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A subgroup analysis of low disease activity and remission from phase 3 study of filgotinib in patients with inadequate response to biologic DMARDs

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INTRODUCTION

- Filgotinib is an oral, selective inhibitor of Janus kinase-1[1]
- Despite effective treatments, many patients with rheumatoid arthritis (RA) do not respond or are intolerant to biologic disease-modifying antirheumatic drugs (bDMARDs); additionally, some patients lose response over time, especially as the number of previous treatments increases[2,3]
- Filgotinib demonstrated efficacy and safety in patients with moderate to severe RA with prior bDMARD failure (FINCH 2 study; NCT02873936)[1]
- The randomised, double-blind, placebo-controlled, phase 3 FINCH 2 study assessed the efficacy of filgotinib in combination with conventional synthetic DMARDs in patients with moderate to severely active RA with inadequate response to bDMARDs (bDMARD-IR) through 24 weeks of treatment[1]

OBJECTIVES

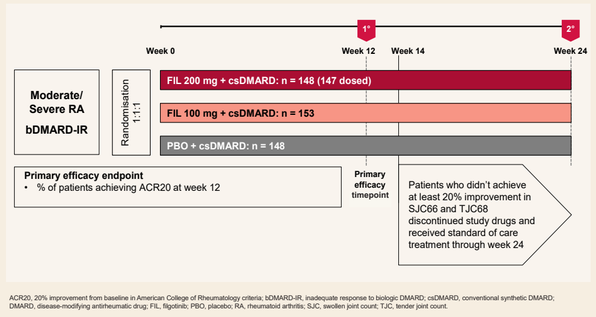
- This post hoc subgroup analysis explores filgotinib efficacy through evaluation of the effect of the number of prior bDMARDs and their mechanisms of action (MOA) on clinical response and attaining treat-to-target objectives compared with placebo

METHODS

Study design

- The global, randomised, double blind, placebo-controlled, phase 3 FINCH 2 (NCT02873936) study treated 448 bDMARD-IR patients with active RA (**Figure 1**)
  - Patients were randomised 1:1:1 to receive once-daily filgotinib 200 mg, filgotinib 100 mg, or placebo for 24 weeks
  - All patients received a background of 1 or 2 conventional synthetic DMARDs for ≥3 months with a stable prescription for at least 4 weeks prior to enrollment
- Efficacy of filgotinib was evaluated in the following subgroups:
  - Number of prior bDMARDs received (1, 2, and ≥3)
  - Prior use of tumour necrosis factor (TNF)-α inhibitors
  - Prior use of interleukin (IL)-6 inhibitors
- Clinical efficacy was assessed by:
  - American College of Rheumatology (ACR) response criteria: ACR20/50/70 at week 12 and 24
  - Percent of patients achieving Disease Activity Score in 28 joints with CRP (DAS28[CRP]) ≤3.2 and <2.6 and Clinical Disease Activity Index (CDAI) ≤10 and ≤2.8 (**Figure 1**)

Figure 1. FINCH 2 study design



ACR20, 20% improvement from baseline in American College of Rheumatology criteria; bDMARD-IR, inadequate response to biologic DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; FIL, filgotinib; PBO, placebo; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count.

Statistical analysis

- The efficacy analysis sets included all randomised patients who received ≥1 dose of study drug
- Binary endpoints were compared between filgotinib and placebo using Fisher's exact method within each subgroup
  - Missing binary data were imputed using nonresponder imputation
- As subgroup comparisons were not adjusted for multiplicity, nominal P-values are presented and should be interpreted as exploratory

RESULTS

- Of the 448 bDMARD-IR patients treated, 80.4% were female with a mean age of 56 years and a mean RA duration of 12.4 years (**Table 1**)
- Demographics and disease characteristics in the overall study population were well balanced across treatment arms
  - At baseline, mean (standard deviation) of DAS28(CRP) and Health Assessment Questionnaire-Disability Index were 5.9 (0.96) and 1.7 (0.7), respectively
- A total of 379 (84.6%) patients had used a TNF-α antagonist, and 117 (26.1%) had used an IL-6 inhibitor
- Among bDMARD-IR patients, 105 (23.4%) had prior experience with 2 bDMARDs and 106 (23.7%) with ≥3 bDMARDs (**Table 1**)
  - 146 (32.5%) patients used prior bDMARDs with >1 MOA
- Overall, 380 (84.8%) patients had lack of efficacy with ≥1 bDMARD

Table 1. Baseline demographics, disease activity, and prior bDMARD use at randomisation

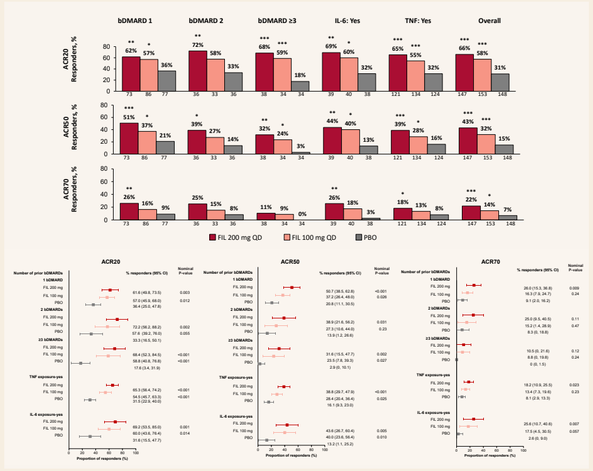
	FIL 200 mg QD n = 147	FIL 100 mg QD n = 153	PBO n = 148	Total N = 448
Age, years	56 (12.5)	55 (12.0)	56 (12.1)	56 (12.2)
Sex at birth, female, n (%)	120 (81.6)	119 (77.8)	121 (81.8)	360 (80.4)
Duration of RA from diagnosis, years	12.6 (9.5)	12.0 (7.7)	12.6 (10.3)	12.4 (9.2)
Presence of RF or anti-CCP antibody	112 (76.2)	118 (77.1)	113 (76.4)	343 (76.6)
Concurrent methotrexate use on first dosing date, n (%)	124 (84.4)	127 (83.0)	116 (78.4)	367 (81.9)
Dose, mg/week	15.5 (5.1)	16.2 (5.6)	15.5 (5.0)	15.8 (5.3)
Concurrent oral glucocorticoid use on first dosing date, n (%)	70 (47.6)	74 (48.4)	73 (49.3)	217 (48.4)
Dose, mg/day	6.4 (2.7)	6.2 (2.5)	6.2 (2.7)	6.3 (2.6)
DAS28(CRP)	5.9 (1.0)	5.9 (0.98)	5.9 (0.86)	5.9 (0.96)
CDAI	41.7 (14.2)	40.4 (13.2)	41.4 (12.0)	41.2 (13.2)
HAQ-DI	1.7 (0.7)	1.6 (0.7)	1.7 (0.6)	1.7 (0.7)
SJC66	18 (12.5)[a]	17 (12.4)	17 (9.7)	17 (11.6)
TJC68	28 (16.1)[a]	26 (15.4)	27 (15.5)	27 (15.7)
hsCRP (mg/L)	17.2 (18.3)	21.5 (28.2)	16.4 (18.3)	18.4 (22.2)
SGA, (mm)	68 (20.6)	69 (20.2)	70 (18.0)	69 (19.6)
PGA, (mm)	69 (17.6)	68 (18.7)	66 (16.7)	67 (17.7)
Prior bDMARDs, n (%)				
0	0	0	1 (0.7)	1 (0.2)
1	73 (49.7)	86 (56.2)	77 (52.0)	236 (52.7)
2	36 (24.5)	33 (21.6)	36 (24.3)	105 (23.4)
≥3	38 (25.9)	34 (22.2)	34 (23.0)	106 (23.7)
Prior bDMARD MOAs, n (%)				
1 MOA	97 (66.0)	111 (72.5)	93 (62.8)	301 (67.2)
>1 MOA	50 (34.0)	42 (27.5)	54 (36.5)	146 (32.5)
Prior TNF, n (%)	121 (82.3)	134 (87.6)	124 (83.8)	379 (84.6)
Prior non-TNF bDMARD, n (%)	74 (50.3)	61 (39.9)	75 (50.7)	210 (46.9)
Prior IL-6 inhibitor, n (%)	39 (26.5)	40 (26.1)	38 (25.6)	117 (26.1)
Lack of efficacy, n (%)				
≥1 bDMARD	125 (85.0)	129 (84.3)	126 (85.1)	380 (84.8)

[a]n = 146.
Data presented as mean (SD) unless otherwise specified.
bDMARD, biologic disease-modifying antirheumatic drug; CCP, cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; DAS28(CRP), Disease Activity Score 28 (C-reactive protein); FIL, filgotinib; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity CRP; IL-6, interleukin-6; MOA, mechanism of action; PBO, placebo; PGA, Physician Global Assessment; QD, once daily; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SGA, Subject Global Assessment; SJC, swollen joint count; TJC, tender joint count; TNF, tumour necrosis factor.

ACR responses

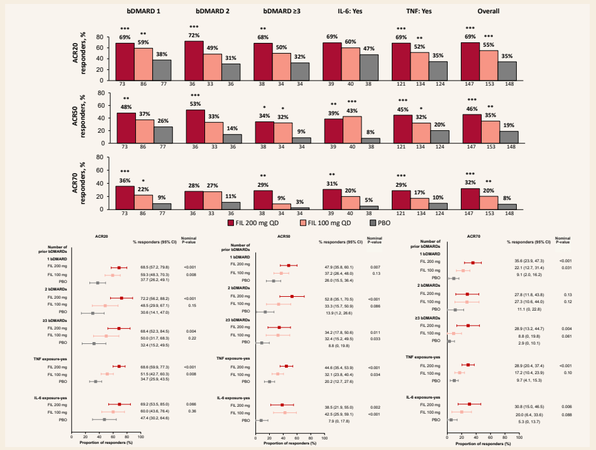
- Treatment with filgotinib 200 or 100 mg once daily vs placebo at week 12 led to nominally significantly higher rates of ACR20/50/70 responses in bDMARD-IR patients with RA independent of the number or MOA of previously received bDMARDs (**Figure 2**)
- By week 24, ACR20 and ACR50 responses were generally maintained while ACR70 continued to improve in the overall population and in patients with ≥3 bDMARDs exposure and prior TNF and IL-6 therapy (**Figure 3**)
- By week 24, ACR responses in patients with exposure to ≥3 bDMARDs were comparable to the other subgroups and overall population (**Figure 3**)
- ACR responses in patients receiving filgotinib after prior TNF or IL-6 therapy were comparable to overall population at week 24

Figure 2. ACR20/50/70 at week 12 by prior bDMARD use



Missing data imputed as nonresponse.
**P <0.001 vs PBO; **P <0.01 vs PBO; *P <0.05 vs PBO; Fisher's exact method to calculate 95% CI and P-value; all nominal P (not adjusted for multiplicity) except for comparisons vs placebo for ACR20. ACR20/50/70, 20%/50%/70% improvement from baseline in American College of Rheumatology core criteria; bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence interval; FIL, filgotinib; IL-6, interleukin 6; PBO, placebo; QD, once daily; TNF, tumour necrosis factor.

Figure 3. ACR20/50/70 at week 24 by prior bDMARD use



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***P <0.001 vs PBO; **P <0.01 vs PBO; *P <0.05 vs PBO; Fisher's exact method to calculate 95% CI and P-value; all nominal P (not adjusted for multiplicity).
ACR20/50/70, 20%/50%/70% improvement from baseline in American College of Rheumatology core criteria; bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence interval; FIL, filgotinib; IL-6, interleukin 6; PBO, placebo; QD, once daily; TNF, tumour necrosis factor.

Disease activity states at week 24

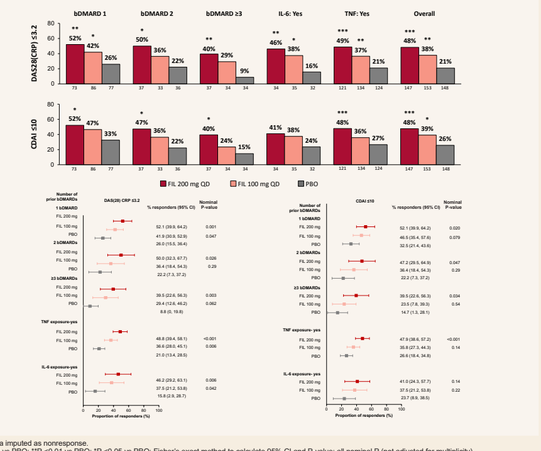
DAS28(CRP) ≤3.2 and CDAI ≤10

- At week 24, higher proportions of patients receiving filgotinib 200 or 100 mg achieved DAS28(CRP) ≤3.2 and CDAI ≤10 compared with placebo, irrespective of the number of prior bDMARDs or MOA
- In patients with ≥3 prior bDMARDs, a nominally significantly greater proportion achieved DAS28(CRP) ≤3.2 and CDAI ≤10 with filgotinib 200 mg vs placebo and a numerically greater proportion with filgotinib 100 mg vs placebo
- Proportions of patients with 1 or 2 prior bDMARDs who achieved DAS28(CRP) ≤3.2 and CDAI ≤10 were comparable to overall FINCH 2 results; filgotinib 200 mg showed nominally statistical significance over placebo while filgotinib 100 mg was numerically greater than placebo (**Figure 4**)
- In patients treated with either filgotinib dose after IL-6 therapy, DAS28(CRP) ≤3.2 was nominally significantly better than placebo and comparable to overall FINCH 2 results
  - For patients with prior IL-6 therapy, CDAI ≤10 was comparable to overall results; however, filgotinib treatment did not reach statistical significance over placebo
- Patients who received filgotinib after prior TNF achieved comparable results to the overall population, with filgotinib 200 mg demonstrating nominally statistical significance over placebo for both DAS28(CRP) ≤3.2 and CDAI ≤10

DAS28(CRP) <2.6 and CDAI ≤2.8

- At week 24, greater proportions of patients receiving filgotinib 200 mg or 100 mg vs placebo achieved DAS28(CRP) <2.6 and CDAI ≤2.8 (**Figure 5**)
- Both filgotinib doses demonstrated numerically better treat-to-target goals over placebo for patients receiving ≥3 prior bDMARDs
- Patients with 1 or 2 prior bDMARDs achieved DAS28(CRP) <2.6 and CDAI ≤2.8 comparable to the overall FINCH 2 results, with both filgotinib doses showing numerical greater difference vs placebo
- Proportions of patients with prior IL-6 therapy achieving DAS28(CRP) <2.6 and CDAI ≤2.8 were nominally significantly higher with filgotinib 100 mg or 200 mg vs placebo at week 24
- Proportions of patients with prior TNF exposure achieving DAS28(CRP) <2.6 and CDAI ≤2.8 were nominally statistically significantly higher in the filgotinib 200 mg group compared with the placebo group; DAS28(CRP) <2.6 and CDAI ≤2.8 in each filgotinib group were comparable to overall population results

Figure 4. DAS28(CRP) ≤3.2 and CDAI ≤10 at week 24 by prior bDMARD use



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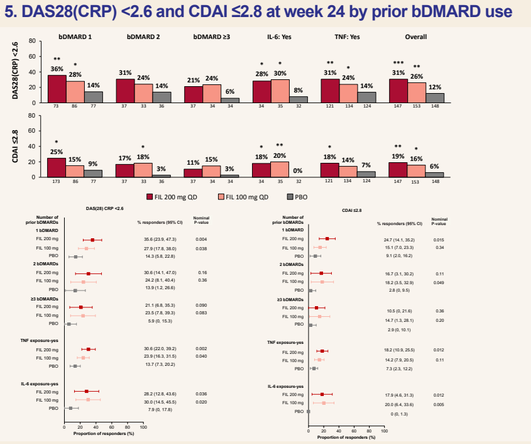
***P <0.001 vs PBO; **P <0.01 vs PBO; *P <0.05 vs PBO; Fisher's exact method to calculate 95% CI and P-value; all nominal P (not adjusted for multiplicity).
bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; CI, confidence interval; DAS28(CRP), Disease Activity Score 28 (C-reactive protein); FIL, filgotinib; IL-6, interleukin 6; PBO, placebo; QD, once daily; TNF, tumour necrosis factor.

Figure 5. DAS28(CRP) <2.6 and CDAI ≤2.8 at week 24 by prior bDMARD use



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CONCLUSIONS

- Treatment with filgotinib 200 or 100 mg once daily vs placebo led to higher rates of ACR20/50/70 responses, low disease activity and remission in bDMARD-IR patients with RA independent of the number of bDMARDs or prior exposure to IL-6 or TNF inhibitors
  - Filgotinib demonstrated efficacy over placebo for patients receiving ≥3 prior bDMARDs, reaching treat to target goals of low disease activity and remission
  - In patients with prior exposure to IL-6 or TNF inhibitors, proportion of patients achieving ACR20/50/70, low disease activity or remission treated with filgotinib was comparable to overall FINCH 2 results
- In patients with RA, the efficacy of filgotinib does not appear to be affected by prior treatment with TNF or IL-6 inhibitors or by number of previous bDMARDs
- Due to a small sample size in some subgroups, data should be interpreted with caution

REFERENCES

1) Genovese MC, et al. *JAMA.* 2019; 322(4):315–25. **2)** Genovese MC, et al. *N Engl J Med.* 2016;374(13):1243–52. **3)** Rendas-Baum R, et al. *Arthritis Res Ther.* 2011;13(1):R25.

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