) was calculated as the total exposure time in years
- Incidence rate was the proportion of patients in a particular analysis set with a specific event of interest
- Major adverse cardiovascular events (MACE) and venous thromboembolisms (VTE) were centrally adjudicated by an independent committee
  - MACE included cardiovascular death, myocardial infarction and stroke
  - VTE included deep vein thrombosis and pulmonary embolism
  - Only positively adjudicated events were included

Results

- Across the 7 trials, 2,227 and 1,600 patients with RA received >1 dose of filgotinib 200 or 100 mg, respectively, for 3,079.2 and 1,465.3 total PYE (**Table 2**)

Table 2. Total exposure to study treatments by safety analysis set

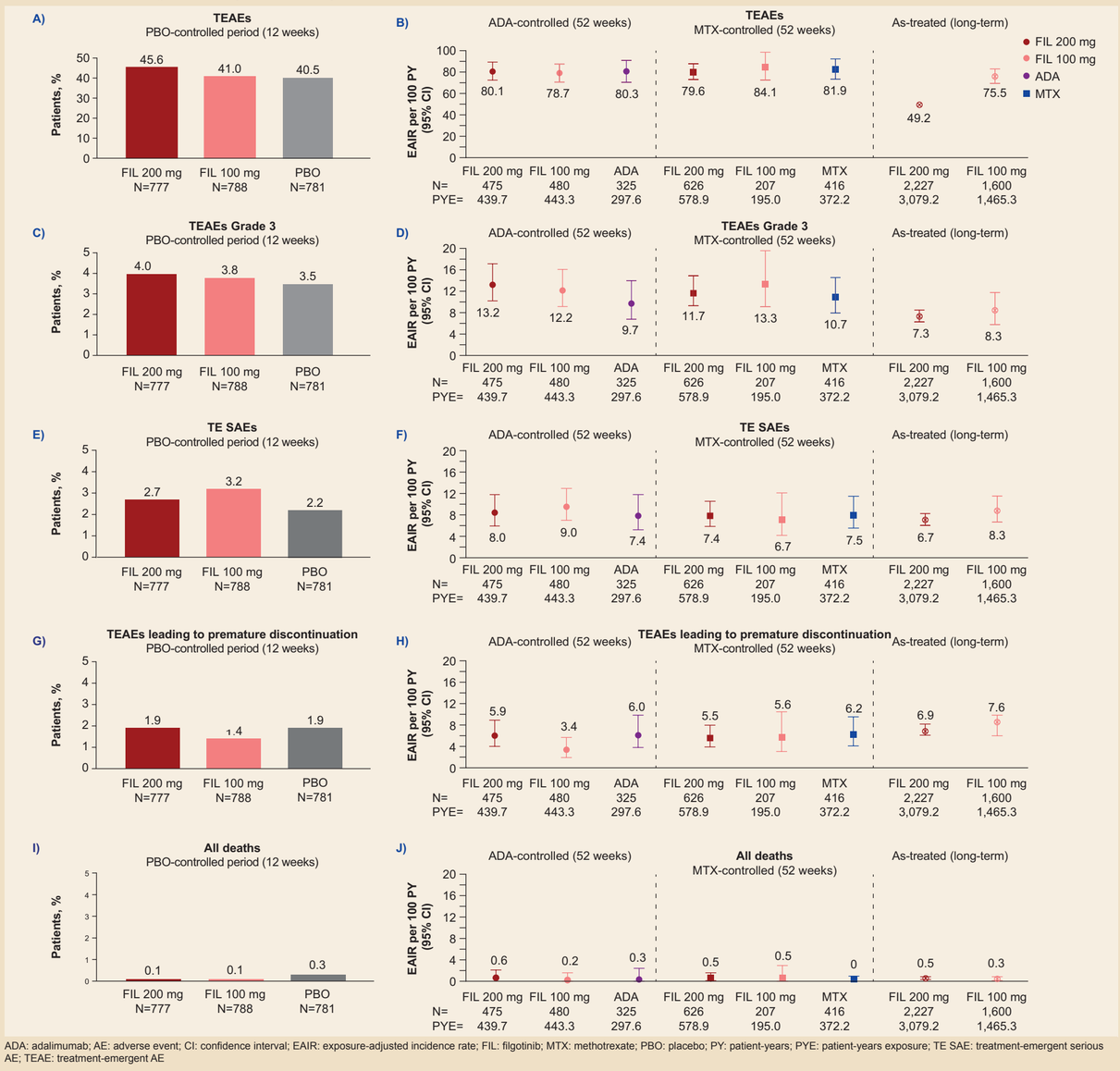
	PBO-controlled (12 weeks)		ADA-controlled (52 weeks)		MTX-controlled (52 weeks)		As-treated	
	N	PYE	N	PYE	N	PYE	N	PYE
FIL 200 mg QD	777	179.8	475	439.7	626	578.9	2,227	3,079.2
FIL 100 mg QD	788	181.6	480	443.4	207	195.0	1,600	1,465.3
PBO	781	178.4						
ADA			325	297.6				
MTX					461	372.2		

ADA: adalimumab; FIL: filgotinib; MTX: methotrexate; PBO: placebo; PYE: patient-years exposure; QD: once daily

Overall summary TEAEs

- Overall summary of TEAEs for all safety analysis sets are shown in **Figure 1**
- In the placebo-controlled safety analysis set, the overall raw incidence rates of TEAEs, TEAEs Grade ≥3, treatment-emergent serious AEs (TE SAEs), TEAEs leading to study drug discontinuation, and all deaths were similar for up to 12 weeks between filgotinib 200 mg, 100 mg and placebo
- In the active-controlled safety analysis sets, EAIRs of TEAEs, TEAEs Grade ≥3, TE SAEs, TEAEs leading to discontinuation, and all deaths were similar for up to 52 weeks between filgotinib 200 mg, 100 mg and the active comparators adalimumab and MTX
- In the long-term (as-treated) safety analysis set, no increase of EAIRs for any key safety event was observed for either filgotinib treatment group

Figure 1. Overall summary TEAE incidence rates in the PBO-controlled analysis set (A, C, E, G, I) and EAIRs in the active-controlled and as-treated analysis sets (B, D, F, H, J)

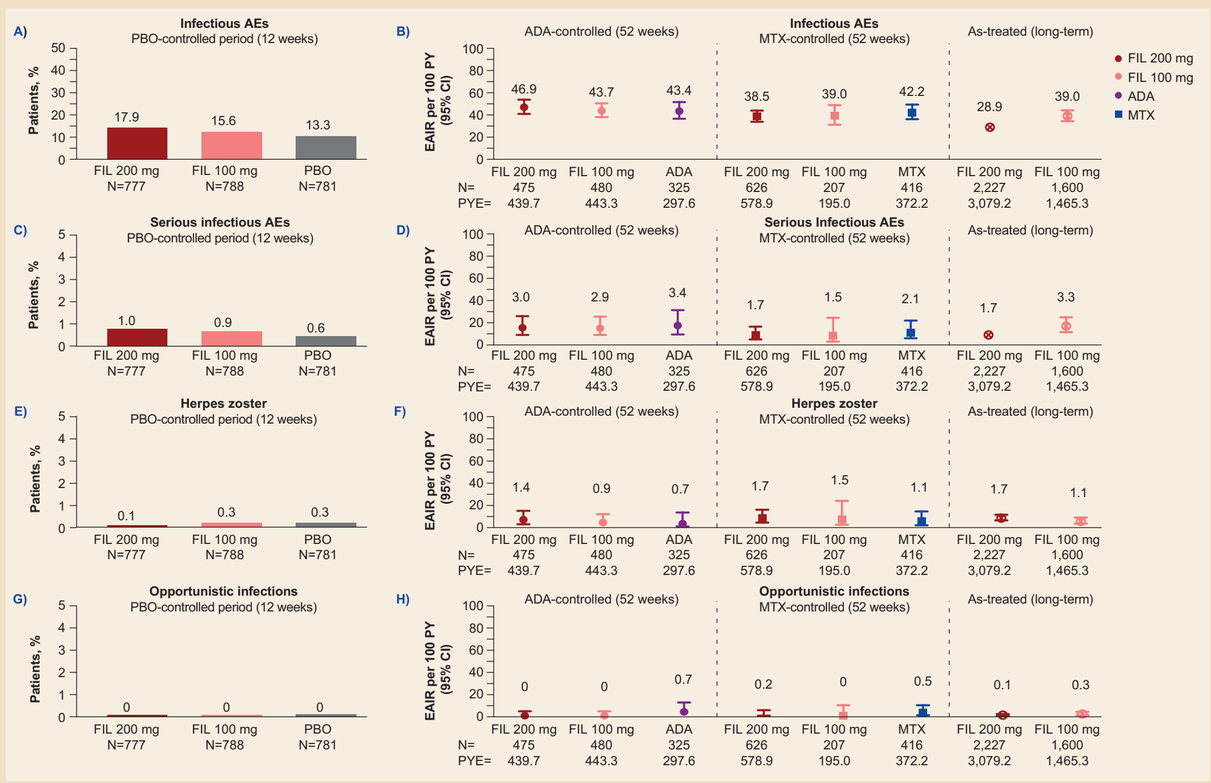


ADA: adalimumab; AE: adverse event; CI: confidence interval; EAIR: exposure-adjusted incidence rate; FIL: filgotinib; MTX: methotrexate; PBO: placebo; PY: patient-years; PYE: patient-years exposure; TE SAE: treatment-emergent serious AE; TEAE: treatment-emergent AE

Infections

- Rates of all infections, serious infections, opportunistic infections and herpes zoster infections are shown in **Figure 2**
- Raw incidence rates of serious infections numerically increased for patients receiving filgotinib treatment vs. placebo in the placebo-controlled safety analysis set up to 12 weeks
- In the active-controlled and long-term (as-treated) safety analysis sets, EAIRs for both filgotinib 200 and 100 mg groups were similar to the active comparators adalimumab and MTX
- In the long-term (as-treated) analysis set, EAIR of serious infections was ≤3.3/100 PYE for either filgotinib dose without apparent dose-dependent effects

Figure 2. Infections, serious infections, herpes zoster and opportunistic infections incidence rates in the PBO-controlled analysis set (A, C, E, G) and EAIRs in the active-controlled and as-treated sets (B, D, F, H)



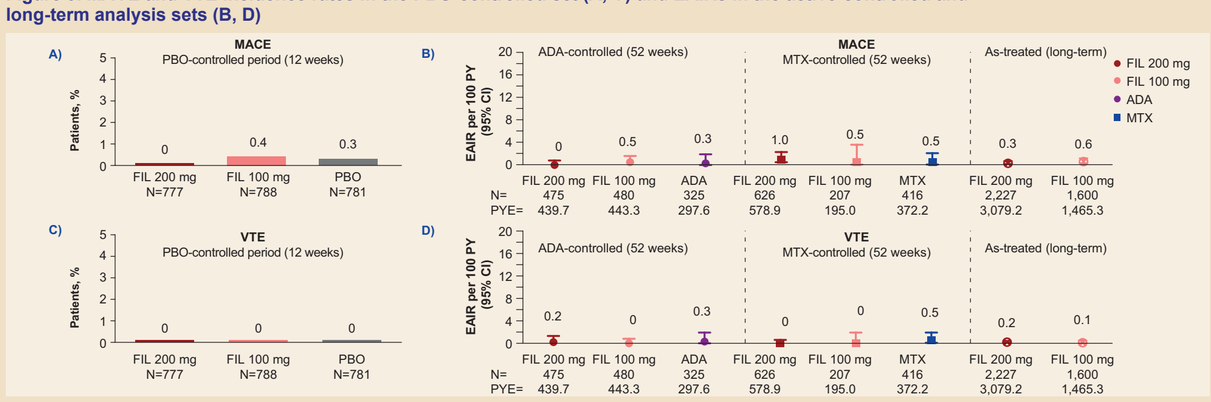
ADA: adalimumab; CI: confidence interval; EAIR: exposure-adjusted incidence rate; FIL: filgotinib; MTX: methotrexate; PBO: placebo; PY: patient-years; PYE: patient-years exposure

- In the placebo-controlled safety analysis set, the raw incidence rates of herpes zoster with filgotinib were similar for both 200 mg and 100 mg doses and placebo up to Week 12
- EAIRs were also comparable to adalimumab and MTX in the active-controlled safety analysis sets, with filgotinib 200 mg slightly numerically higher
- In the long-term (as-treated) analysis set, there was a numeric increase in EAIR for herpes zoster with filgotinib 200 mg compared with the 100 mg dose
- Most cases of herpes zoster were mild to moderate and not serious
- EAIRs for opportunistic infections (including tuberculosis [TB]) were similar across treatment groups in the active-controlled and long-term (as-treated) safety analysis sets
- There were no opportunistic infections during the placebo-controlled period or patients receiving filgotinib in the adalimumab-controlled period
- In the long-term (as-treated) safety analysis set, which includes the longest duration of exposure to filgotinib, 11 patients overall experienced opportunistic infections, including TB
  - Filgotinib 200 mg, 3 patients; filgotinib 100 mg, 4 patients; adalimumab, 2 patients; MTX, 2 patients
- TB occurred in 4 patients (adalimumab, 1 patient; filgotinib 100 mg, 3 patients)

MACE and VTE

- Rates of centrally adjudicated MACE and VTE are shown in **Figure 3**
- In the placebo-controlled safety analysis set, raw incidence rates of MACE with filgotinib for both 200 mg and 100 mg doses were similar to placebo
- In the active-controlled analysis sets, EAIR of MACE were similar with filgotinib, adalimumab and MTX, and remained stable in the long-term (as-treated) analysis set for both doses of filgotinib
- In the placebo-controlled safety analysis set, no VTE events were observed
- In the active-controlled analysis sets, EAIR for VTE were similar across filgotinib, adalimumab and MTX, and remained stable in the long-term (as-treated) analysis set for both doses of filgotinib

Figure 3. MACE and VTE incidence rates in the PBO-controlled set (A, C) and EAIRs in the active-controlled and long-term analysis sets (B, D)

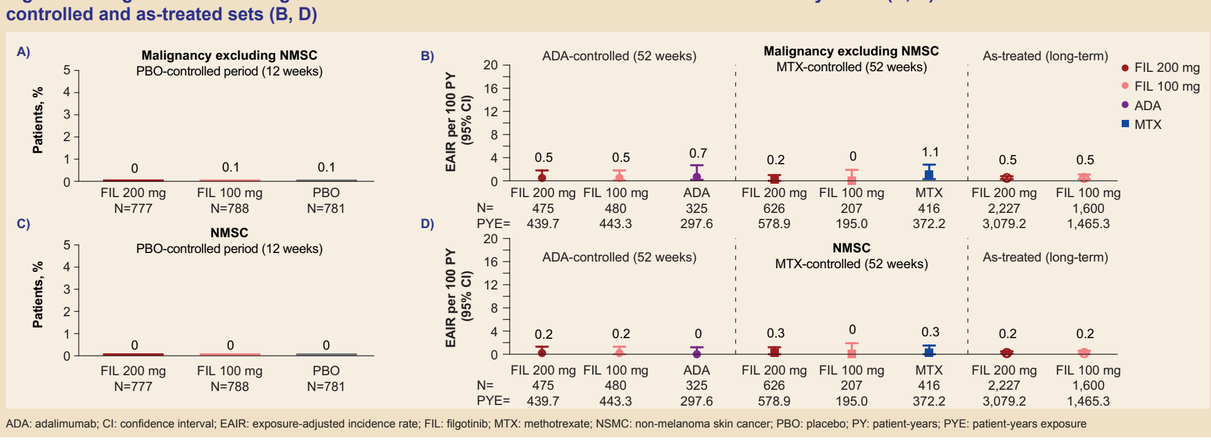


ADA: adalimumab; CI: confidence interval; EAIR: exposure-adjusted incidence rate; FIL: filgotinib; MACE: major adverse cardiovascular event; MTX: methotrexate; PBO: placebo; PY: patient-years; PYE: patient-years exposure; VTE, venous thromboembolism

Malignancies

- Rates of malignancies are shown in **Figure 4**
- Non-melanoma skin cancer (NMSC) and other malignancies occurred infrequently. During the placebo-controlled period, there were no NMSC and 2 non-NMSC malignancies (filgotinib 100 mg, cervix carcinoma; and placebo, malignant glioma)
- In the active-controlled analysis sets, EAIR for non-NMSC malignances and NMSC were comparable across patients treated with filgotinib and active comparators. No dose-dependent increase in EAIR was observed in the long-term (as-treated) data set

Figure 4. Malignancies excluding NMSC and NMSC incidence rates in the PBO-controlled analysis set (A, C) and EAIRs in the active-controlled and as-treated sets (B, D)



ADA: adalimumab; CI: confidence interval; EAIR: exposure-adjusted incidence rate; FIL: filgotinib; MTX: methotrexate; NSMC: non-melanoma skin cancer; PBO: placebo; PY: patient-years; PYE: patient-years exposure

Discussion

- In this integrated analysis, filgotinib was well tolerated, and no new safety concerns were identified in patients with RA
- Both doses of filgotinib had a favourable safety profile in the context of clinically meaningful improvement in RA
- With filgotinib, EAIR of serious infections and herpes zoster were generally similar to adalimumab and MTX
- MACE and VTE were infrequently reported and comparable between arms
- Safety results were consistent with selective JAK-1 inhibition

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Disclosures

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