Safety and Efficacy of Filgotinib in a Phase 3 Trial of Patients with Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Biologic DMARDs

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Introduction

- Limited treatment options are available for patients with active rheumatoid arthritis (RA) who have failed to adequately respond to biologic disease-modifying antirheumatic drugs (bDMARDs)
- Filgotinib (FIL), an orally administered, selective inhibitor of Janus kinase 1 (JAK1), was effective in phase 2 studies[1,2] of active RA in patients with insufficient response to methotrexate (MTX), warranting further evaluation in phase 3
- Patients with active RA who fail to achieve a low disease state with conventional synthetic DMARDs (csDMARDs) and who failed bDMARDs constitute a treatment-refractory population in need of additional treatment options
- This report describes efficacy and safety of FIL in patients with moderately to severely active RA with inadequate response to bDMARDs

Objectives

- To evaluate the effects of FIL versus placebo (PBO) for the treatment of signs and symptoms of RA in a treatment-refractory population
- To evaluate the safety and tolerability of FIL

Methods

Study Overview

- FINCH 2 (NCT02873936) is an international, multicenter, randomized, double-blind, PBO-controlled, 24-week, phase 3 study to evaluate the effects of FIL versus PBO for the treatment of RA
  - Primary endpoint: % patients with ACR20 response at Week 12
  - Secondary endpoints include: disease activity score 28-joint count C-reactive protein (DAS28[CRP]), Health Assessment Questionnaire Disability Index (HAQ-DI), 36-Item Short Form Health Survey (SF-36), Functional Assessment of Chronic Illness (FACIT)-Fatigue
- There was no rescue medication. At Week 14, patients who failed to achieve ≥20% improvement from Day 1 in both swollen joint count (SJC) and tender joint count (TJC) discontinued study drug to receive standard of care treatment
- Patients completing the study could enroll in an extension study (NCT03025308) to evaluate long-term safety through 36 months

Study Design

- Patients were randomized **(Figure 1)** in a 1:1:1 ratio to once daily FIL 200 mg, 100 mg, or PBO (matched in appearance)
- Patients were stratified by geographic region, prior exposure to bDMARDs (<3 or ≥3), and the presence of rheumatoid factor or anti-cyclic citrullinated peptide antibodies at screening

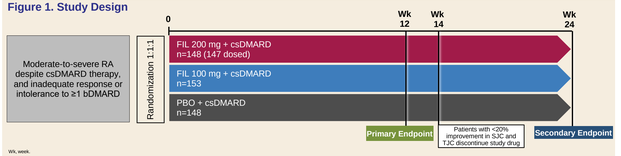
Key Inclusion Criteria

- Diagnosis of RA (2010 ACR/EULAR criteria for RA), and are ACR functional class I-III
- ≥ 6 swollen joints (from SJC66) and ≥6 tender joints (from TJC68) at screening and Day 1
- Ongoing treatment with a stable prescription of 1 or 2 csDMARDs
- Received ≥1 bDMARD for the treatment of RA to which they have had an inadequate response or intolerance

Key Exclusion Criteria

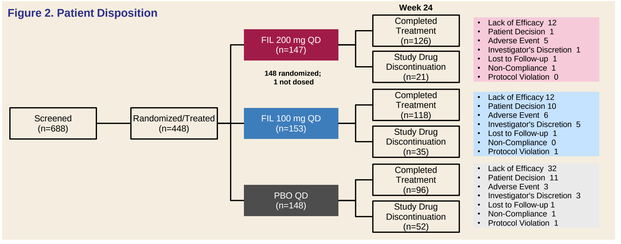
- Previous treatment with any JAK inhibitor

Figure 1. Study Design



- 448 patients randomized and treated; 340 patients (76%) completed treatment **(Figure 2)**
- Reasons for premature discontinuation: withdrew consent 5%, investigator discretion 2%, adverse event 3%, other 2%

Figure 2. Patient Disposition



Results

- This was a treatment refractory population (DAS28[CRP] 5.9±0.96 mean±SD at baseline) with 90% of patients on one csDMARD on the first dosing date and 23.4% with prior exposure to ≥3 bDMARDs **(Table 1)**

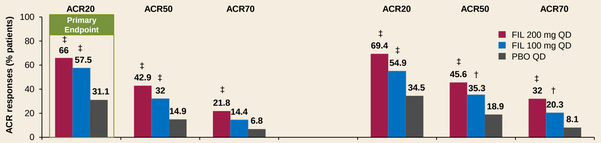
Table 1. Baseline Demographics, Disease Characteristics and Treatment History

n (%) unless otherwise noted	FIL 200 mg QD (n=147)	FIL 100 mg QD (n=153)	PBO QD (n=148)
Age (yrs); mean (SD)	56 (12.5)	55 (12.0)	56 (12.1)
Female	120 (81.6)	119 (77.8)	121 (81.8)
Duration of RA from diagnosis (yrs); mean (SD)	12.6 (9.48)	12.0 (7.74)	12.6 (10.30)
Number of prior bDMARDs exposure			
< 3 bDMARDs	110 (74.8)	119 (77.8)	114 (77.0)
≥ 3 bDMARDs	37 (25.2)	34 (22.2)	34 (23.0)
Prior anti-TNF exposure	121 (82.3)	134 (87.6)	124 (83.3)
Prior non-TNF bDMARDs exposure	73 (49.7)	62 (40.5)	75 (50.7)
Concurrent oral steroid use[a]	68 (46.3)	68 (44.4)	71 (48.0)
Steroid dose (mg/day); mean (SD)	6.4 (2.70)	6.3 (2.58)	6.2 (2.69)
csDMARDs at baseline			
Concurrent MTX use[a]	124 (84.4)	127 (83.0)	116 (78.4)
MTX dose (mg/week), mean (SD)	15.5 (5.12)	16.2 (5.58)	15.5 (5.02)
Number of csDMARDs[a]			
0	0	0	1 (0.7)
1	133 (90.5)	135 (88.2)	135 (91.2)
2	14 (9.5)	18 (11.8)	12 (8.1)
RF (+)	104 (70.7)	107 (69.9)	92 (62.2)
Anti-CCP Ab (+)	99 (67.3)	113 (73.9)	105 (70.9)
RF (+) and ACPA (+)	91 (61.9)	102 (66.7)	84 (56.8)
TJC68, mean (SD)	28 (16.1)	26 (15.4)	27 (15.5)
SJC66, mean (SD)	18 (12.5)	17 (12.4)	17 (9.7)
DAS28(CRP), mean (SD)	5.9 (1.03)	5.9 (0.98)	5.9 (0.86)
CDAI, mean (SD)	41.7 (14.23)	40.4 (13.23)	41.4 (12.00)
hsCRP (mg/L), mean (SD)	17.21 (18.275)	21.49 (28.206)	16.42 (18.321)
HAQ-DI, mean (SD)	1.70 (0.656)	1.64 (0.683)	1.65 (0.633)

[a]On 1st dose date. Ab, antibody; ACPA, anti-citrullinated peptide antibody; CCP, cyclic citrullinated peptide; CDAI, Crohn's Disease Activity Index; hsCRP, high-sensitivity C-reactive protein; RF, rheumatoid factor; SD, standard deviation; TNF, tumor necrosis factor alpha.

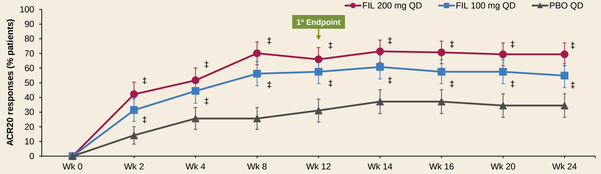
- In patients who failed to achieve a low disease state despite prior use of bDMARDs, FIL demonstrated significant improvement in clinical, functional, and patient-reported outcomes
  - The primary endpoint of ACR20 response at Week 12 was achieved by 66.0%, 57.5%, and 31.1% of patients in the FIL 200 mg, 100 mg, and PBO groups, respectively; both p<0.001 versus PBO **(Figure 3)**
  - ACR20 improvements are evident from Week 2, the earliest timepoint assessed **(Figure 4)**
  - In patients previously treated with ≥3 bDMARDs, the ACR20 response rates at Week 12 were 70.3%, 58.8%, and 17.6% for patients receiving FIL 200 mg or 100 mg or PBO; both p<0.001 vs PBO **(Figure 5)**
  - Indicators of low disease activity, including the key secondary endpoints of DAS28(CRP) ≤3.2 and <2.6, as well as CDAI and SDAI were achieved by a greater proportion of patients with FIL 200 mg and FIL 100 mg compared with PBO **(Figure 6)**
  - Patients receiving FIL had significantly improved scores on HAQ-DI at Week 2, and these improvements were maintained or enhanced through Week 24 **(Figure 7)**

Figure 3. ACR Responses at Weeks 12 and 24 (NRI)



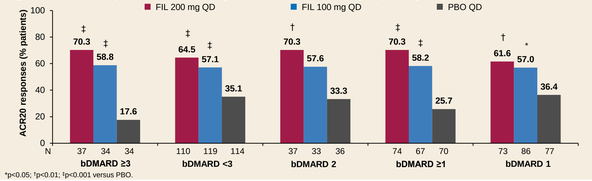
†p<0.05; ‡p<0.01; §p<0.001 versus PBO.
NRI, non-responder imputation.

Figure 4. ACR20 Responses Over 24 Weeks (NRI)



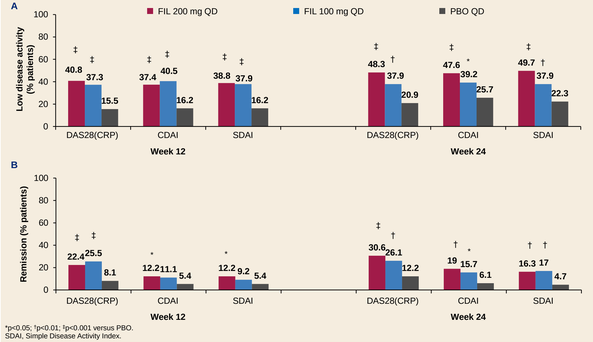
‡p≤0.001 versus PBO.

Figure 5. ACR20 Responses at Week 12 by Prior bDMARD Use Subgroup Analysis (NRI)



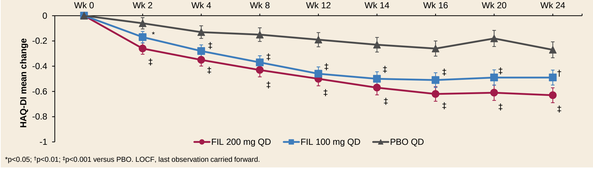
*p<0.05; †p<0.01; ‡p<0.001 versus PBO.

Figure 6. Responses at Weeks 12 and 24 for A) Low Disease Activity (DAS28[CRP] ≤3.2, CDAI ≤10, or SDAI ≤11), and B) Disease Remission (DAS28[CRP] <2.6, CDAI ≤2.8, or SDAI ≤3.3) (NRI)



*p<0.05; †p<0.01; ‡p<0.001 versus PBO.
SDAI, Simple Disease Activity Index.

Figure 7. HAQ-DI Mean Change From Baseline Over 24 Weeks (LOCF)



*p<0.05; †p<0.01; ‡p<0.001 versus PBO. LOCF, last observation carried forward.

- Treatment-emergent adverse events occurred in a similar proportion of patients in each treatment group **(Table 2)**
  - Most were Grade 1 or 2
  - There were no clinically relevant changes in hemoglobin, neutrophil count, or platelet count over the course of the study **(Figure 8)**
  - Laboratory abnormalities occurred at similar rates with FIL and PBO, were mostly mild to moderate, and resolved spontaneously **(Table 3)**
- There were few cases of serious infections, only 4 cases of herpes zoster, 2 cases of major adverse cardiovascular events (MACE) and no cases of opportunistic infection, active tuberculosis, pulmonary embolus, malignancy, gastrointestinal perforation or death

Table 2. Safety Data, Week 0 to Week 12 and Week 0 to Week 24[a]

	Week 0 to 12			Week 0 to 24		
	FIL 200 mg QD (n=147)	FIL 100 mg QD (n=153)	PBO QD (n=148)	FIL 200 mg QD (n=147)	FIL 100 mg QD (n=153)	PBO QD (n=148)
Treatment emergent adverse events	82 (55.8)	77 (50.3)	80 (54.1)	102 (69.4)	97 (63.4)	100 (67.6)
Serious adverse events	4 (2.7)	6 (3.9)	4 (2.7)	6 (4.1)	8 (5.2)	5 (3.4)
Adverse event leading to premature discontinuation of study	3 (2.0)	5 (3.3)	3 (2.0)	3 (2.0)	5 (3.3)	3 (2.0)
Infection	34 (23.1)	29 (19.0)	27 (18.2)	53 (36.1)	52 (34.0)	38 (25.7)
Herpes zoster (uncomplicated)	1 (0.7)	2 (1.3)	0	2 (1.4)	2 (1.3)	0
Active tuberculosis	0	0	0	0	0	0
Opportunistic infection	0	0	0	0	0	0
Serious Infection	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)	3 (2.0)	2 (1.4)
Malignancy (excluding NMSC)	0	0	0	0	0	0
NMSC	0	0	0	0	0	0
MACE (adjudicated)	0	1 (0.7)	1 (0.7)	0	1 (0.7)[b]	1 (0.7)[c]
Gastrointestinal perforation	0	0	0	0	0	0
Retinal vein thrombosis[a]	0	0	0	1 (0.7)	0	0
Death	0	0	0	0	0	0

[a]Week 0-12 data includes events that began on or after the study drug start date to Study Day 92 and Week 0-24 data includes events from the study drug start date up to 30 days after permanent discontinuation of study drug or led to premature study drug discontinuation; [b]Myocardial ischemia; [c]Subarachnoid hemorrhage; [a]No events of deep vein thrombosis or pulmonary embolism. NMSC, non-melanoma skin cancer.

Figure 8. Lab Values of A) Hemoglobin and B) Platelets Over 24 Weeks

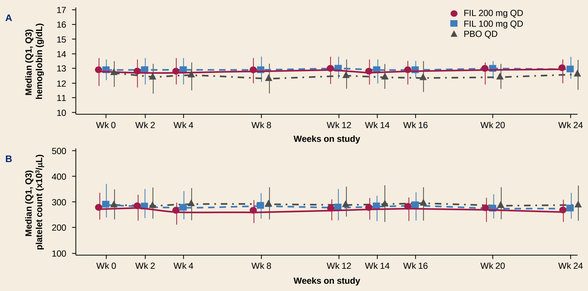


Table 3. Laboratory Abnormalities

Any grade (%)/Grade 3-4 (%)	FIL 200 mg QD (n=147)	FIL 100 mg QD (n=153)	PBO QD (n=148)
Hemoglobin decreased	19.0 / 0.7	15.7 / 0.7	29.1 /1.4
Neutrophil count decreased	11.6 / 1.4	5.2 / 0	4.7 / 0.7
Lymphocyte count decreased	14.3 / 2.7	7.2 / 0.7	12.8 / 2.0
Platelet count decreased	0.7 / 0	0.7 / 0	2.7 / 0
Alanine aminotransferase increased	23.1 / 0	19.6 / 0	14.2 / 0
Aspartate aminotransferase increased	25.9 / 0	19.6 / 0	12.2 / 0
Creatinine increased	8.2 / 0	2.6 / 0	2.0 / 0
Creatine kinase increased	29.3 / 0	14.4 / 2.0	10.8 / 0.7

Conclusions

- In this phase 3 study of patients with moderately to severely active RA and prior inadequate response/intolerance to bDMARDs, treatment with FIL over a 24-week period was associated with significant improvement in the signs and symptoms of RA, with a favorable safety profile and stable laboratory parameters consistent with phase 2 data
- ACR20 and HAQ-DI were significantly improved with FIL vs PBO by Week 2
- ACR20 response was independent of number of prior bDMARDs
- FIL may be a novel treatment option for patients who continue to have active RA despite prior biologic therapies

References

1. Westhovens R, et al. *Ann Rheum Dis.* 2017;76:998-1008. 2. Kavanaugh A, et al. *Ann Rheum Dis.* 2017;76:1009-1019.

Disclosures

M.C. Genovese: Gilead, Galapagos, AbbVie, Lilly, Pfizer; **K.C. Kalunian:** Gilead; **D. Walker**, **J.E. Gottenberg**, **K. de Vlam**, and **T. Takeuchi**: None; **N. Mozaffarian**, **B. Bartok**, **F. Matzkies**, **J. Gao**, **Y. Guo**, and **J. Sundy**: Gilead; **C. Tasset:** Galapagos.

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