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Efficacy of filgotinib in patients with rheumatoid arthritis with poor prognostic factors: Post hoc analysis of FINCH 3

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INTRODUCTION

- Patients with rheumatoid arthritis (RA) with poor prognostic factors are at higher risk for early accrual of joint damage and long-term disability without initiation of an effective therapy
- In FINCH 3 (NCT02886728), filgotinib—an oral, potent, highly selective Janus kinase (JAK)-1 inhibitor—demonstrated rapid and sustained efficacy for up to 52 weeks, including higher rates of low disease activity and remission, compared with methotrexate (MTX) treatment in MTX-naïve patients[1]
- This post hoc analysis examined filgotinib efficacy vs MTX in FINCH 3 patients with multiple poor prognostic factors at baseline: seropositivity for rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP), high-sensitivity C-reactive protein (hsCRP) ≥4 mg/L, high disease activity based on Disease Activity Score in 28 joints with CRP (DAS28[CRP]) >5.1, and presence of erosions on radiographs

METHODS

Study design and patients

- The global, phase 3, double-blind, active-controlled FINCH 3 study randomised MTX-naïve patients with moderately to severely active RA 2:1:1:2 to oral filgotinib 200 mg once daily plus MTX ≤20 mg weekly, filgotinib 100 mg plus MTX, filgotinib 200 mg plus MTX placebo (filgotinib 200 mg monotherapy), or filgotinib placebo plus MTX (MTX monotherapy) for up to 52 weeks

Efficacy assessments

- Proportions of patients achieving 20%/50%/70% improvement in American College of Rheumatology (ACR) criteria (ACR20/50/70)
- Health Assessment Questionnaire-Disability Index (HAQ-DI) change from baseline
- Proportions of patients achieving DAS28(CRP) <2.6, Clinical Disease Activity Index (CDAI) ≤2.8, Simplified Disease Activity Index (SDAI) ≤3.3, and Boolean remission
- van der Heijde modified total Sharp score (mTSS) change from baseline

Statistical analysis

- Baseline characteristics and AEs were summarised using descriptive statistics
- Binary endpoints were compared using logistic regression for the overall population and Fisher's exact test for subjects with 4 poor prognostic factors for comparisons between each dose of filgotinib vs MTX monotherapy; missing data were imputed as nonresponse. The 95% confidence interval (CI) of the response rate and the difference in response rates based on normal approximation were provided for each treatment group or between treatment groups
  - Proportions of subjects with no radiographic progression at week 52 were analysed using a generalised mixed effect model including data from Campaign A (through week 24) and Campaign B (through week 52). The odds ratio and 95% CI and P-value were reported
- Changes from baseline in continuous endpoints were compared using a mixed-effect model for repeated measures with treatment, visit, treatment by visit interaction, stratification factors, and baseline value included as fixed effects and patient as a random effect; missing data were not imputed. The stratification factors were not included in analyses of patients with poor prognostic factors
  - mTSS change from baseline at week 52 included data from Campaign A and Campaign B, and the model included campaign as an additional random effect
- Comparisons were not adjusted for multiplicity and nominal P-values are reported unless otherwise noted

RESULTS

Patients

- Of 1249 patients randomised and treated in FINCH 3, 510 had all 4 poor prognostic factors at baseline
- Baseline patient demographics and disease characteristics in patients with 4 poor prognostic factors were comparable to the overall population (**Table 1**)
  - 77% of patients were female, and mean age was 52 years
  - Disease duration was similar compared with the overall FINCH 3 population
  - Proportions of patients with prior DMARD experience and concurrent corticosteroid use were comparable to the overall population
- As expected, frequency of seropositivity for RF, anti-CCP, or both was higher in patients with 4 poor prognostic factors relative to the overall FINCH 3 population (**Table 1**)
- In general, mean baseline disease activity and severity measures were higher in patients with 4 poor prognostic factors relative to the overall population (**Table 1**)

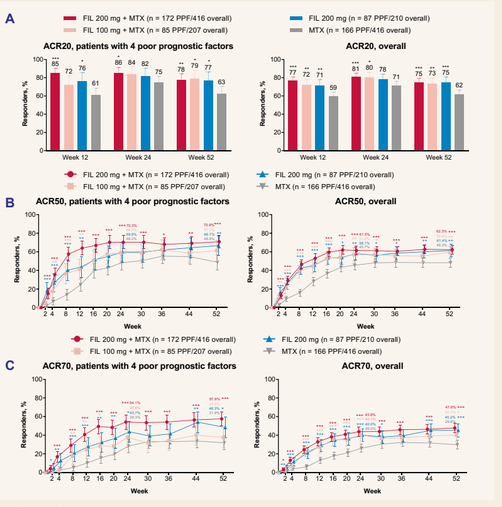
Table 1. Baseline characteristics

	Poor Prognostic Factors Subgroup					Overall
	FIL 200 mg + MTX n = 172	FIL 100 mg + MTX n = 85	FIL 200 mg n = 87	MTX n = 166	Total n = 510	Total N = 1249
Age, years	51 ± 12.9	53 ± 12.9	50 ± 12.8	53 ± 12.9	52 ± 12.9	53 ± 13.6
Female, n (%)	133 (77.3)	65 (76.5)	67 (77.0)	128 (77.1)	393 (77.1)	961 (76.9)
RA duration, years	1.8 ± 3.40	2.8 ± 5.50	2.4 ± 6.27	2.7 ± 6.16	2.4 ± 5.29	2.2 ± 4.97
Median, years	0.4	0.6	0.3	0.6	0.5	0.4
≤6 months, n (%)	89 (51.7)	41 (48.2)	50 (57.5)	78 (47.0)	258 (50.6)	686 (54.9)
DMARD naïve, n (%)	137 (79.7)	63 (74.1)	67 (77.0)	123 (74.1)	390 (76.5)	964 (77.2)
Prior non-MTX csDMARD use, n (%)	25 (14.5)	17 (20.0)	15 (17.2)	35 (21.1)	92 (18.0)	222 (17.8)
Concurrent oral steroid use, n (%)	61 (35.5)	45 (52.9)	45 (51.7)	78 (47.0)	229 (44.9)	494 (39.6)
Steroid dose, mg/day	6.9 ± 2.44	7.2 ± 2.59	6.5 ± 2.09	6.3 ± 2.31	6.7 ± 2.37	6.6 ± 2.43
RF-positive, n (%)	162 (94.2)	75 (88.2)	77 (88.5)	148 (89.2)	462 (90.6)	848 (67.9)
Anti-CCP positive, n (%)	162 (94.2)	76 (89.4)	76 (87.4)	157 (94.6)	471 (92.4)	855 (68.5)
RF and anti-CCP positive, n (%)	152 (88.4)	66 (77.6)	66 (75.9)	139 (83.7)	423 (82.9)	744 (59.6)
mTSS erosions >0, n (%)	172 (100)	85 (100)	87 (100)	166 (100)	510 (100)	1173 (93.9)
mTSS units[a]	13.2 ± 23.1	18.1 ± 35.9	24.2 ± 44.3	19.3 ± 37.2	17.9 ± 34.5	13.3 ± 26.7
DAS28(CRP)	6.4 ± 0.73	6.3 ± 0.72	6.2 ± 0.67	6.3 ± 0.72	6.3 ± 0.72	5.7 ± 0.99
CDAI	44.8 ± 12.0	45.1 ± 11.1	42.7 ± 11.9	44.2 ± 11.1	44.3 ± 11.5	39.8 ± 12.6
SDAI	47.9 ± 12.3	47.9 ± 11.8	45.0 ± 11.7	46.8 ± 11.8	47.1 ± 11.9	41.5 ± 13.4
HAQ-DI	1.73 ± 0.59	1.79 ± 0.63	1.72 ± 0.69	1.81 ± 0.55	1.76 ± 0.60	1.56 ± 0.63
hsCRP, mg/L	31.6 ± 31.3	28.0 ± 28.5	23.3 ± 24.6	26.3 ± 27.1	27.9 ± 28.5	17.5 ± 25.0
SJC66	20 ± 11.4	19 ± 10.8	19 ± 10.8	19 ± 10.8	19 ± 10.8	16.0 ± 9.6
TJC68	30 ± 14.3	29 ± 13.1	28 ± 13.6	28 ± 14.3	29 ± 14.0	26.0 ± 14.0
SGA (VAS)	75 ± 15.8	73 ± 16.7	72 ± 18.3	73 ± 15.9	73 ± 16.4	66.0 ± 20.8
PGA (VAS)	71 ± 15.8	74 ± 12.8	67 ± 15.0	70 ± 15.7	71 ± 15.3	67.0 ± 16.4
Pain (VAS)	73 ± 17.0	73 ± 19.0	72 ± 16.4	73 ± 17.0	73 ± 17.2	65 ± 21.3

Data shown as mean ± SD unless otherwise specified.
[a]Campaign A.
CCP, cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic DMARD; DAS28(CRP), Disease Activity Score in 28 joints with C-reactive protein; DMARD, disease-modifying antirheumatic drug; FIL, filgotinib; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C-reactive protein; mTSS, van der Heijde modified total Sharp score; MTX, methotrexate; PGA, Physician Global Assessment; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SDAI, Simplified Disease Activity Index; SGA, Subject Global Assessment; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale.

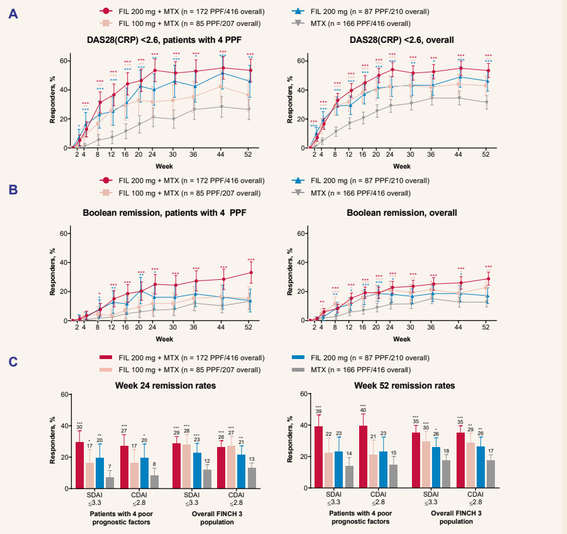
Clinical outcomes

Figure 1. A) ACR20, B) ACR50, and C) ACR70 response rates



Missing data were imputed as nonresponse.
Error bars represent the 95% confidence interval.
*Nominal P <0.05; **nominal P <0.01; ***nominal P <0.001 vs MTX monotherapy; not adjusted for multiplicity except for ACR20 in the overall population at week 24.
ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; FIL, filgotinib; MTX, methotrexate; PPF, patients with 4 poor prognostic factors.

Figure 2. Proportions of patients achieving A) DAS28(CRP) <2.6 and B) Boolean remission through week 52, and C) CDAI and SDAI remission at weeks 24 and 52



Missing data were imputed as nonresponse.
Error bars represent the 95% confidence interval.
*Nominal P <0.05; **nominal P <0.01; ***nominal P <0.001 vs MTX monotherapy; not adjusted for multiplicity except DAS28(CRP) <2.6 for filgotinib 200 or 100 mg plus MTX in overall population at week 24.
CDAI, Clinical Disease Activity Index; DAS28(CRP), Disease Activity Score in 28 joints with C-reactive protein; FIL, filgotinib; MTX, methotrexate; PPF, patients with 4 poor prognostic factors; SDAI, Simplified Disease Activity Index.

- Patients with 4 poor prognostic factors receiving filgotinib 200 mg with or without MTX had higher ACR20/50/70 response rates compared with patients receiving MTX monotherapy at weeks 12, 24, and 52; ACR20 response rate following filgotinib 100 mg plus MTX was numerically higher vs MTX monotherapy, reaching significance only at week 52 (**Figure 1**)
- Onset of action was earlier for all filgotinib treatment regimens vs MTX monotherapy in patients with 4 poor prognostic factors and the overall population (**Figure 1B–C**)
- ACR20/50/70 response rates were comparable in patients with 4 poor prognostic factors relative to the overall FINCH 3 population
- Compared with patients receiving MTX monotherapy, larger proportions of patients with 4 poor prognostic factors receiving filgotinib 200 mg with or without MTX achieved DAS28(CRP) <2.6, CDAI ≤2.8, SDAI ≤3.3, and Boolean remission at week 24 (**Figure 2**)
  - Remission rates were numerically higher following treatment with filgotinib 200 mg with or without MTX compared with filgotinib 100 mg plus MTX
- Efficacy was sustained or further improved following treatment with filgotinib 200 mg plus MTX vs MTX monotherapy through week 52 (**Figure 2**)

Physical function

Table 2. Change from baseline in HAQ-DI at weeks 24 and 52

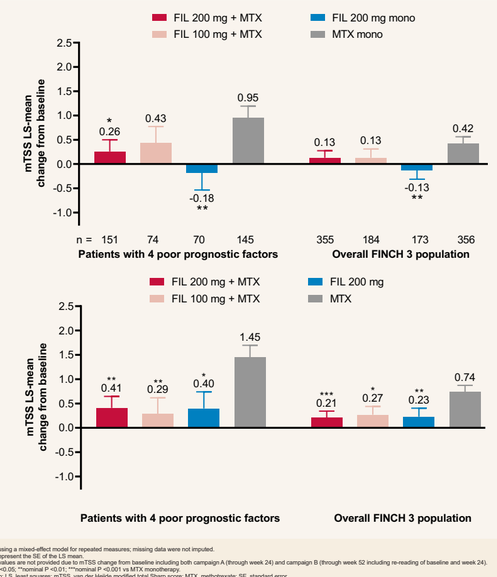
	FIL 200 mg + MTX		FIL 100 mg + MTX		FIL 200 mg		MTX	
	PPF	Overall	PPF	Overall	PPF	Overall	PPF	Overall
Week 24								
n	154	372	77	190	77	185	148	370
Δ from baseline, mean ± SD	−1.19 ± 0.73	−0.94 ± 0.72	−1.02 ± 0.69	−0.90 ± 0.68	−1.00 ± 0.63	−0.89 ± 0.63	−0.86 ± 0.63	−0.79 ± 0.63
LSM difference (95% CI)	−0.37 (−0.50 to −0.24)	−0.20 (−0.27 to −0.12)	−0.18 (−0.34 to −0.02)	−0.13 (−0.23 to −0.03)	−0.17 (−0.33 to −0.02)	−0.11 (−0.20 to −0.01)		
P	<0.001	<0.001	0.024	0.008	0.031	0.029		
Week 52								
n	139	332	71	169	72	171	117	307
Δ from baseline, mean ± SD	−1.26 ± 0.72	−1.00 ± 0.73	−1.07 ± 0.75	−0.97 ± 0.72	−1.09 ± 0.68	−0.95 ± 0.69	−0.99 ± 0.66	−0.88 ± 0.69
LSM difference (95% CI)	−0.33 (−0.47 to −0.19)	−0.17 (−0.25 to −0.08)	−0.11 (−0.28 to 0.06)	−0.10 (−0.20 to 0.01)	−0.17 (−0.34 to −0.00)	−0.11 (−0.22 to −0.01)		
P	<0.001	<0.001	0.20	0.077	0.044	0.039		

LSM difference represents treatment difference vs MTX monotherapy.
Calculated using a mixed-effect model for repeated measures; missing data were not imputed.
Comparisons were not adjusted for multiplicity and nominal P values are presented except for FIL 200 mg + MTX and FIL 100 mg + MTX vs MTX monotherapy in the overall population at week 24.
Δ, change; CI, confidence interval; FIL, filgotinib; HAQ-DI, Health Assessment Questionnaire-Disability Index; LSM, least-squares mean; MTX, methotrexate; PPF, patients with 4 poor prognostic factors; SD, standard deviation.

- Among patients with 4 poor prognostic factors, improvement in HAQ-DI from baseline was greater following treatment with all filgotinib regimens relative to MTX monotherapy at week 24 and following treatment with filgotinib 200 mg with or without MTX relative to MTX monotherapy at week 52 (**Table 2**)

Radiographic outcomes

Figure 3. mTSS change from baseline at A) week 24 and B) week 52



Calculated using a mixed-effect model for repeated measures; missing data were not imputed.
Error bars represent the SE of the LS mean.
Week 52 n values are not provided due to mTSS change from baseline including both campaign A (through week 24) and campaign B (through week 52 including re-reading of baseline and week 24).
*Nominal P <0.05; **nominal P <0.01; ***nominal P <0.001 vs MTX monotherapy.
FIL, filgotinib; LS, least squares; mTSS, van der Heijde modified total Sharp score; MTX, methotrexate; SE, standard error.

Table 3. Patients with no radiographic progression from baseline at week 24

	FIL 200 mg + MTX		FIL 100 mg + MTX		FIL 200 mg		MTX	
	PPF	Overall	PPF	Overall	PPF	Overall	PPF	Overall
n	151	355	74	184	70	173	145	356
ΔmTSS ≤0								
% (95% CI)	77.5 (70.5 to 84.5)	80.6 (76.3 to 84.8)	59.5 (47.6 to 71.3)	76.6 (70.2 to 83.0)	77.1 (66.6 to 87.7)	82.7 (76.7 to 88.6)	61.4 (53.1 to 69.6)	72.5 (67.7 to 77.3)
Difference vs MTX (95% CI)	16.1 (5.1 to 27.1)	8.1 (1.6 to 14.6)	−1.9 (−16.6 to 12.8)	4.2 (−3.9 to 12.2)	15.8 (2.1 to 29.5)	10.2 (2.5 to 17.9)		
P[a]	0.004	0.015	0.88	0.33	0.030	0.013		

Proportions of subjects with no radiographic progression at week 52 are presented in the text as odds ratios from a generalized linear model (multilevel) including mTSS obtained from both campaign A (through week 24) and campaign B (through week 52 including re-reading of baseline and week 24).
[a]Not adjusted for multiplicity.
Δ, change; CI, confidence interval; FIL, filgotinib; mTSS, van der Heijde modified total Sharp score; MTX, methotrexate; PPF, patients with 4 poor prognostic factors.

- Radiographic progression at week 24 was lower in patients with 4 poor prognostic factors receiving filgotinib 200 mg plus MTX or filgotinib 200 mg monotherapy vs MTX monotherapy (**Figure 3A**); treatment with all filgotinib regimens was associated with decreased radiographic progression relative to MTX monotherapy at week 52 (**Figure 3B**)
- At week 24, more patients with 4 poor prognostic factors treated with filgotinib 200 mg with or without MTX had no radiographic progression (mTSS change from baseline ≤0) relative to patients treated with MTX monotherapy (**Table 3**)
- At week 52, odds ratio for no radiographic progression among patients with 4 poor prognostic factors compared with MTX monotherapy was 2.3 (95% CI 1.3–4.1, nominal P = 0.004) following treatment with filgotinib 200 mg plus MTX, 1.8 following treatment with filgotinib 100 mg plus MTX (95% CI 1.0–3.5, nominal P = 0.068), and 1.8 following treatment with filgotinib 200 mg monotherapy (95% CI 0.9–3.5, nominal P = 0.078)

Safety

- Adverse events in patients with 4 poor prognostic factors were generally similar to those observed in the overall FINCH 3 population (**Table 4**)
  - Frequencies of all AEs, serious AEs, and infections were generally comparable following treatment with filgotinib vs MTX monotherapy
    - Rates of serious infections were numerically higher in patients with 4 poor prognostic factors receiving filgotinib with MTX relative to those treated with filgotinib monotherapy or MTX monotherapy
  - Herpes zoster was infrequent and occurred in all treatment arms
  - Venous thromboembolism was observed only in patients treated with MTX monotherapy

Table 4. Treatment-emergent adverse events of special interest through week 52

	FIL 200 mg + MTX		FIL 100 mg + MTX		FIL 200 mg		MTX	
	PPF	Overall	PPF	Overall	PPF	Overall	PPF	Overall
n	172	416	85	207	87	210	166	416
All AEs	125 (72.7)	318 (76.4)	68 (80.0)	164 (79.2)	57 (65.5)	43 (68.1)	118 (71.1)	305 (73.3)
Serious AEs	8 (4.7)	26 (6.3)	9 (10.6)	13 (6.3)	7 (8.0)	17 (8.1)	15 (9.0)	28 (6.7)
Infection	56 (32.6)	148 (35.6)	35 (41.2)	76 (36.7)	37 (42.5)	75 (35.7)	55 (33.1)	157 (37.7)
Serious infection	4 (2.3)	5 (1.2)	3 (3.5)	3 (1.4)	1 (1.1)	5 (2.4)	3 (1.8)	8 (1.9)
Herpes zoster	2 (1.2)	6 (1.4)	2 (2.4)	3 (1.4)	3 (3.4)	4 (1.9)	1 (0.6)	4 (1.0)
Opportunistic infection	1 (0.6)	1 (0.2)	0	0	0	0	1 (0.6)	2 (0.5)
VTE	0	0	0	0	0	0	3 (1.8)	4 (1.0)
MACE[a]	0	4 (1.0)	1 (1.2)	1 (0.5)	1 (1.1)	2 (1.0)	1 (0.6)	2 (0.5)
Malignancy (excluding NMSC)	0	1 (0.2)	0	0	0	0	0	4 (1.0)
NMSC	1 (0.6)	2 (0.5)	0	0	0	0	1 (0.6)	1 (0.2)
Death	0	3 (0.7)	1 (1.2)	1 (0.5)	0	0	0	0

Data presented as n (%).
[a]Positively adjudicated.
AE, adverse event; FIL, filgotinib; MACE, major adverse cardiovascular event; MTX, methotrexate; NMSC, nonmelanoma skin cancer; PPF, patients with 4 poor prognostic factors; VTE, venous thromboembolism.

CONCLUSIONS

- Filgotinib treatment provided rapid and clinically meaningful improvement in disease control including higher rates of remission, improved physical function, and less radiographic progression compared with MTX alone in MTX-naïve patients with multiple poor prognostic factors, a population at higher risk for severe progressive disease
- Safety data were similar to results in the overall FINCH 3 population and consistent with the integrated safety analysis
- Prospective studies are needed to confirm the findings of this post hoc analysis

REFERENCES

1) Westhovens et al., *Ann Rheum Dis*. 2019; 78 (Suppl 2): 259–60.

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