Rheumatoid Arthritis Treatment with Filgotinib: Week 156 Safety and Efficacy Data from a Phase 2b Open-Label Extension Study

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Background

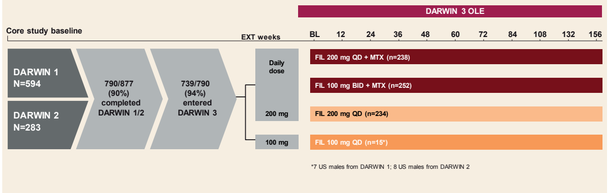
- Filgotinib (FIL) is an orally administered, selective Janus kinase 1 (JAK1) inhibitor in phase 3 development for the treatment of rheumatoid arthritis (RA) and other chronic inflammatory diseases
- In phase 2 and 3 studies to date, treatment with FIL appeared to be effective and safe in patients with RA
- DARWIN 3 (NCT02065700) is an ongoing, open-label, long-term extension study of earlier phase 2b studies evaluating the longer-term safety and efficacy of FIL in RA[1,2]

Objectives

- To evaluate the longer-term safety and tolerability of FIL for the treatment of RA
- Secondary objectives include evaluation of FIL long-term efficacy
- This interim analysis presents 156-week data from the DARWIN 3 long-term extension study

Methods

Figure 1. Study Schematic



*7 US males from DARWIN 1; 8 US males from DARWIN 2

Numbers of patients in DARWIN 3 represent populations at baseline. Patients could continue their core study dosing regimen in DARWIN 3
19 patients who received FIL monotherapy in core studies went on to take MTX in DARWIN 3. One patient from DARWIN 1 had no MTX exposure in DARWIN 3; this patient also had no MTX exposure in DARWIN 1, although DARWIN 1 was a combination treatment study
BID, twice daily; BL, baseline; EXT, extension; FIL, filgotinib; MTX, methotrexate; OLE, open-label extension; QD, once daily

Study Design

- Phase 2b DARWIN 1 and 2 studies (core studies) evaluated FIL with and without methotrexate (MTX), respectively, for 24 weeks in patients with moderate to severely active RA and inadequate response to MTX (**Figure 1**)
  - All patients completing the 24-week DARWIN 1 (FIL + MTX) and DARWIN 2 (FIL monotherapy) studies were eligible to roll over into DARWIN 3
- All patients in DARWIN 3 received FIL 200 mg/day, with the exception of 15 males in the US, who received FIL 100 mg/day (7 enrolled from DARWIN 1, 8 enrolled from DARWIN 2)

Week 156 Analyses

- The week 156 (extension 156) interim data cutoff was May 30, 2018
- Exposure was calculated up to the data cutoff date for patients continuing the study at the time of analysis
  - Safety analyses included all safety data up to the data cutoff date for patients who received at least one dose of study drug in DARWIN 3
  - Efficacy analyses present data from the first dose date of study drug in DARWIN 3 up to week 156
- Patients from DARWIN 1 were included in the FIL + MTX group; patients from DARWIN 2 were included in the FIL monotherapy group. Data are presented for all patients
- The event rate was calculated as total events/total patient-years of exposure (PYE) to FIL and are presented per 100 PYE

Results

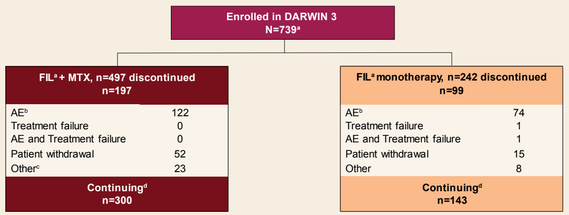
Table 1. Patient Demographics and Disease Characteristics at Core Study Baseline by Treatment

Characteristic	FIL + MTX n=497	FIL monotherapy n=242	Total N=739
Age, years, mean ± SD	53 ± 11.7	52 ± 12.2	53 ± 11.9
Gender, female	405 (81.5)	198 (81.8)	603 (81.6)
Race			
Asian	1 (0.2)	1 (0.4)	2 (0.3)
Black or African American	3 (0.6)	3 (1.2)	6 (0.8)
Native Hawaiian or Pacific Islander	0	1 (0.4)	1 (0.1)
White	374 (75.3)	181 (74.8)	555 (75.1)
Other	119 (23.9)	56 (23.1)	175 (23.7)
Ethnicity, Hispanic or Latino	208 (41.9)	85 (35.1)	293 (39.6)
Body mass index, kg/m², mean ± SD	28.3 ± 5.74	27.6 ± 5.55	28.1 ± 5.69
Duration of RA, years, mean ± SD	8.3 ± 7.10	8.9 ± 7.11	8.5 ± 7.10
RF present	382 (76.9)	180 (74.4)	562 (76.0)
Anti-CCP present	402 (80.9)	192 (79.3)	594 (80.4)
Prior exposure to bDMARDs	40 (8.0)	18 (7.4)	58 (7.8)
Concurrent glucocorticoid use on first dosing date	227 (45.7)	135 (55.8)	362 (49.0)
Methotrexate dose on first dosing date, mg/day, mean ± SD[a]	16.8 ± 4.22	N/A	16.8 ± 4.22

Data are shown as n (%) unless otherwise indicated
[a]496 patients in the FIL + MTX treatment arm were receiving MTX on first dosing date; n=493 for mean ± SD dose
bDMARD, biologic disease-modifying antirheumatic drug; CCP, cyclic citrullinated peptide; FIL, filgotinib; MTX, methotrexate; N/A, not applicable; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation

- Of 790 patients completing the parent studies, 739 patients enrolled in DARWIN 3 (497 from DARWIN 1, 242 from DARWIN 2)
- The majority of patients in DARWIN 1 and 2 were female (81.5%, 81.8%) and white (75.3%, 74.8%) with a mean age of 53 and 52 years, respectively (**Table 1**)

Figure 2. Week 156 Interim Analysis Patient Disposition



156 weeks elapsed since start of FIL treatment in the core studies or long-term extension study. All patients either completed the week 156 study visit or discontinued the study early
[a]200 mg daily except in 15 US males who received FIL 100 mg; [b]Many of the AEs leading to treatment discontinuation were protocol driven; [c]Includes lost to follow-up, sponsor request, noncompliance with procedures, physician decision, use of nonpermitted concurrent therapy, and other not specified; [d]By data cutoff of May 30, 2018
AE, adverse event; FIL, filgotinib; MTX, methotrexate

- At the week 156 interim analysis, 443/739 (59.9%) patients were continuing in the study (**Figure 2**)
- The most common reasons for discontinuation were adverse events (26.5%) and patient request (9.1%) (**Figure 2**)

Table 2. Exposure and Key Safety Outcomes (TEAEs)

	FIL + MTX[a] n=497	FIL monotherapy[a] n=242	Total N=739
Exposure			
Total FIL, PYE	1,511	692	2,203
Median FIL exposure, years	3.55	3.47	3.53
Key safety outcomes, events/100 PYE (# events)[b]			
TEAEs	148.3 (2,241)	146.5 (1,014)	147.8 (3,255)
Infections	41.4 (626)	36.1 (250)	39.8 (876)
SAEs	5.0 (75)	6.2 (43)	5.4 (118)
Infections	0.7 (11)	1.7 (12)	1.0 (23)
Deaths[c]	0.1 (2)	0.4 (3)	0.2 (5)

[a]For the week 156 interim analysis, patients enrolled from DARWIN 1 were grouped as FIL + MTX and those from DARWIN 2 as FIL monotherapy. 19 patients enrolled from DARWIN 2 had MTX exposure during DARWIN 3 but were grouped as FIL monotherapy; [b]Treatment-emergent adverse events began on or after FIL start date in the core studies or in DARWIN 3 up to 30 days after permanent discontinuation of filgotinib; [c]Deaths were due to meningococcal meningitis, pneumonia, non-Hodgkin's lymphoma (2), and deep vein thrombosis with pulmonary embolism; none occurred after the week 132 analysis
AE, adverse event; FIL, filgotinib; MTX, methotrexate; PYE, patient-years of exposure; SAE, serious adverse event; TEAE, treatment-emergent adverse event

- Total exposure to FIL was 2,203 PYE, mean ± standard deviation (SD) exposure was 3.04 ± 1.22 years for FIL + MTX and 2.86 ± 1.21 years for FIL monotherapy, and median time on study drug was 3.5 years (**Table 2**)

Table 3. Exposure-Adjusted Event Rates of TEAEs at Week 156 Interim Analysis

Events/100 PYE (# events)[b]	FIL + MTX[a] n=497 (PYE=1,511)	FIL monotherapy[a] n=242 (PYE=692)	Total[a] N=739 (PYE=2,203)
Urinary tract infection	5.4 (81)	6.2 (43)	5.6 (124)
Upper respiratory tract infection	4.0 (61)	5.8 (40)	4.6 (101)
Nasopharyngitis	4.9 (74)	3.3 (23)	4.4 (97)
Hypercholesterolemia	2.8 (42)	5.9 (41)	3.8 (83)
Mycobacterium tuberculosis complex test positive[c]	3.2 (48)	4.8 (33)	3.7 (81)
Hypertension	3.2 (49)	3.9 (27)	3.4 (76)
Bronchitis	4.0 (60)	1.9 (13)	3.3 (73)
Headache	2.3 (34)	4.9 (34)	3.1 (68)
Rheumatoid arthritis[d]	3.2 (48)	2.0 (14)	2.8 (62)
Hypertriglyceridemia	1.1 (17)	5.2 (36)	2.4 (53)
Dyslipidemia	2.3 (34)	2.2 (15)	2.2 (49)
Influenza	2.4 (36)	1.6 (11)	2.1 (47)
Lymphopenia	2.2 (33)	1.3 (9)	1.9 (42)
Back pain	1.9 (28)	1.9 (13)	1.9 (41)
Diarrhea	2.1 (31)	1.3 (9)	1.8 (40)
Pharyngitis	1.9 (29)	1.6 (11)	1.8 (40)
Lymphocyte count decreased	1.1 (16)	2.5 (17)	1.5 (33)
Blood cholesterol increased	0.6 (9)	2.9 (20)	1.3 (29)
Blood creatinine increased	0.6 (9)	2.9 (20)	1.3 (29)

TEAEs reported in >5% of patients presented in descending order of total frequency
[a]For the week 156 interim analysis, patients enrolled from DARWIN 1 were grouped as FIL + MTX and those from DARWIN 2 as FIL monotherapy. 19 patients enrolled from DARWIN 2 had MTX exposure during DARWIN 3 but were grouped as FIL monotherapy; [b]Treatment-emergent adverse events began on or after FIL start date in the core studies or in DARWIN 3 up to 30 days after permanent discontinuation of filgotinib; [c]None were active tuberculosis; [d]Worsening of existing RA
FIL, filgotinib; MTX, methotrexate; PYE, patient-years of exposure; RA, rheumatoid arthritis; TEAE, treatment-emergent adverse event

Table 5. Proportions of Patients with Grade 1 or Higher Treatment-Emergent Laboratory Abnormalities over Time

	FIL + MTX[a] (n=497)									FIL monotherapy[a] (n=242)								
	Grade 1 lab abnormality N (%) Year			Grade 2 lab abnormality N (%) Year			≥Grade 3 lab abnormality N (%) Year			Grade 1 lab abnormality N (%) Year			Grade 2 lab abnormality N (%) Year			≥Grade 3 lab abnormality N (%) Year		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Hematology (decreased)	n=496	n=438	n=386	n=496	n=438	n=386	n=496	n=438	n=386	n=242	n=209	n=172	n=242	n=209	n=172	n=242	n=209	n=172
Hemoglobin	69 (13.9)	38 (8.7)	26 (6.7)	23 (4.6)	10 (2.3)	13 (3.4)	2 (0.4)	1 (0.2)	1 (0.3)	39 (16.1)	17 (8.1)	11 (6.4)	12 (5.0)	8 (3.8)	5 (2.9)	0	0	1 (0.6)
Leukocytes	36 (7.3)	38 (8.7)	25 (6.5)	6 (1.2)	1 (0.2)	5 (1.3)	1 (0.2)	0	1 (0.3)	16 (6.6)	9 (4.3)	13 (7.6)	1 (0.4)	2 (1.0)	2 (1.2)	0	0	1 (0.6)
Lymphocytes	18 (3.6)	15 (3.4)	10 (2.6)	31 (6.3)	30 (6.8)	27 (7.0)	6 (1.2)	4 (0.9)	9 (2.3)	3 (1.2)	4 (1.9)	5 (2.9)	16 (6.6)	5 (2.4)	10 (5.8)	1 (0.4)	1 (0.5)	1 (0.6)
Neutrophils	21 (4.2)	11 (2.5)	10 (2.6)	9 (1.8)	7 (1.6)	8 (2.1)	3 (0.6)	0	1 (0.3)	12 (5.0)	1 (0.5)	6 (3.5)	2 (0.8)	5 (2.4)	4 (2.3)	2 (0.8)	1 (0.5)	0
Platelet count	11 (2.2)	11 (2.5)	4 (1.0)	0	1 (0.2)	0	1 (0.2)	1 (0.2)	0	2 (0.8)	1 (0.5)	0	1 (0.4)	0	0	0	0	0
Chemistry (increased)	n=496	n=437	n=386	n=496	n=437	n=386	n=496	n=437	n=386	n=242	n=209	n=172	n=242	n=209	n=172	n=242	n=209	n=172
Creatinine	5 (1.0)	5 (1.1)	6 (1.6)	3 (0.6)	2 (0.5)	4 (1.0)	0	1 (0.2)	1 (0.3)	7 (2.9)	3 (1.4)	2 (1.2)	5 (2.1)	7 (3.3)	3 (1.7)	0	0	0
ALT	73 (14.7)	53 (12.1)	48 (12.4)	6 (1.2)	7 (1.6)	3 (0.8)	1 (0.2)	1 (0.2)	1 (0.3)	26 (10.7)	20 (9.6)	14 (8.1)	1 (0.4)	0	0	1 (0.4)	0	0
Lipids (increased)[b]	n=439	n=369	n=316	n=439	n=369	n=316	n=439	n=369	n=316	n=203	n=176	n=142	n=203	n=176	n=142	n=203	n=176	n=142
Total cholesterol	158 (36.0)	113 (30.6)	116 (36.7)	20 (4.6)	26 (7.0)	19 (6.0)	2 (0.5)	1 (0.3)	1 (0.3)	83 (40.9)	80 (45.5)	64 (45.1)	22 (10.8)	22 (12.5)	19 (13.4)	0	0	1 (0.7)
Triglycerides	79 (18.0)	61 (16.5)	48 (15.2)	38 (8.7)	19 (5.1)	13 (4.1)	3 (0.7)	4 (1.1)	4 (1.3)	45 (22.2)	30 (17.0)	27 (19.0)	16 (7.9)	12 (6.8)	11 (7.7)	4 (2.0)	3 (1.7)	3 (2.1)

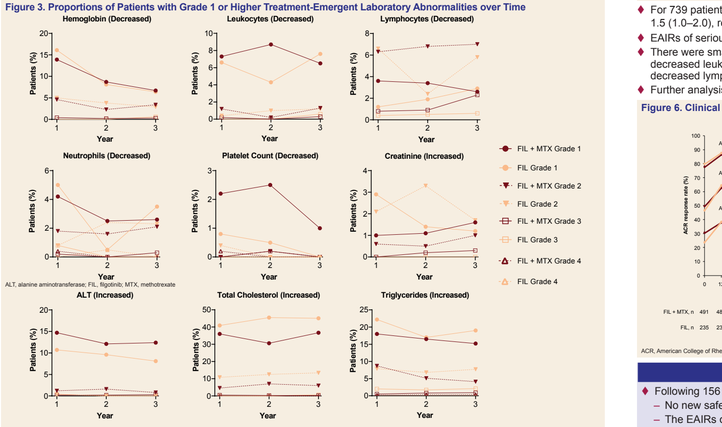
[a]For the week 156 interim analysis, patients enrolled from DARWIN 1 were grouped as FIL + MTX and those from DARWIN 2 as FIL monotherapy. 19 patients enrolled from DARWIN 2 had MTX exposure during DARWIN 3 but were grouped as FIL monotherapy; [b]All lipids reported using fasting data
ALT, alanine aminotransferase; FIL, filgotinib; MTX, methotrexate

Table 4. Rates of AEs of Special Interest at Week 156 (TE and non-TE)

Events/100 PYE (# events)	FIL + MTX[a] n=497 (PYE=1,511)	FIL monotherapy[a] n=242 (PYE=692)
Herpes zoster	1.5 (23)	1.6 (11)
Serious infections	0.9 (13)	2.0 (14)
Malignancy excluding NMSC	0.4 (6)	0.7 (5)
NMSC	0.4 (6)	0.1 (1)
Major adverse cardiac events[b]	0.1 (2)	0.1 (1)
Deep vein thrombosis and pulmonary embolism	0.1 (2)[c]	0
Active tuberculosis	0	0

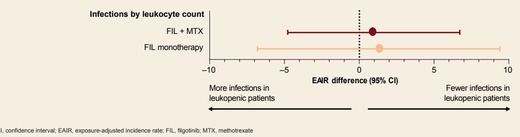
Adverse events with onset date on or after filgotinib first dose date in the core studies or DARWIN 3 were included
[a]For the week 156 interim analysis, patients enrolled from DARWIN 1 were grouped as FIL + MTX and those from DARWIN 2 as FIL monotherapy. 19 patients enrolled from DARWIN 2 had MTX exposure during DARWIN 3 but were grouped as FIL monotherapy; [b]Positively adjudicated events; [c]1 deep vein thrombosis and 1 recurrent pulmonary embolism with fatal outcome
AE, adverse event; FIL, filgotinib; MTX, methotrexate; NMSC, nonmelanoma skin cancer; PYE, patient-years of exposure; TE, treatment-emergent

Figure 3. Proportions of Patients with Grade 1 or Higher Treatment-Emergent Laboratory Abnormalities over Time



ALT, alanine aminotransferase; FIL, filgotinib; MTX, methotrexate

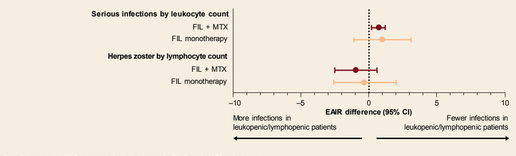
Figure 4. Difference in Incidence of Infections by Leukocyte Count



CI, confidence interval; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; MTX, methotrexate

- For 739 patients in DARWIN 3, the exposure-adjusted incidence rate (EAIR) for infections was 17.7 (95% confidence interval [CI], 15.9–19.4)
- EAIRs of infection were similar for patients with normal and decreased leukocyte counts
- There were 330 infections in 622 patients with normal leukocytes and 50 infections in 116 patients with decreased leukocytes

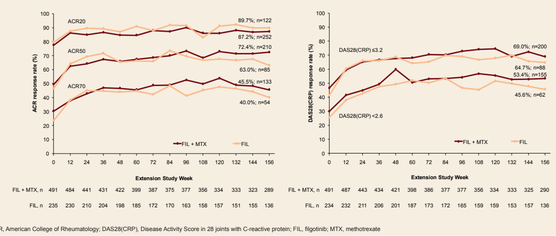
Figure 5. Differences in Incidence of Serious Infections by Leukocyte Count and Herpes Zoster Infection Incidence by Lymphocyte Count



CI, confidence interval; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; MTX, methotrexate

- For 739 patients in DARWIN 3, the EAIRs for serious and herpes zoster (HZV) infections were 1.0 (0.5–1.4) and 1.5 (1.0–2.0), respectively
- EAIRs of serious and HZV infections were similar for patients with normal and decreased leukocyte counts
- There were small numbers of serious infections (20 in patients with normal leukocyte counts and 1 in a patient with decreased leukocytes) and HZV infections (21 in patients with normal lymphocyte counts and 12 in patients with decreased lymphocytes)
- Further analysis of the relationship between the onset of lymphopenia and HZV infection is planned across all FIL trials in RA

Figure 6. Clinical Efficacy Using Observed Cases by ACR20/50/70 and DAS28(CRP) Response



ACR, American College of Rheumatology; DAS28(CRP), Disease Activity Score in 28 joints with C-reactive protein; FIL, filgotinib; MTX, methotrexate

Conclusions

- Following 156 weeks of treatment with FIL:
  - No new safety signals emerged
  - The EAIRs of serious and HZV infections in DARWIN 3 were:
    - Serious infections: 1.0 (95% CI, 0.5–1.4)
    - HZV infections: 1.5 (95% CI, 1.0–2.0)
  - There appeared to be no important safety difference between patients receiving FIL 200 mg as monotherapy or in combination with MTX
  - Efficacy could be sustained for some patients up through week 156 in both the monotherapy and MTX combination groups

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

CA is an employee of Gilead Sciences, Inc., and may hold shares. **AK** reports research support, honoraria or personal fees from Abbott, Amge, AstraZeneca, Bristol-Myers Squibb, Celgene Corporation, Centocor-Janssen, Eli Lilly and Company, Gilead Sciences, Inc., Janssen Research & Development, LLC, Novartis, Pfizer, Inc., Roche and UCB Pharma. **RRW** reports research support, honoraria or personal fees from Celltrion, Inc., Galapagos NV and Gilead Sciences, Inc. **KLW** reports research support, honoraria or personal fees from AbbVie, Inc., Bristol-Myers Squibb, Eli Lilly and Company, Galapagos NV, Gilead Sciences, Inc., GSK; Pfizer, Inc., Roche and UCB Pharma. **SJL, JMG, ADZ, DA, LY** and **JSS** are all employees of Gilead Sciences, Inc., and may hold shares. **RB** and **LM** are employees of Galapagos NV. **RA** reports research support, honoraria or personal fees from Galapagos NV, Gilead Sciences, Inc., Novartis and Pfizer, Inc. **MCG** reports others from Gilead Sciences, Inc., Galapagos NV, AbbVie, Inc. and Pfizer, Inc.

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