SUPPLEMENTAL MATERIAL

Supplemental Methods

In the first Phase 2 study (NCT01888874), patients receiving background methotrexate (MTX) were randomised 1:1:1:1:1:1 to placebo (PBO) or filgotinib 200 mg once daily (QD), 100 mg QD or twice daily (BID), or 50 mg QD or BID for 24 weeks.[1] In the second Phase 2 study (NCT01894516), patients were randomised 1:1:1:1 to PBO or filgotinib 200, 100, or 50 mg QD monotherapy for 24 weeks.[2] Patients completing the parent Phase 2 studies could enter the open-label long-term extension (NCT02065700) and receive filgotinib 200 mg QD or 100 mg BID (for males in the USA, 100 mg QD).[3]

In the first Phase 3 study (NCT02889796), patients were randomised 3:3:2:3 to filgotinib 200 mg QD, 100 mg QD, adalimumab (ADA), or PBO for 24 weeks.[4] At week 24, patients assigned to PBO were rerandomised 1:1 to filgotinib 200 or 100 mg QD up to week 52; patients receiving filgotinib or ADA continued to week 52.[4] In the second Phase 3 study (NCT02873936), patients were randomised 1:1:1 to filgotinib 200 or 100 mg QD or PBO for 24 weeks.[5] In the third Phase 3 study (NCT02886728), patients were randomised 2:1:1:2 to filgotinib 200 mg QD with MTX, filgotinib 100 mg QD with MTX, filgotinib 200 mg QD, or MTX for 52 weeks.[6] Eligible patients completing the parent Phase 3 studies could enter the open-label long-term extension (LTE; NCT03025308) and receive blinded filgotinib 200 or 100 mg QD; patients receiving PBO, ADA, or MTX were rerandomised 1:1 to filgotinib 200 or 100 mg QD.

Winthrop KL, *et al. Ann Rheum Dis* 2021;0:1–9. doi: 10.1136/annrheumdis-2021-221051

References

1. Westhovens R, Taylor PC, Alten R, et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). *Ann Rheum Dis*. 2017;76(6):998-1008.

2. Kavanaugh A, Kremer J, Ponce L, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). *Ann Rheum Dis*. 2017;76(6):1009-19.

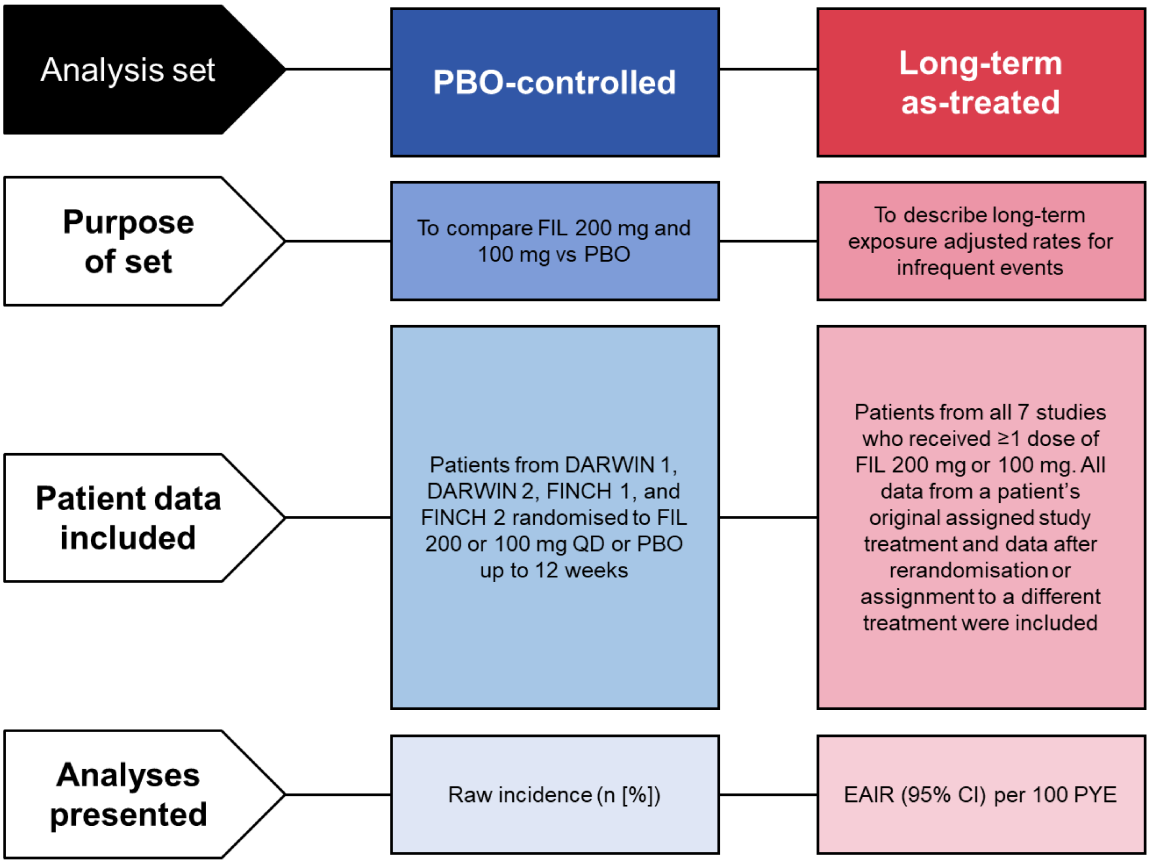
3. Kavanaugh A, Westhovens R, Winthrop K, et al. Safety and efficacy of filgotinib: up to 4-year results from an open-label extension study of phase II rheumatoid arthritis programs. *J Rheumatol*. 2021;48:1230-8.

4. Combe B, Kivitz A, Tanaka Y, et al. Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. *Ann Rheum Dis*. 2021;80:848-58.

5. Genovese MC, Kalunian K, Gottenberg JE, et al. Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomized clinical trial. *JAMA*. 2019;322(4):315-25.

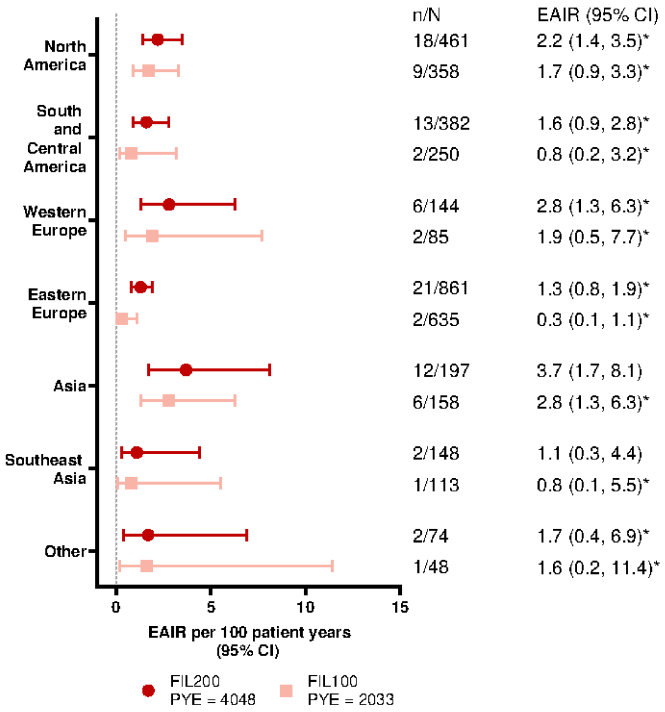
6. Westhovens R, Rigby WFC, van der Heijde D, et al. Filgotinib in combination with methotrexate or as monotherapy versus methotrexate monotherapy in patients with active rheumatoid arthritis and limited or no prior exposure to methotrexate: the phase 3, randomised controlled FINCH 3 trial. *Ann Rheum Dis*. 2021;80:727-38.

Figure S1. Safety analysis sets



CI, confidence interval; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; PBO, placebo; PYE, patient-years exposure; QD, once daily.

Figure S2. Exposure-adjusted incidence rate of herpes zoster infection/reactivation by geographic region, long-term, as-treated dataset



Asia includes Japan, Taiwan, Republic of Korea, and Hong Kong. **Southeast Asia** includes India, Thailand, and Malaysia. **Other** includes South Africa, New Zealand, Australia, and Israel. EAIR, exposure-adjusted incidence rate; FIL, filgotinib; PYE, patient years of exposure.

Table S1. Causes of all deaths in the long-term, as-treated analysis set

Study	Treatment	Study day	Treatment emergent?	Cause of death
DARWIN 3	FIL 200 mg QD	420	No	Pneumonia
DARWIN 3	FIL 200 mg QD	706	No	Non-Hodgkin's lymphoma
DARWIN 3	FIL 200 mg QD	541	No	Non-Hodgkin's lymphoma
FINCH 1	PBO	14	Yes	Toxic reaction to amoksiklav
FINCH 1	PBO, FIL 200 mg QD	224	Yes	Acute deep vein thrombosis
FINCH 1	PBO	84	No	Septic shock
FINCH 1	FIL 200 mg QD	30	Yes	Septic shock secondary to multisegmental pneumonia
FINCH 1	PBO, FIL 100 mg QD	368	Yes	Varicella
FINCH 1	FIL 200 mg QD	234	No	Alveolitis
FINCH 1	FIL 200 mg QD	123	Yes	Septic shock
FINCH 1	FIL 100 mg QD	14	Yes	Myocardial infarction
FINCH 3	FIL 200 mg QD	279	No	Unknown – likely cardiac-related
FINCH 3	FIL 200 mg QD	274	Yes	Atypical interstitial pneumonia
FINCH 3	FIL 100 mg QD	318	Yes	Subarachnoid haemorrhage of left middle cerebral artery
FINCH 3	FIL 200 mg QD	7	Yes	Lupus myocardiopathy
FINCH 4	FIL 200 mg QD	268	Yes	Initial: ischaemic stroke; secondary: sepsis; direct: heart failure
FINCH 4	FIL 200 mg QD	237	Yes	Metastatic adenocarcinoma of the lung
FINCH 4	FIL 200 mg QD	499	Yes	Acute myocardial infarction
FINCH 4	FIL 200 mg QD	189	Yes	Refractory septic shock
FINCH 4	FIL 200 mg QD	637	No	Squamous cell carcinoma of the oesophagus
FINCH 4	FIL 200 mg QD	468	No	Worsening of *Staphylococcus aureus* and severe dysphagia
FINCH 4	FIL 200 mg QD	237	Yes	Heart failure caused by pericardial effusion due to neoplasm
FINCH 4	FIL 200 mg QD	104	Yes	Exudative pericarditis with thrombosis of inferior vena cava and left brachiocephalic vein

FINCH 4	FIL 200 mg QD	NP	Yes	Stroke
FINCH 4	FIL 100 mg QD	241	Yes	Acute left ventricular failure
FINCH 4	FIL 100 mg QD	132	Yes	Cardiac arrest
FINCH 4	FIL 100 mg QD	117	Yes	Cardiorespiratory failure

Treatment-emergent AEs (TEAEs) were defined as any AE with an onset date on or after the first dose of study drug and no later than the earliest date of either 30 days after the last dose of study drug or the first dose date of the switched treatment minus 1 day.

FIL, filgotinib; NP, not provided; PBO, placebo; QD, once daily.

Table S2: Graded laboratory abnormalities in the PBO-controlled analysis set

	FIL 200 mg N = 777	FIL 100 mg N = 788	PBO N = 781
Haemoglobin decreased, any grade, n/N (%)	87/776 (11.2)	106/786 (13.5)	150/776 (19.3)
G2, n (%)	14 (1.8)	29 (3.7)	28 (3.6)
G3, n (%)	3 (0.4)	1 (0.1)	6 (0.8)
Platelets decreased, any grade, n/N (%)	14/776 (1.8)	19/786 (2.4)	14/776 (1.8)
G2, n (%)	0	2 (0.3)	0
G3, n (%)	0	0	0
G4, n (%)	0	0	0
Neutrophils decreased, any grade, n/N (%)	75/775 (9.7)	37/786 (4.7)	31/776 (4.0)
G2, n (%)	18 (2.3)	9 (1.1)	6 (0.8)
G3, n (%)	8 (1.0)	3 (0.4)	3 (0.4)
G4, n (%)	0	2 (0.3)	0
Lymphocytes decreased, any grade, n/N (%)	61/775 (7.9)	44/786 (5.6)	64/776 (8.2)
G2, n (%)	40 (5.2)	31 (3.9)	37 (4.8)
G3, n (%)	7 (0.9)	3 (0.4)	4 (0.5)
G4, n (%)	0	1 (0.1)	0
ALT increased, any grade, n/N (%)	122/776 (15.7)	113/786 (14.4)	92/776 (11.9)
G2, n (%)	10 (1.3)	7 (0.9)	6 (0.8)
G3, n (%)	1 (0.1)	0	1 (0.1)
G4, n (%)	0	0	0
AST increased, any grade, n/N (%)	111/776 (14.3)	93/786 (11.8)	70/776 (9.0)
G2, n (%)	3 (0.4)	2 (0.3)	3 (0.4)
G3, n (%)	2 (0.3)	1 (0.1)	0
G4, n (%)	0	0	0
Creatinine increased, any grade, n/N (%)	23/776 (3.0)	11/786 (1.4)	9/776 (1.2)
G2, n (%)	11 (1.4)	2 (0.3)	1 (0.1)
G3, n (%)	0	1 (0.1)	2 (0.3)
G4, n (%)	0	0	0
Creatine kinase increased, any grade, n/N (%)[a]	92/621 (14.8)	64/631 (10.1)	30/618 (4.9)
G2, n (%)	9 (1.4)	2 (0.3)	3 (0.5)
G3, n (%)	1 (0.2)	0	3 (0.5)
G4, n (%)	1 (0.2)	2 (0.3)	0
Fasting HDL low, any increase or decrease, n/N (%)	42/575 (7.3)	62/567 (10.9)	108/555 (19.5)
Normal (≥40–<60 mg/dL), n (%)	36 (6.3)	39 (6.9)	76 (13.7)
Low (<40 mg/dL), n (%)	6 (1.0)	23 (4.1)	32 (5.8)

Fasting LDL high, any increase, n/N (%)	238/575 (41.4)	219/567 (38.6)	140/555 (25.2)
Near optimal (≥100–<130 mg/dL), n (%)	70 (12.2)	79 (13.9)	60 (10.8)
Borderline high (≥130–<160 mg/dL), n (%)	92 (16.0)	85 (15.0)	47 (8.5)
High (≥130–<160 mg/dL), n (%)	55 (9.6)	40 (7.1)	22 (4.0)
Very high (≥160 mg/dL), n (%)	21 (3.7)	15 (2.6)	11 (2.0)

[a]Including patients from Phase 3 studies only.

Abnormality grade was based on CTCAE v 4.03 criteria. No patient fulfilled Hy's law criteria.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; FIL, filgotinib; G, Grade; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PBO, placebo.