Summary Report of Benefit-Risk Assessment

JYSELECA FILM-COATED TABLET 100MG AND 200MG

NEW DRUG APPLICATION

Active Ingredient(s)	Filgotinib maleate
Product Registrant	Eisai (Singapore) Pte. Ltd.
Product Registration Number	SIN16980P and SIN16981P
Application Route	Abridged evaluation
Date of Approval	27 March 2024

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A INTRODUCTION

Jyseleca is indicated for the treatment of:

- Moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Jyseleca may be used as monotherapy or in combination with methotrexate (MTX).
- Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.

The active substance, filgotinib, is an adenosine triphosphate (ATP)-competitive and reversible inhibitor of the janus kinase (JAK) family, with preferential inhibition of JAK-1/2 involved in inflammatory cytokine signalling. Filgotinib modulates the JAK-signal transducer and activator of transcription (STAT) pathway, which is implicated in several inflammatory pathologies, by preventing the phosphorylation and activation of STATs, therefore resulting in reduced proinflammatory cytokine signalling.

Jyseleca is available as film-coated tablets containing 100 mg and 200 mg of filgotinib. Other ingredients in the tablet cores are microcrystalline cellulose, lactose monohydrate, pregelatinized starch, colloidal silicon dioxide, fumaric acid and magnesium stearate. Ingredients in the film coating include polyvinyl alcohol, titanium dioxide (E171), macrogol, talc iron oxide yellow (E172) and iron oxide red (E172).

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, filgotinib maleate, is manufactured at Gilead Alberta ULC, Canada and Cambrex Charles City Inc, United States. The drug product, Jyseleca Film-Coated Tablet 200 mg and 100 mg, are manufactured at Rottendorf Pharma GmbH, Nordrhein-Westfalen, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities were adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A and the impurity limits have been appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The packaging is double polyethylene bags closed with plastic or wire ties and contained in a heat sealed, polyethylene-lined aluminum foil pouch, and stored in high-density polyethylene

drums. The stability data presented was adequate to support the storage of the drug substance below 30ºC with a re-test period of 24 months.

Drug product:

The manufacturing of the drug product, Jyseleca Film-Coated Tablet 200 mg and 100 mg, involved dry granulation and tablet compression followed by film-coating which are standard process for tablet dosage form.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The container closure system is a PVC/PCTFE/aluminium foil blister pack containing 14 tablets, stored in an aluminium pouch with silica gel desiccant. The stability data submitted was adequate to support the approved shelf-life of 36 months when stored below 30ºC.

C ASSESSMENT OF CLINICAL EFFICACY

Clinical efficacy in rheumatoid arthritis (RA)

The clinical efficacy of filgotinib for the treatment of moderate to severe RA was based on four studies in adult subjects with moderately to severely active RA who had responded inadequately to DMARDs:

- Phase 3 study GS-US-417-0301 (FINCH 1): Combination with methotrexate (MTX) in MTX inadequate responders (MTX-IR) (second-line);
- Phase 3 study GS-US-417-0302 (FINCH 2): Combination with conventional disease modifying anti-rheumatic drugs (cDMARD) in biologic DMARD (bDMARD) inadequate responders (second- or third-line);
- Phase 2 study GLPG0634-CL-204 (DARWIN 2): Monotherapy in MTX-IR (second-line); and
- Phase 3 long-term extension study GS-US-417-0304 (FINCH 4).

The design and results of the studies are summarised in Tables 1 and 2.

The primary efficacy endpoint of the studies was the proportion of subjects who achieved an American College of Rheumatology 20% improvement (ACR20) response at Week 12, defined as ≥20% improvement from baseline in total joint count (TJC), swollen joint count (SJC), and at least 3 of the following 5 items: Physician's Global Assessment (PGA), Subject's Global Assessment (SGA), Subject's Pain Assessment, Health Assessment Questionnaire-Disability Index (HAQ-DI) score, and high-sensitivity C-reactive protein (hsCRP). The key secondary endpoints included the change from baseline in the HAQ-DI score, 36-Item Short Form Survey (SF-36) Physical Component Summary (PCS) score and Functional Assessment of Chronic

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Illness Therapy-Fatigue (FACIT-Fatigue) score at Week 12 and in the van der Heijde modified Total Sharp Score (mTSS) at Week 24, as well as the proportion of subjects who achieved Disease Activity Score for 28 Joint Count using C-reactive Protein (DAS28-CRP) <2.6 and DAS28-CRP ≤3.2 at Week 12. Multiplicity was controlled via hierarchical testing procedures. The endpoints and statistical methods employed were considered to be appropriate.

Across the studies, the results showed that when compared to placebo, filgotinib as second-line monotherapy or in combination with MTX or other DMARDs as second- and third-line therapies resulted in statistically significantly higher ACR20 (range 57.5% to 76.6% vs 29.2% to 49.9%) and low disease activity responder rates (range 27.1% to 49.7% vs 13.9% to 23.4%) as well as lesser structural damage (mTSS range 0.13 to 0.17 vs 0.37). When compared to the active comparator adalimumab, filgotinib also resulted in similar or statistically significantly better improvements in the endpoints (ACR20 responder rates range 69.8 to 76.6% vs 70.8%, disease activity responder rates range 38.8% to 49.7% vs 43.4%, mTSS range 0.13 to 0.17 vs 0.16).

The use of filgotinib as monotherapy was not investigated beyond the second-line setting. Nonetheless, given that the efficacy in terms of ACR20 and low disease activity responder rates were similar for third-line versus second-line filgotinib combination therapies, the results of filgotinib second-line monotherapy could be reasonably extrapolated to third-line monotherapy.

Overall, the clinical efficacy of filgotinib in moderate to severe RA patients was considered to be adequately demonstrated as there were similar or statistically significant improvements in clinically relevant endpoints such as ACR20 and low disease activity responder rates as well as lesser structural damage in the filgotinib groups compared to the placebo group or adalimumab. Comparing the two filgotinib doses investigated, 200 mg produced numerically better results compared to 100 mg, and the effects of filgotinib could be maintained till Week 48.

Table 1: Study design for RA studies

Study	Study design	Study population	Demographics and baseline characteristics	Endpoints
FINCH 1 (52 weeks)	Phase 3, randomised, double-blind, placebo- and active-controlled study (N=1,755)	Adult subjects with moderately to severely active RA; methotrexate inadequate responders (MTX-IR)	The majority of subjects were female (81.8%) and White (67.5%), and 23.4% were Asian. The mean age was 53 years (range: 18 to 86 years) and 18.9% of subjects were at least 65 years of age. 47 subjects (2.7%) were exposed to bDMARDs.	Primary Proportion of subjects who achieved an ACR20 response at Week 12. Key secondary • Change from baseline in the HAQ-DI score at Week 12 • Proportion of subjects who achieved DAS28-CRP <2.6 at Week 12 • Change from baseline in the mTSS at Week 24 • Proportion of subjects who achieved DAS28-CRP ≤3.2 at Week 12 • Change from baseline in SF-36 PCS score at Week 12 • Change from baseline in FACIT-Fatigue score at Week 12
FINCH 2 (24 weeks)	Phase 3, randomised, double-blind, placebo-controlled study (N=448)	Adult subjects with moderately to severely active RA; biologic disease modifying anti-rheumatic drug	The majority of subjects were female (80.4%) and White (70.5%), and 11.2% were Asian. The mean age was 56 years (range: 20 to 83 years)	Primary Proportion of subjects who achieved an ACR20 response at Week 12. Key secondary

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		inadequate responders (bDMARD-IR)	and 25.2% of subjects were at least 65 years of age. 105 subjects (23.4%) were exposed to 3 or more bDMARDs.	• Change from baseline in the HAQ-DI score at Week 12 • Proportion of subjects who achieved DAS28-CRP ≤3.2 at Week 12 • Change from baseline in SF-36 PCS score at Week 12 • Proportion of subjects who achieved DAS28-CRP <2.6 at Week 24 • Change from baseline in FACIT-Fatigue score at Week 12
DARWIN 2 (24 weeks)	Phase 2b, randomised, double-blind, placebo-controlled, monotherapy, dose-finding study (N=283)	Adult subjects with moderately to severely active RA; MTX-IR	The majority of subjects were female (86.1%) and White (75.3%). The mean age was 52 years. All subjects had used prior RA medication such as cDMARDs (97.5%), steroids (66.8%), NSAIDs (61.8%) and analgesics (18.0%).	Primary Proportion of subjects who achieved an ACR20 response at Week 12. Key secondary • Proportion of subjects who achieved ACR50/70 response at Week 12 • ACR/EULAR remission rate, defined as scores on TJC28, SJC28, CRP, and Patient Global Assessment of Disease Activity were all ≤1 • Change from baseline in DAS28-CRP to Week 12 and Week 24 • Proportion of subjects who achieved DAS28-CRP remission (i.e., DAS28-CRP score <2.6) at Week 12 • Proportion of subjects who achieved DAS28-CRP remission or low disease activity (LDA) at Week 12 • Change from baseline in Clinical Disease Activity Index (CDAI) • Change from baseline in Simplified Disease Activity Index (SDAI)
FINCH 4 (6 years, ongoing)	Phase 3, double-blind, long-term extension (LTE) study (N=2,423)	Eligible subjects who had completed parent FINCH studies listed above.	The majority of subjects were female (80.3%) and White (69.4%), and 19.4% were Asian. The mean age was 54 years (range: 19 to 87 years) and 21.7% of subjects were at least 65 years of age. 637 subjects (26.3%) were exposed to prior bDMARDs.	• ACR 20/50/70 response rate • Rate of DAS28-CRP <2.6 and ≤3.2

Table 2: Efficacy results for RA studies

Study	Treatment arms	Results				
		Endpoint	Filgotinib dose	Comparator	Primary Analysis (On-Treatment Data)	
					Filgotinib vs Comparator Difference (95% CI)	p-value
FINCH 1	Combination with MTX (2nd-line): • Filgotinib 200 mg QD (N=475) • Filgotinib 100 mg QD (N=480) • Adalimumab 40 mg SC Q2W (N=325) • Placebo (N=475)	ACR20 (%)	200 mg	Placebo	76.6 vs 49.9 26.7 (20.6, 32.8)	<0.001
		ACR20 (%)	100 mg	Placebo	69.8 vs 49.9 19.9 (13.6, 26.2)	<0.001
		Change in HAQ-DI Mean (95% CI)	200 mg	Placebo	-0.69 vs -0.42 -0.29 (-0.36, -0.22)	<0.001
		Change in HAQ-DI	100 mg	Placebo	-0.56 vs -0.42	<0.001

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		Mean (95% CI)			-0.17 (-0.24, -0.10)	
		DAS28-CRP <2.6 (%)	200 mg	Placebo	34.1 vs 9.3 24.8 (19.6, 30.0)	<0.001
		DAS28-CRP <2.6 (%)	100 mg	Placebo	23.8 vs 9.3 14.5 (9.7, 19.3)	<0.001
		Change in mTSS Mean (95% CI)	200 mg	Placebo	0.13 vs 0.37 -0.27 (-0.43, -0.12)	<0.001
		Change in mTSS Mean (95% CI)	100 mg	Placebo	0.17 vs 0.37 -0.25 (-0.40, -0.10)	0.001
		DAS28-CRP ≤3.2 (%)	200 mg	Adalimumab	49.7 vs 43.4[a]	<0.001[a]
		DAS28-CRP ≤3.2 (%)	100 mg	Adalimumab	38.8 vs 43.4[a]	0.054[a]
		Change in SF-36 PCS Mean (95% CI)	200 mg	Placebo	9.2 vs 5.8 3.7 (2.8, 4.6)	<0.001[b]
		Change in SF-36 PCS Mean (95% CI)	100 mg	Placebo	8.5 vs 5.8 3.1 (2.2, 4.0)	<0.001[b]
		Change in FACIT-Fatigue Score Mean (95% CI)	200 mg	Placebo	9.2 vs 6.8 2.8 (1.7, 3.9)	<0.001[b]
		Change in FACIT-Fatigue Score Mean (95% CI)	100 mg	Placebo	9.1 vs 6.8 2.6 (1.5, 3.7)	<0.001[b]
		DAS28-CRP ≤3.2 (%)	200 mg	Adalimumab	49.7 vs 43.4 6.3 (-1.0, 13.6)	0.069[b]
		DAS28-CRP ≤3.2 (%)	100 mg	Adalimumab	38.8 vs 43.4 -4.6 (-11.8, 2.6)	0.18[b]
		DAS28-CRP <2.6 (%)	200 mg	Adalimumab	34.1 vs 23.7[a]	<0.001[a,b]
		DAS28-CRP <2.6 (%)	100 mg	Adalimumab	23.8 vs 23.7[a]	0.002[a,b]
		DAS28-CRP <2.6 (%)	200 mg	Adalimumab	34.1 vs 23.7 10.4 (3.9, 17.0)	0.001[b]
		DAS28-CRP <2.6 (%)	100 mg	Adalimumab	23.8 vs 23.7 0.1 (-6.2, 6.3)	0.99[b]

[a] Non-inferiority test.
[b] Nominal p-value.

FINCH 2

Combination with cDMARDs (3rd-line):
- Filgotinib 200 mg QD (N=147)
- Filgotinib 100 mg QD (N=153)
- Placebo (N=148)

Endpoint	Filgotinib dose	Primary Analysis (On-Treatment Data)	
		Filgotinib vs Placebo Difference (95% CI)	p-value
ACR20 (%)	200 mg	66.0 vs 31.1 34.9 (23.5, 46.3)	<0.001
ACR20 (%)	100 mg	57.5 vs 31.1 26.4 (15.0, 37.9)	<0.001
Change in HAQ-DI Mean (95% CI)	200 mg	-0.55 vs -0.23 -0.32 (-0.45, -0.19)	<0.001
Change in HAQ-DI Mean (95% CI)	100 mg	-0.48 vs -0.23 -0.27 (-0.40, -0.14)	<0.001
DAS28-CRP ≤3.2 (%)	200 mg	40.8 vs 15.5 25.3 (14.7, 35.8)	<0.001
DAS28-CRP ≤3.2 (%)	100 mg	37.3 vs 15.5 21.7 (11.4, 32.0)	<0.001
Change in SF-36 PCS Mean (95% CI)	200 mg	7.6 vs 3.6 4.3 (2.5, 6.1)	<0.001

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		Change in SF-36 PCS Mean (95% CI)	100 mg	6.8 vs 3.6 3.4 (1.6, 5.2)	<0.001
		DAS28-CRP <2.6 (%)	200 mg	30.6 vs 12.2 18.5 (8.6, 28.3)	<0.001
		DAS28-CRP <2.6 (%)	100 mg	26.1 vs 12.2 14.0 (4.6, 23.4)	0.003
		Change in FACIT-Fatigue Score Mean (95% CI)	200 mg	9.6 vs 4.5 5.0 (2.6, 7.3)	<0.001
		Change in FACIT-Fatigue Score Mean (95% CI)	100 mg	8.3 vs 4.5 3.2 (0.9, 5.5)	0.007

DARWIN 2

Monotherapy (2nd-line):

- Filgotinib 50 mg QD (N=72)
- Filgotinib 100 mg QD (N=70)
- Filgotinib 200 mg QD (N=69)
- Placebo QD (N=72)

Endpoint	Placebo	Filgotinib QD dose groups		
		50 mg	100 mg	200 mg
ACR20 responder Week 12, n (%)	21 (29.2)	48 (66.7)	46 (65.7)	50 (72.5)
p-value vs placebo		<0.0001	<0.0001	<0.0001
ACR20 responder Week 24, n (%)	-	41 (56.9)	55 (78.6)	46 (66.7)
ACR50 responder Week 12, n (%)	8 (11.1)	25 (34.7)	26 (37.1)	30 (43.5)
p-value vs placebo		0.0006	0.0005	<0.0001
ACR50 responder Week 24, n (%)	-	24 (33.3)	27 (38.6)	31 (44.9)
ACR70 responder Week 12, n (%)	2 (2.8)	6 (8.3)	13 (18.6)	9 (13.0)
p-value vs placebo		0.1184	0.0095	0.0274
ACR70 responder Week 24, n (%)	-	14 (19.4)	18 (25.7)	17 (24.6)
DAS28-CRP change from baseline to Week 12, Mean (SE)	-0.99 (0.163)	-1.75 (0.145)	-2.04 (0.162)	-2.32 (0.155)
p-value vs placebo		0.0002	<0.0001	<0.0001
DAS28-CRP change from baseline to Week 24, Mean (SE)	-	-1.95 (0.168)	-2.61 (0.163)	-2.62 (0.165)
DAS28-CRP remission rate at Week 12, n (%)	5 (6.9)	9 (12.5)	10 (14.3)	12 (17.4)
p-value vs placebo		0.3024	0.2599	0.1291
DAS28-CRP remission rate at Week 24, n (%)	-	14 (19.4)	15 (21.4)	17 (24.6)
DAS28-CRP remission or LDA rate at Week 12, n (%)	10 (13.9)	17 (23.6)	19 (27.1)	31 (44.9)
p-value vs placebo		0.1229	0.0621	<0.0001
DAS28-CRP remission or LDA rate at Week 24, n (%)	-	25 (34.7)	35 (50.0)	29 (42.0)
SDAI remission rate at Week 12	2 (2.8)	2 (2.8)	5 (7.1)	5 (7.2)
p-value vs placebo		0.9481	0.4084	0.3572
SDAI remission rate at Week 24	-	8 (11.1)	8 (11.4)	8 (11.6)
CDAI remission rate at Week 12	2 (2.8)	2 (2.8)	4 (5.7)	6 (8.7)
p-value vs placebo		0.9487	0.7181	0.3329
CDAI remission rate at Week 24	-	9 (12.5)	8 (11.4)	9 (13.0)
ACR/EULAR remission rate at Week 12	1 (1.4)	1 (1.4)	3 (4.3)	3 (4.3)
p-value vs placebo		0.9460	0.6423	0.6665
HAQ-DI change from baseline to Week 12, Mean (SE)	-0.226 (0.0699)	-0.661 (0.0832)	-0.677 (0.0754)	-0.739 (0.0758)

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		p-value vs placebo		<0.0001	<0.0001	<0.0001
		HAQ-DI change from baseline to Week 24, Mean (SE)	-	-0.690 (0.0850)	-0.786 (0.0775)	-0.850 (0.0802)
FINCH 4	• Filgotinib 200 mg QD (N=1,530) • Filgotinib 100 mg QD (N=1,199)		**Filgotinib 200mg**			**Filgotinib 100mg**	
			With prior Filgotinib exposure (N=1,195)	**Without prior Filgotinib exposure (N=335)**	**Total Filgotinib 200 mg (N=1,530)**	**With prior Filgotinib exposure (N=863)**	**Without prior Filgotinib exposure (N=336)**	**Total Filgotinib 100 mg (N=1,199)**
		ACR20, n (%)					
		LTE Baseline	1084/1191 (91.0)	264/333 (79.3)	1348/1524 (88.5)	745/858 (86.8)	269/336 (80.1)	1014/1194 (84.9)
		LTE Week 48	997/1078 (92.5)	262/300 (87.3)	1259/1378 (91.4)	662/768 (86.2)	270/301 (89.7)	932/1069 (87.2)
		ACR50, n (%)					
		LTE Baseline	851/1187 (71.7)	202/324 (60.5)	1053/1521 (69.2)	576/855 (67.4)	212/336 (63.1)	788/1191 (66.2)
		LTE Week 48	786/1079 (72.8)	223/301 (74.1)	1009/1380 (73.1)	501/771 (65.0)	200/300 (66.7)	701/1071 (65.5)
		ACR70, n (%)					
		LTE Baseline	625/1188 (52.6)	119/333 (35.7)	744/1521 (48.9)	358/856 (41.8)	139/334 (41.6)	497/1190 (41.8)
		LTE Week 48	558/1077 (51.8)	163/301 (54.2)	721/1378 (52.3)	338/774 (43.7)	141/300 (47.0)	479/1074 (44.6)
		DAS28-CRP <2.6					
		LTE Baseline	694/1191 (58.3)	151/334 (45.2)	845/1525 (55.4)	423/855 (49.5)	143/333 (42.9)	566/1188 (47.6)
		LTE Week 48	697/1078 (64.7)	192/301 (63.8)	889/1379 (64.5)	398/769 (51.8)	163/300 (54.3)	561/1069 (52.5)
		DAS28-CRP ≤3.2					
		LTE Baseline	919/1191 (77.2)	208/334 (62.3)	1127/1525 (73.9)	592/855 (69.2)	210/333 (63.1)	802/1188 (67.5)
		LTE Week 48	860/1078 (79.8)	229/301 (76.1)	1089/1379 (79.0)	540/769 (70.2)	226/300 (75.3)	766/1069 (71.7)

Clinical efficacy in ulcerative colitis (UC)

The clinical efficacy of filgotinib in the treatment of UC was based primarily on one pivotal Phase 2b/3 study GS-US-418-3898 (SELECTION) and the long-term extension safety study GS-US-418-3899 (SELECTION LTE) in adult subjects with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.

The design and results of the studies are summarised in Tables 3 and 4.

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For the induction phase of the pivotal study, the primary endpoint was the endoscopy/bleeding/stool frequency (EBS) remission rate at Week 10, defined as an endoscopic subscore of 0 or 1 (centrally read), rectal bleeding (RB) subscore of 0, and at least a 1-point decrease in stool frequency (SF) from baseline to achieve a subscore of 0 or 1. The secondary endpoints included the Mayo Clinic Score (MCS), MCS (alternative definition) and Geboes histologic remission rates and the proportion of subjects with an endoscopic subscore of 0 (centrally read) at Week 10. For the maintenance phase, the primary endpoint was the EBS remission rate at Week 58. The secondary endpoints included 6-month corticosteroid-free EBS, sustained EBS, MCS, MCS (alternative definition), Geboes histologic remission rates, and the proportion of subjects with an endoscopic subscore of 0 (centrally read) at Week 58. Multiplicity was controlled via the Bonferroni approach. The endpoints and statistical methods employed were considered to be appropriate.

The results showed a statistically significantly higher EBS remission rates at Week 10 (biologic-naïve: 26.1% vs 15.3%, p=0.0157, biologic-experienced: 11.5% vs 4.2%, p=0.0103) and Week 58 (pooled biologic-naïve and -experienced: 37.2% vs 11.2%, p<0.0001) with filgotinib 200 mg compared to placebo. For filgotinib 100 mg, the EBS remission rate was statistically significantly higher compared to placebo at Week 58 only (23.8% vs 13.5%, p=0.0420).

The key secondary endpoint of the proportion of subjects who achieved MCS remission was also statistically significantly or numerically higher in the filgotinib 200 mg group compared to placebo at Week 10 (biologic-naïve: 12.2% vs 4.4%, p=0.0105, biologic-experienced: 3.8% vs 2.1%, p=0.3084) and Week 58 (pooled biologic-naïve and -experienced: 34.7% vs 9.2%, p<0.0001). For the filgotinib 100 mg group, the proportion of subjects who achieved MCS remission was similar or numerically higher compared to the placebo at Week 10 (biologic-naïve: 8.7% vs 4.4%, p=0.1062, biologic-experienced: 2.1% vs 2.1%, p=0.9109) and Week 58 (pooled biologic-naïve and -experienced: 22.7% vs 13.5%, p=0.0658).

Overall, the clinical efficacy of filgotinib in moderately to severely active UC patients was considered to be adequately demonstrated based on statistically significantly higher EBS and MCS remission rates with filgotinib 200mg compared to placebo. Comparing the two filgotinib doses investigated, 200 mg produced numerically better results compared to 100 mg and the effects of filgotinib could be maintained till Week 108.

Table 3: Study design for UC studies

Study	Study design	Study population	Demographics and baseline characteristics	Endpoints
SELECTION (10 weeks induction and 58 weeks maintenance)	Phase 2b/3, randomised, double-blind, placebo-controlled, induction and maintenance study (N=1,351)	Adult subjects with moderately to severely active UC; biologic-naïve (Cohort A), biologic-experienced (Cohort B)	<u>Cohort A Induction</u> Most of the subjects were male (55.7%) and White (68.6%), and 29.4% were Asian. The mean age of subjects was 42 years (range: 18 to 73 years). The mean duration of UC from diagnosis to first dose of study drugs was 6.8 years. The mean MCS at baseline was 8.6, and 52.4% of subjects had an MCS ≥9. In total, 55.8% of subjects had an endoscopic subscore of 3 at baseline. The proportions of subjects taking only systemic corticosteroids or only immunomodulators at baseline were 23.5% and 22.6%, respectively. Overall, 7.1% of subjects were taking both systemic corticosteroids and immunomodulators, while 46.7% were	<u>Induction</u> <u>Primary</u> EBS remission at Week 10 <u>Key secondary</u> • MCS remission at Week 10, defined as MCS of 2 or less and no single subscore higher than 1 • Endoscopic subscore of 0 at Week 10 • Geboes histologic remission at Week 10 • MCS remission (alternative definition) at Week 10, defined as RB, SF, and Physician's Global Assessment subscores of 0 and

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			taking neither systemic corticosteroids nor immunomodulators. <u>Cohort B Induction</u> Most of the subjects were male (61.0%) and White (72.6%) or Asian (18.6%). The mean duration of UC from diagnosis to first dose of study drugs was 9.8 years. The mean MCS at baseline was 9.3, and 73.7% of subjects had an MCS ≥9. In total, 77.8% of subjects had an endoscopic subscore of 3 at baseline. The proportions of subjects taking only systemic corticosteroids or only immunomodulators at baseline were 36.0% and 12.9%, respectively. Overall, 9.7% of subjects were taking both systemic corticosteroids and immunomodulators, while 41.4% were taking neither systemic corticosteroids nor immunomodulators. <u>Maintenance</u> 58.9% of subjects entered the maintenance study from Cohort A (biologic-naive subjects) and 41.1% entered the maintenance study from Cohort B (biologic-experienced subjects). The mean duration of UC from diagnosis to baseline in the induction studies was 8.3 years. The proportions of subjects taking only systemic corticosteroids or only immunomodulators were 31.2% and 17.8%, respectively. Overall, 9.2% of subjects were taking both systemic corticosteroids and immunomodulators at baseline, while 41.9% of subjects were taking neither systemic corticosteroids nor immunomodulators	an endoscopic subscore of 0 or 1, and overall MCS of ≤1 <u>Maintenance</u> <u>Primary</u> EBS remission at Week 58 <u>Secondary</u> • 6-month corticosteroid-free EBS remission at Week 58 • Sustained EBS remission at Week 58, defined as EBS remission at both Week 10 and Week 58 • MCS remission at Week 58 • Endoscopic subscore of 0 at Week 58 • Geboes histologic remission at Week 58 • MCS remission (alternative definition) at Week 58
SELECTION LTE (108 weeks)	Phase 3, long-term safety study (N=1,161)	Eligible subjects who completed study SELECTION Note: Subjects who did not achieve clinical response or remission at Week 10 in SELECTION could receive filgotinib 200 mg for additional 12 weeks.	The mean age of subjects was 44 years. The majority of subjects were aged <65 years old (92.8%), male (59.2%), and most subjects were White (70.5%) or Asian (24.3%). Overall, 224 subjects (19.3%) were on systemic corticosteroids only, 224 subjects (19.3%) were on immunomodulators only, and 60 subjects (5.2%) were on both systemic corticosteroids and immunomodulators.	Change from baseline in partial MCS which included only the non-invasive components of the MCS such as SF, RB, and Physician's Global Assessment (PGA) (i.e., excluding endoscopic findings).

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Table 4: Efficacy results for UC studies

Study	Treatment arms	Results
SELECTION (10 weeks induction and 58 weeks maintenance)	▪ Filgotinib 200 mg QD ▪ Filgotinib 100 mg QD ▪ Placebo QD	See below

Induction

Number (%) of subjects:	Cohort A Induction Study (Biologic-naïve)			Cohort B Induction Study (Biologic-experienced)		
	Figotinib 200 mg (N=245)	Filgotinib 100 mg (N=277)	Placebo (N=137)	Filgotinib 200 mg (N=262)	Filgotinib 100 mg (N=285)	Placebo (N=142)
EBS remission	64 (26.1)	53 (19.1)	21 (15.3)	30 (11.5)	27 (9.5)	6 (4.2)
Difference vs PBO (%)	10.8	3.8	-	7.2	5.2	-
(95% CI)	(2.1, 19.5)	(-4.3, 12.0)	-	(1.6, 12.8)	(0.0, 10.5)	-
p-value	0.0157[a]	0.3379	-	0.0103[a]	0.0645	-
Endoscopic subscore 0	30 (12.2)	16 (5.8)	5 (3.6)	9 (3.4)	6 (2.1)	3 (2.1)
Difference vs PBO (%)	8.6	2.1	-	1.3	-0.0	-
(95% CI)	(2.9, 14.3)	(-2.6, 6.8)	-	(-2.5, 5.1)	(-3.4, 3.4)	-
p-value	0.0047[a]	0.3495	-	0.4269	0.9987	-
Geboes histologic remission	86 (35.1)	66 (23.8)	22 (16.1)	52 (19.8)	39 (13.7)	12 (8.5)
Difference vs PBO (%)	19.0	7.8	-	11.4	5.2	-
(95% CI)	(9.9, 28.2)	(-0.7, 16.2)	-	(4.2, 18.6)	(-1.4, 11.8)	-
p-value	<0.0001[a]	0.0672	-	0.0019	0.1286	-
MCS remission	30 (12.2)	24 (8.7)	6 (4.4)	10 (3.8)	6 (2.1)	3 (2.1)
Difference vs PBO (%)	7.9	4.3	-	1.7	-0.0	-
(95% CI)	(1.9, 13.8)	(-1.0, 9.6)	-	(-2.2, 5.6)	(-3.4, 3.4)	-
p-value	0.0105[a]	0.1062	-	0.3084	0.9109	-

[a] Statistically significant p-value (<0.02499)

Maintenance

Number (%) of subjects:	Induction Filgotinib 200 mg		Induction Filgotinib 100 mg	
	Maintenance Filgotinib 200 mg (N=199)	Maintenance Placebo (N=98)	Maintenance Filgotinib 100 mg (N=172)	Maintenance Placebo (N=89)
EBS remission	74 (37.2)	11 (11.2)	41 (23.8)	12 (13.5)
Difference vs PBO (%)	26.0	-	10.4	-
(95% CI)	(16.0, 35.9)	-	(-0.0, 20.7)	-
p-value	<0.0001[b]	-	0.0420[c]	-
6-month corticosteroid-free EBS remission (%)	25 (27.2)	3 (6.4)	11 (13.6)	2 (5.4)
Difference vs PBO (%)	20.8	-	8.2	-
(95% CI)	(7.7, 33.9)	-	(-4.2, 20.6)	-
p-value	0.0055[b]	-	0.1265	-
Sustained EBS remission	36 (18.1)	5 (5.1)	15 (8.7)	7 (7.9)

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		Difference vs PBO (%) (95% CI) p-value	13.0 (5.3, 20.6) 0.0024[b]	- - -	0.9 (-7.0, 8.7) 0.7951	- - -
		MCS remission Difference vs PBO (%) (95% CI) p-value	69 (34.7) 25.5 (16.0, 35.0) <0.0001[b]	9 (9.2) - - -	39 (22.7) 9.2 (-1.1, 19.5) 0.0658	12 (13.5) - - -
		Endoscopic subscore of 0 Difference vs PBO (%) (95% CI) p-value	31 (15.6) 9.5 (1.8, 17.1) 0.0157[b]	6 (6.1) - - -	23 (13.4) 5.5 (-2.9, 13.9) 0.1808	7 (7.9) - - -
		Geboes histologic remission Difference vs PBO (%) (95% CI) p-value	76 (38.2) 24.9 (14.6, 35.2) <0.0001[b]	13 (13.3) - - -	48 (27.9) 9.9 (-1.3, 21.2) 0.0521	16 (18.0) - - -
		[b] Statistically significant p-value (<0.025) [c] Statistically significant p-value (<0.05)				
SELECTION LTE (108 weeks)		The mean change from baseline in partial MCS at Weeks 12, 24, and 48 was as follows: • Week 12: filgotinib 200 mg −2.6, filgotinib 100 mg −1.0, and placebo −0.2 • Week 24: filgotinib 200 mg −3.1, filgotinib 100 mg −0.7, and placebo −0.3 • Week 48: filgotinib 200 mg −3.4, filgotinib 100 mg −1.4, and placebo 0.0				

D ASSESSMENT OF CLINICAL SAFETY

Safety data from the RA studies

The safety data of filgotinib for treatment of RA was derived from four Phase 3 studies (FINCH 1, FINCH 2, FINCH 3, and FINCH 4) and three Phase 2 studies (DARWIN 1, DARWIN 2, and DARWIN 3). A total of 4,120 subjects with RA had received at least one dose of filgotinib for a total of 7,218.36 patient-years of exposure (PYE). Of these, 2,928 subjects have received any dose of filgotinib for over 1 year (PYE = 6,647.91).

Table 5: Overall Safety Profile (Pooled Safety Population, As Treated Subjects)

	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE = 290.1)	MTX monotherapy (N=416) (PYE = 356.2)	Placebo (N=781) (PYE = 302.4)
	+cDMARD (N=1817) (PYE = 3003.3)	Monotherapy (N=450) (PYE = 1044.4)	Total (N=2267) (PYE = 4047.7)	+cDMARD (N=1494) (PYE = 1964.7)	Monotherapy (N=153) (PYE = 68.3)	Total (N=1647) (PYE = 2032.9)			
TEAE	1412 (77.7)	359 (79.8)	1771 (78.1)	1081 (72.4)	59 (38.6)	1140 (69.2)	239 (73.5)	305 (73.3)	426 (54.5)
EAIR	47.0	34.4	43.8	55.0	86.4	56.1	82.4	85.6	140.9
TEAE related to study drug	656 (36.1)	170 (37.8)	826 (36.4)	455 (30.5)	23 (15.0)	478 (29.0)	91 (28.0)	175 (42.1)	126 (16.1)
EAIR	21.8	16.3	20.4	23.2	33.7	23.5	31.4	49.1	41.7
TEAE ≥Grade 3	260 (14.3)	49 (10.9)	309 (13.6)	204 (13.7)	2 (1.3)	206 (12.5)	29 (8.9)	40 (9.6)	44 (5.6)
EAIR	8.7	4.7	7.6	10.4	2.9	10.1	10.0	11.2	14.6
TEAE ≥Grade 3 related to study drug	107 (5.9)	19 (4.2)	126 (5.6)	63 (4.2)	1 (0.7)	64 (3.9)	13 (4.0)	15 (3.6)	16 (2.0)
EAIR	3.6	1.8	3.1	3.2	1.5	3.1	4.5	4.2	5.3

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	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE = 290.1)	MTX monotherapy (N=416) (PYE = 356.2)	Placebo (N=781) (PYE = 302.4)
	+cDMARD (N=1817) (PYE = 3003.3)	Monotherapy (N=450) (PYE = 1044.4)	Total (N=2267) (PYE = 4047.7)	+cDMARD (N=1494) (PYE = 1964.7)	Monotherapy (N=153) (PYE = 68.3)	Total (N=1647) (PYE = 2032.9)			
TE Serious AE	198 (10.9)	56 (12.4)	254 (11.2)	162 (10.8)	4 (2.6)	166 (10.1)	22 (6.8)	28 (6.7)	31 (4.0)
EAIR	6.6	5.4	6.3	8.2	5.9	8.2	7.6	7.9	10.3
TE Serious AE related to study drug	69 (3.8)	16 (3.6)	85 (3.7)	42 (2.8)	1 (0.7)	43 (2.6)	10 (3.1)	8 (1.9)	5 (0.6)
EAIR	2.3	1.5	2.1	2.1	1.5	2.1	3.4	2.2	1.7
TE Serious AE leading to death	14 (0.8)	2 (0.4)	16 (0.7)	6 (0.4)	0	6 (0.4)	1 (0.3)	0	1 (0.1)
EAIR	0.5	0.2	0.4	0.3	0.0	0.3	0.3	0.0	0.3
TE Death	11 (0.6)	1 (0.2)	12 (0.5)	6 (0.4)	0	6 (0.4)	1 (0.3)	0	1 (0.1)
EAIR	0.4	0.1	0.3	0.3	0.0	0.3	0.3	0.0	0.3
All Deaths	15 (0.8)	4 (0.9)	19 (0.8)	6 (0.4)	0	6 (0.4)	1 (0.3)	0	2 (0.3)
EAIR	0.5	0.4	0.5	0.3	0.0	0.3	0.3	0.0	0.7
TEAE leading to premature discontinuation of study drug	164 (9.0)	76 (16.9)	240 (10.6)	85 (5.7)	10 (6.5)	95 (5.8)	18 (5.5)	25 (6.0)	24 (3.1)
EAIR	5.5	7.3	5.9	4.3	14.6	4.7	6.2	7.0	7.9
TEAE leading to temporary interruption of study drug	492 (27.1)	92 (20.4)	584 (25.8)	361 (24.2)	6 (3.9)	367 (22.3)	45 (13.8)	97 (23.3)	72 (9.2)
EAIR	16.4	8.8	14.4	18.4	8.8	18.1	15.5	27.2	23.8

PYE: patient-years of exposure

The common treatment emergent adverse events (TEAEs) reported with filgotinib were nasopharyngitis, upper respiratory tract infection, urinary tract infection, headache, bronchitis, hypertension, nausea, anaemia, and diarrhoea. The exposure-adjusted incidence rate (EAIR) of TEAEs related to study drug was lower in the filgotinib 200 mg and 100 mg arms compared to the adalimumab and MTX (20.4 vs 23.5 vs 31.4 vs 49.1 per 100 PYE).

The EAIR of treatment-emergent serious AEs (SAEs) was also lower in the filgotinib 200 mg arm compared to the filgotinib 100 mg, adalimumab, and MTX (6.3 vs 8.2 vs 7.6 vs 7.9 per 100 PYE). Pneumonia was the most common SAE reported across treatment arms, nonetheless the incidences were similar between the filgotinib arms and adalimumab (range: 0.9 to 1.1 vs 1.0 per 100 PYE).

There were 19 deaths in the filgotinib 200 mg arm and 6 deaths in the filgotinib 100 mg arm. The causes of deaths were consistent with the common causes of mortality in RA population, which included cardiovascular (CV) death, infection and malignancy. The mortality EAIR was slightly higher in the filgotinib 200 mg arm than in the filgotinib 100 mg and adalimumab (0.5 vs 0.3 vs 0.3 per 100 PYE) however, given the short exposure duration and low death events, no firm conclusion could be drawn on the clinical relevance of the numerical differences in the mortality EAIR. It was also noted that the mortality EAIR with filgotinib was consistent with currently registered JAK inhibitors (range 0.2 to 1.0 per 100 PYE).

The adverse events of special interest (AESIs) included major adverse cardiovascular event (MACE), venous thromboembolism (VTE), infectious AEs and malignancies. There was no

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dose response for the AESIs as the incidences were generally similar between filgotinib 200 mg and 100 mg. In addition, the incidences of the AESIs were lower in the filgotinib arms compared to adalimumab, MTX or placebo except for the following observations. For MACE, although the EAIR was higher in the filgotinib groups compared to adalimumab (range 0.5 to 0.6 vs 0.3 per 100 PYE), it was within the range observed with MTX or placebo (range 0.6 to 1.0 per 100 PYE). For VTE, the EAIR was observed to be higher with filgotinib 200 mg than 100 mg (0.2 vs 0.0 per 100 PYE). Nonetheless, it was reassuring that the incidence was lower than that for the active comparators or placebo (range 0.3 to 0.6 per 100 PYE).

Table 6: Summary of AESIs (Pooled Safety Population, As Treated Subjects)

Number (%) of subjects with any:	Filgotinib 200 mg QD			Filgotinib 100 mg QD			Adalimumab + MTX (N=325) (PYE = 290.1)	MTX monotherapy (N=416) (PYE = 356.2)	Placebo (N=781) (PYE = 302.4)
	+cDMARD (N=1817) (PYE = 3003.3)	Monotherapy (N=450) (PYE = 1044.4)	Total (N=2267) (PYE = 4047.7)	+cDMARD (N=1494) (PYE = 1964.7)	Monotherapy (N=153) (PYE = 68.3)	Total (N=1647) (PYE = 2032.9)			
MACE	13 (0.7)	6 (1.3)	19 (0.8)	13 (0.9)	0	13 (0.8)	1 (0.3)	2 (0.5)	3 (0.4)
EAIR	0.4	0.6	0.5	0.7	0.0	0.6	0.3	0.6	1.0
VTE (DVT/PE)	8 (0.4)	0	8 (0.4)	1 (<0.1)	0	1 (<0.1)	1 (0.3)	2 (0.5)	2 (0.3)
EAIR	0.3	0.0	0.2	0.1	0.0	0.0	0.3	0.6	0.7
Infectious AEs	864 (47.6)	210 (46.7)	1074 (47.4)	623 (41.7)	25 (16.3)	648 (39.3)	129 (39.7)	157 (37.7)	167 (21.4)
EAIR	28.8	20.1	26.5	31.7	36.6	31.9	44.5	44.1	55.2
Malignancy excluding NMSC	18 (1.0)	4 (0.9)	22 (1.0)	11 (0.7)	0	11 (0.7)	2 (0.6)	4 (1.0)	3 (0.4)
EAIR	0.6	0.4	0.5	0.6	0.0	0.5	0.7	1.1	1.0

Overall, filgotinib was well tolerated in RA patients with majority of the AEs being mild to moderate in severity. The incidences of AEs with filgotinib were generally similar to or lower compared to adalimumab, MTX or placebo; as well as between filgotinib 200 mg and 100 mg. The safety profile of filgotinib was consistent with that known for the active comparators and the JAK inhibitor class of drugs. Adequate warnings on the AEs and a class warning on all-cause mortality and CV death with JAK inhibitors compared with TNF-α inhibitors were included in the package insert to mitigate the risks.

Safety data from the UC studies

The safety data of filgotinib for the treatment of UC was derived from the pivotal Phase 3 study SELECTION and the long-term extension study SELECTION LTE. A total of 1,253 subjects with UC received at least one dose of filgotinib for a total of 1,567.4 PYE (median treatment duration: 68.1 weeks, range 0.3 to 166.7 weeks) across the integrated safety dataset. Of these, 800 (63.8%) subjects received filgotinib 200 mg or filgotinib 100 mg for at least a year.

Table 7: Overall Safety Profile

Subjects with any:	Non-model-based Descriptive Statistics			Model-based EAIR ratio		
	Filgotinib 200 mg (N=971) (PYE=1233.9)	Filgotinib 100 mg (N=583) (PYE=370.7)	Placebo (N=469) (PYE=324.7)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs Filgotinib 100 mg
TEAE, n (EAIR)	3280 (265.8)	1182 (318.9)	1004 (309.2)	0.8	0.9	0.9
TEAE with Grade ≥3, n (EAIR)	226 (18.3)	107 (28.9)	81 (24.9)	0.7	1.0	0.6
TE SAE, n (EAIR)	147 (11.9)	68 (18.3)	40 (12.3)	0.8	1.4	0.6
TEAE leading to premature discontinuation of study drug, n (EAIR)	171 (13.9)	69 (18.6)	43 (13.2)	0.9	1.3	0.7
TEAE SAE leading to death, n (EAIR)	4 (0.3)	0	0	-	-	-

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Subjects with any:	Non-model-based Descriptive Statistics			Model-based EAIR ratio		
	Filgotinib 200 mg (N=971) (PYE=1233.9)	Filgotinib 100 mg (N=583) (PYE=370.7)	Placebo (N=469) (PYE=324.7)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs Filgotinib 100 mg
Death, n (EAIR)	3 (0.2)	0	0	-	-	-

The TEAEs reported in UC were generally similar to that reported in RA. Common TEAEs reported at higher EAIR in the filgotinib 200 mg arm than in the placebo arm were nasopharyngitis (15.1 vs 11.4 per 100 PYE), upper respiratory tract infection (6.8 vs 5.9 per 100 PYE), urinary tract infection (4.0 vs 1.5 per 100 PYE), and hypophosphatemia (3.2 vs 1.5 per 100 PYE).

The EAIRs for SAEs were generally similar or lower in the filgotinib groups compared to placebo. During the induction phase, the most common SAEs were UC (range 6.5 to 6.7 vs 13.6 per 100 PYE) and anaemia (range 0.9 to 1.7 vs 1.7 per 100 PYE). During the maintenance phase, the most common SAEs were appendicitis (range 0.6 to 1.7 vs 0.0 per 100 PYE), ulcerative colitis (0.0 vs 1.9 per 100 PYE), and pyrexia (range 0.7 to 0.8 vs 0.0 per 100 PYE). A total of three deaths due to asthma, left ventricular failure and myocardial infarction and ischaemic stroke were reported in the filgotinib arms but they were assessed to be not related to study drug by the investigator.

The AESIs included thromboembolic events, infections and malignancies. Pulmonary embolism and arterial thrombosis were only reported with filgotinib, nonetheless the incidence was low (range 0.1 to 0.3 for 100 PYE). Although the incidence of infections was higher in the filgotinib 200 mg arm compared to the filgotinib 100 mg and placebo, it was reassuring that the incidence of serious infections was similar between filgotinib 200 mg and placebo. Malignancies (excluding NMSC) were also only reported with filgotinib (range 0.8 to 1.3 per 100 PYE). The majority of malignancies were reported as colon adenocarcinoma which is known to be associated with higher risk in UC patients. However, given the latency for development of malignancies, treatment duration with filgotinib in the study, and the inherent risks in the study population, no firm conclusion could be drawn on the association of malignancies with filgotinib.

Table 8: Summary of AESIs

Subjects with any:	Non-model-based Descriptive Statistics			Model-based EAIR ratio		
	Filgotinib 200 mg (N=971) (PYE=1233.9)	Filgotinib 100 mg (N=583) (PYE=370.7)	Placebo (N=469) (PYE=324.7)	Filgotinib 200 mg vs Placebo	Filgotinib 100 mg vs Placebo	Filgotinib 200 mg vs Filgotinib 100 mg
Thromboembolic events						
Pulmonary embolism, n (EAIR)	1 (0.1)	0	0	-	-	-
Arterial Thrombosis, n (EAIR)	3 (0.2)	1 (0.3)	0	-	-	-
Infections						
All Infections, n (EAIR)	857 (69.5)	217 (58.5)	198 (61.0)	1.0	0.8	1.2
Serious Infections, n (EAIR)	27 (2.2)	13 (3.5)	7 (2.2)	1.0	2.0	0.5
Malignancies excluding NMSC, n (EAIR)	10 (0.8)	5 (1.3)	0	-	-	0.7

Overall, filgotinib was well tolerated and the safety profile in the UC population was generally consistent with that in the RA population. Adequate warnings and precautions were included in the package insert to mitigate the risks.

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Safety data from the non-clinical reproductive toxicity and clinical testicular safety studies

In a 26-week study in dogs (N=5), lesions in testis which consisted of germ cell depletion/degeneration and/or tubular vacuolation with corresponding changes in epididymitis such as reduced sperm content and/or increased cell debris were observed. The adverse testicular effects in dogs occurred at doses above 5 mg/kg/day which corresponded to 0.97-fold AUC exposure margin compared to the clinical exposure at 200 mg, indicating that the adverse effects could occur at clinical doses in human. The non-clinical reproductive toxicity findings were further investigated in two human safety studies, MANTA and MANTA-RAY, to characterise the clinical relevance.

Studies MANTA and MANTA-RAY were similarly designed Phase 2, randomised, double-blind, placebo-controlled, testicular safety studies to evaluate the effects of filgotinib on semen parameters in adult males with inflammatory bowel and arthritic diseases, respectively. The studies comprised a double-blind treatment phase for 13 weeks, an open-label extension phase (up to 195 weeks for study MANTA and 156 weeks for study MANTA-RAY), and a monitoring phase for up to 52 weeks.

The primary endpoint was the proportion of subjects with a ≥50% decrease from baseline in sperm concentration at Week 13. Other endpoints included the proportion of subjects who achieved reversibility among subjects who experienced a ≥50% decrease from baseline in sperm concentration and/or motility and/or morphology in the monitoring phase, as well as the change from baseline in sex hormones, including luteinising hormone (LH), follicle stimulating hormone (FSH), inhibin B and total testosterone at Weeks 13 and 26.

The results showed that the proportion of subjects with a ≥50% decrease in sperm concentration from baseline was numerically lower for the filgotinib group (8 of 120 [6.7%] subjects) compared with the placebo group (10 of 120 [8.3%] subjects) (Δ=−1.7% [95% CI: -9.3, 5.8]) at Week 13. There was no subject in the filgotinib group whereas there was 1 subject in the placebo group who had a ≥50% decrease from baseline in sperm total motility and/or sperm morphology.

Table 9: Efficacy results at Week 13 (combined data from studies MANTA and MANTA-RAY)

Number (%) of subjects with:	Filgotinib (N=120)	Placebo (N=120)
Primary endpoint		
≥50% decrease from baseline in sperm concentration	8 (6.7)	10 (8.3)
Difference in proportions, 95% CI	-1.7 (-9.3, 5.8)	
Sperm decrease threshold criteria		
≥50% decrease from baseline in sperm total motility (%)	0	1 (0.8)
≥50% decrease from baseline in sperm morphology (% Normal)	0	1 (0.8)
≥50% decrease from baseline in sperm concentration and ≥50% decrease from baseline in sperm total motility and/or morphology	0	1 (0.8)
Components of and overall criteria for confirmed semen abnormality		
Sperm concentration <5 M/mL	0	1 (0.8)
Sperm total motility <20%	0	1 (0.8)
Sperm morphology (% Normal) <10%	0	1 (0.8)
Confirmed semen abnormality[a]	0	1 (0.8)

[a] Confirmed semen abnormality (adapted by Jarvi, et al 2008) was defined as sperm concentration <5 M/mL or sperm total motility <20% or sperm morphology (% normal) <10%. Sperm morphology assessed using WHO 1992 criteria (WHO, 1992); concentration and total motility using WHO 2010 criteria (WHO, 2010).

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However, at Week 52, all the 10 subjects in the placebo group who experienced a ≥50% decrease from baseline in sperm concentration achieved reversibility whereas 2 out of 8 filgotinib-treated subjects did not. Of the 2 subjects, 1 subject discontinued after Week 13 and the other subject still did not achieve reversibility at Week 52 despite the levels of sex hormones of this subject were within the normal range.

Overall, the concerns on adverse effects on male fertility and sperm parameters remains. Given the impaired spermatogenesis observed in dogs at clinical doses and there was a small number of human subjects who did not achieve reversibility in sperm concentration following drug administration, the potential risk of impaired spermatogenesis could not be ruled out although a mechanistic explanation by which filgotinib could result in impairment in spermatogenesis was not established.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Rheumatoid arthritis and ulcerative colitis are chronic inflammatory conditions and the goal of treatment is to induce and maintain remission. Despite the availability of cDMARDs and biologics for the treatment of RA and UC, there are patients who are intolerant, and about one-third of patients do not respond adequately as well as an additional 10% of patients who lose their initial response to treatment over time. Hence, there is a need for new therapies to provide more options for these patients.

Filgotinib demonstrated efficacy across four studies in patients with moderate to severe RA. When administered as second-line monotherapy or in combination with MTX or other DMARDs as second- and third-line therapy, filgotinib resulted in statistically significantly higher ACR 20 (range 57.5% to 76.6% vs 29.2% to 49.9%) and low disease activity responder rates (range 27.1% to 49.7% vs 13.9% to 23.4%) as well as lesser structural damage (mTSS range 0.13 to 0.17 vs 0.37) compared to placebo. Filgotinib also performed similarly or statistically significantly better compared to adalimumab in the endpoints investigated. Although the use of filgotinib as monotherapy was not investigated beyond the second-line setting, the results of filgotinib second-line monotherapy was extrapolated to third-line monotherapy given that the efficacy of filgotinib was similar between third-line and second-line combination therapies. The effects of filgotinib was also observed to be maintained up to 48 weeks and the magnitude of treatment effect was greater with the 200 mg compared to the 100 mg dose.

Filgotinib also demonstrated efficacy in patients with moderately to severely active UC who had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent. In study SELECTION, filgotinib 200 mg resulted in statistically significantly higher EBS remission rates compared to placebo at Week 10 in both biologic-naïve and -experienced subgroups (range 11.5% to 26.1% vs 4.2% to 15.3%) and at Week 58 in the overall population (37.2% vs 11.2%). The proportion of patients who achieved MCS remission was also numerically or statistically significantly higher in the filgotinib 200 mg group compared to placebo at Weeks 10 and 58, and the effects could be maintained up to 108 weeks. Similar to the observation in RA, a higher dose of fligotinib 200 mg produced numerically better results compared to 100 mg. Nonetheless, filgotinib 100 mg showed a consistent trend as it resulted in statistically significantly higher EBS remission rate compared to placebo at Week 58, as well as improvement in the MCS remission rate albeit not reaching statistical significance.

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In terms of safety, the common TEAEs reported in filgotinib-treated subjects with RA and UC were similar, and included nasopharyngitis, upper respiratory tract infection, urinary tract infection, headache, nausea, bronchitis, hypertension, anaemia, arthralgia and asthenia. The AEs were generally mild to moderate in severity and consistent with the known safety profile of JAK inhibitors. The incidences of SAEs, deaths, and AESIs such as malignancies and thromboembolic events were also comparable between filgotinib and adalimumab, MTX or placebo. As the higher dose of filgotinib 200 mg did not result in an overt increase in AEs compared to 100 mg, coupled with the numerically better efficacy demonstrated, the recommended dose of 200 mg for the general patient population was considered to be supported. In patients at increased risk of VTE, MACE and malignancy to mitigate the known risks of the JAK inhibitor class of drugs in susceptible individuals, a lower dose of 100mg is recommended. Nonetheless, there is an option to increase the dose to 200 mg in case of insufficient disease control in order to further optimise the benefit risk in these patients.

In addition, given that impaired spermatogenesis was observed in animal studies in dogs at clinical exposure and in a small number of subjects in the human testicular studies MANTA and MANTA-RAY, impaired spermatogenesis remains a potential risk. While the signal is considered weak and no mechanistic explanation was found, the potential adverse impact on male fertility could not be ruled out. Warnings have been included in the package insert to inform clinicians and patients about the observations in the clinical testicular safety studies and the potential risk of impaired spermatogenesis and male fertility to guide clinicians on the consideration of use taking into account individual patient's factors.

Overall, the benefit-risk of Jyseleca for the treatment of moderate to severe RA and UC is considered positive as the clinical efficacy of filgotinib was adequately demonstrated and the safety profile of the drug was acceptable and manageable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Jyseleca for the treatment of the following indications was deemed favourable and approval of the product registration was granted on 27 March 2024:

- Moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Jyseleca may be used as monotherapy or in combination with MTX.
- Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.

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APPROVED PACKAGE INSERT AT REGISTRATION

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1. NAME OF THE MEDICINAL PRODUCT

Jyseleca film-coated tablet 100 mg
Jyseleca film-coated tablet 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Jyseleca film-coated tablet 100 mg

Each film-coated tablet contains filgotinib maleate equivalent to 100 mg of filgotinib.

Excipient with known effect
Each 100 mg film-coated tablet contains 76 mg of lactose (as monohydrate).

Jyseleca film-coated tablet 200 mg

Each film-coated tablet contains filgotinib maleate equivalent to 200 mg of filgotinib.

Excipient with known effect
Each 200 mg film-coated tablet contains 152 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Jyseleca film-coated tablets 100 mg

Beige 12 mm × 7 mm, capsule-shaped, film-coated tablet debossed with “GSI” on one side and “100” on the other side.

Jyseleca film-coated tablets 200 mg

Beige 17 mm × 8 mm, capsule-shaped, film-coated tablet debossed with “GSI” on one side and “200” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Jyseleca is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease -modifying anti-rheumatic drugs (DMARDs). Jyseleca may be used as monotherapy or in combination with methotrexate (MTX).

Ulcerative colitis

Jyseleca is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.

4.2 Posology and method of administration

Treatment with filgotinib should be initiated by a physician experienced in the treatment of rheumatoid arthritis or ulcerative colitis.

Posology

Rheumatoid arthritis
The recommended dose of filgotinib for adult patients is 200 mg once daily.
In adults at increased risk of VTE, MACE and malignancy (see section 4.4), the recommended dose is 100 mg once daily and may be escalated to 200 mg once daily in case of insufficient disease control. For long term treatment, the lowest effective dose should be used.

Ulcerative colitis
Induction treatment
The recommended dose for induction treatment is 200 mg once daily.

For patients with ulcerative colitis who do not show an adequate therapeutic benefit during the initial 10 weeks of treatment, 12 additional weeks of induction treatment with filgotinib 200 mg once daily may provide additional relief of symptoms (see section 5.1). Patients who have not shown any therapeutic benefit after 22 weeks of treatment should discontinue filgotinib.

Maintenance treatment
The recommended dose for maintenance treatment is 200 mg once daily.
In adults at higher risk of VTE, MACE and malignancy (see section 4.4), the recommended dose for maintenance treatment is 100 mg once daily. In case of flare of the disease, the dose may be escalated to 200 mg once daily. For long term treatment, the lowest effective dose should be used.

Laboratory monitoring, and dose initiation or interruption
Guidance for laboratory monitoring, and dose initiation or interruption is provided in Table 1. Treatment should be interrupted if a patient develops a serious infection until the infection is controlled (see section 4.4).

Table 1: Laboratory measures and monitoring guidance

Laboratory measure	Action	Monitoring guidance
Absolute neutrophil count (ANC)	Treatment should not be initiated, or should be interrupted, if ANC is $< 1 \times 10^9$ cells/L. Treatment may be restarted once ANC returns above this value	Before treatment initiation and thereafter according to routine patient management
Absolute lymphocyte count (ALC)	Treatment should not be initiated, or should be interrupted, if ALC is $< 0.5 \times 10^9$ cells/L. Treatment may be restarted once ALC returns above this value	
Haemoglobin (Hb)	Treatment should not be initiated, or should be interrupted, if Hb is < 8 g/dL. Treatment may be restarted once Hb returns above this value	
Lipid parameters	Patients should be managed according to international clinical guidelines for hyperlipidaemia	12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia

Special populations

Elderly
Rheumatoid arthritis
In patients with rheumatoid arthritis aged 65 years of age and older, the recommended dose is 100 mg once daily and may be escalated to 200 mg once daily in case of insufficient disease control (see section 4.4). For long term treatment, the lowest effective dose should be used.

Ulcerative colitis
In patients with ulcerative colitis aged 65 years of age and older, the recommended dose is 200 mg once daily for the induction treatment and 100 mg once daily for maintenance treatment (see section 4.4). In case of flare of the disease, the dose may be escalated to 200 mg once daily. For long term treatment, the lowest effective dose should be used. Filgotinib is not recommended in patients aged 75 years and older as there is no data in this population.

Renal impairment
No dose adjustment is required in patients with mild renal impairment (creatinine clearance [CrCl] ≥ 60 mL/min). A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (CrCl 15 to < 60 mL/min). Filgotinib has not been studied in patients with end stage renal disease (CrCl < 15 mL/min) and is therefore not recommended for use in these patients (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh A or B). Filgotinib has not been studied in patients with severe hepatic impairment (Child-Pugh C) and is therefore not recommended for use in these patients (see section 5.2).

Paediatric population
The safety and efficacy of filgotinib in children under the age of 18 years have not yet been established. No data are available.

Method of administration

Oral use.
Jyseleca can be taken with or without food (see section 5.2). It has not been studied if tablets can be split, crushed, or chewed, and it is recommended that tablets are swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active tuberculosis (TB) or active serious infections (see section 4.4).

Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Filgotinib should only be used if no suitable treatment alternatives are available in patients:
-65 years of age and older;
-patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers);
-patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

Immunosuppressive medicinal products

Combination of filgotinib with other potent immunosuppressants such as ciclosporin, tacrolimus, biologics or other Janus kinase (JAK) inhibitors is not recommended as a risk of additive immunosuppression cannot be excluded.

Infections

Infections, including serious infections, have been reported in patients receiving filgotinib. The most frequent serious infection reported with filgotinib was pneumonia (see section 4.8). Among opportunistic infections, TB, oesophageal candidiasis, and cryptococcosis were reported with filgotinib.

The risks and benefits of treatment should be considered prior to initiating filgotinib in patients:

- with chronic or recurrent infection
- who have been exposed to TB
- with a history of a serious or an opportunistic infection
- who have resided or travelled in areas of endemic TB or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infections during and after filgotinib treatment. If an infection develops during treatment with filgotinib, the patient should be carefully monitored and filgotinib treatment should be temporarily interrupted if the patient is not responding to standard antimicrobial therapy. Filgotinib treatment may be resumed once the infection is controlled.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients 65 years of age and older, filgotinib should only be used if no suitable treatment alternatives are available (see section 4.2).

Tuberculosis
Patients should be screened for TB before initiating filgotinib. Filgotinib should not be administered to patients with active TB (see section 4.3). In patients with latent TB, standard antimycobacterial therapy should be initiated before administering filgotinib.

Patients should be monitored for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating treatment.

Viral reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies (see section 4.8). In rheumatoid arthritis clinical studies, the risk of herpes zoster appeared to be higher in female patients, Asian patients, patients ≥ 50 years of age, patients with a medical history of herpes zoster, patients with a medical history of chronic lung disease and patients treated with filgotinib 200 mg once daily. If a patient develops herpes zoster, filgotinib treatment should be temporarily interrupted until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during treatment with filgotinib. Patients who were positive for both hepatitis C antibody and hepatitis C virus RNA were excluded from clinical studies. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical studies.

Malignancy

Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including filgotinib. In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and non melanoma skin cancer (NMSC) was observed with tofacitinib compared to TNF inhibitors.

In patients 65 years of age and older, patients who are current or past long-time smokers, or with other malignancy risk factors (e.g. current malignancy or history of malignancy), filgotinib should only be used if no suitable treatment alternatives are available.

Non-melanoma skin cancer
NMSCs have been reported in patients treated with filgotinib. Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer.

Haematological abnormalities

ANC < 1×10^9 cells/L (see section 4.8) and ALC < 0.5×10^9 cells/L were reported in ≤ 1% of patients in the rheumatoid arthritis clinical studies and in < 3% of patients in the ulcerative colitis clinical studies. Treatment should not be initiated, or should be temporarily interrupted, in patients with an ANC < 1×10^9 cells/L, ALC < 0.5×10^9 cells/L or haemoglobin < 8 g/dL observed during routine patient management (see section 4.2).

Vaccinations

Use of live vaccines during, or immediately prior to, filgotinib treatment is not recommended. It is recommended that immunisations, including prophylactic zoster vaccinations, be updated in agreement with current immunisation guidelines prior to initiating filgotinib treatment.

Lipids

Treatment with filgotinib was associated with dose-dependent increases in lipid parameters, including total cholesterol, and high-density lipoprotein (HDL) levels, while low-density-lipoprotein (LDL) levels were slightly increased (see section 4.8). LDL cholesterol returned to pre-treatment levels in the majority of patients who started statin therapy while taking filgotinib. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined (see section 4.2 for monitoring guidance).

Major adverse cardiovascular events (MACE)

Events of MACE have been observed in patients taking filgotinib.

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke, was observed with tofacitinib compared to TNF inhibitors.

Therefore, in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, filgotinib should only be used if no suitable treatment alternatives are available.

Venous thromboembolism

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including filgotinib.

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a dose dependent higher rate of VTE including deep venous thrombosis (DVT) and pulmonary embolism (PE) was observed with tofacitinib compared to TNF inhibitors.

In patients with cardiovascular or malignancy risk factors (see also section 4.4 “Major adverse cardiovascular events (MACE)” and “Malignancy”) filgotinib should only be used if no suitable treatment alternatives are available.

In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, filgotinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder.

Patients should be re-evaluated periodically during filgotinib treatment to assess for changes in VTE risk.

Promptly evaluate patients with signs and symptoms of VTE and discontinue filgotinib in patients with suspected VTE, regardless of dose.

Use in patients over 65 years of age and older

Considering the increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomised study of tofacitinib (another JAK inhibitor), filgotinib should only be used in these patients if no suitable treatment alternatives are available.

Lactose content

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Mortality

In a large, randomised, postmarketing safety study of another JAK inhibitor in rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with tumour necrosis factor inhibitors.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with filgotinib.

Gastrointestinal perforation

Events of gastrointestinal perforation have been reported in patients receiving JAK inhibitors including filgotinib. Filgotinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis, patients with concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory drugs). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on filgotinib

Filgotinib is primarily metabolised by carboxylesterase 2 (CES2), which can be inhibited *in vitro* by medicinal products such as fenofibrate, carvedilol, diltiazem or simvastatin. The clinical relevance of this interaction is unknown.

Effect of filgotinib on other medicinal products

Filgotinib is not a clinically relevant inhibitor or inducer of most enzymes or transporters commonly involved in interactions such as cytochrome P450 (CYP) enzymes and UDP-glucuronosyltransferases (UGT).

In vitro studies are inconclusive regarding the potential of filgotinib to induce CYP2B6. *In vivo* induction cannot be excluded.

In vitro studies are inconclusive regarding the potential of filgotinib to induce or inhibit CYP1A2. No clinical studies have been performed to investigate interactions with CYP1A2 substrates and therefore the potential *in vivo* effect of concomitant induction and inhibition of CYP1A2 by filgotinib is unknown. Caution is recommended when filgotinib is co-administered with CYP1A2 substrates with a narrow therapeutic index.

In a clinical pharmacology study, there was no effect on the pharmacokinetics of the combined contraceptive ethinyl estradiol and levonorgestrel when co-administered with filgotinib; thus no dose adjustment of oral contraceptives is required.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception

Women of childbearing potential have to use effective contraception during and for at least 1 week after cessation of filgotinib treatment.

Pregnancy

There are no or limited amount of data from the use of filgotinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Based on findings in animals, filgotinib may cause foetal harm and is therefore contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is unknown whether filgotinib is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded. Therefore, Jyseleca should not be used during breast-feeding.

Fertility

In animal studies, decreased fertility, impaired spermatogenesis, and histopathological effects on male reproductive organs including lesions in testis which consisted of germ cell depletion/degeneration and/or tubular vacuolation with corresponding changes in epididymitis, such as reduced sperm content and/or increased cell debris were observed at exposures close to the clinical dose of 200 mg hence the risk of these adverse effects occurring at clinical doses for human use could not be ruled out (see section 5.3). The data from two dedicated clinical studies (MANTA and MANTA-RAy, n=240) to evaluate the testicular safety in men with inflammatory rheumatic diseases and inflammatory bowel diseases (IBD) showed a similar proportion of patients who had a 50% or more decrease from baseline

in semen parameters at week 13 (pooled primary endpoint: 8 patients in the filgotinib group [6.7%], 10 patients in the placebo group [8.3%]). All 10 patients in the placebo group who experienced a ≥50% decrease from baseline in sperm concentration achieved reversibility by the Monitoring Phase (MP) week 52 whereas 2 out of 8 patients in the filgotinib group did not achieve reversibility. Of the 2 patients, 1 discontinued the study after the MP week 13 and the other patient did not demonstrate reversibility at the end of study despite completing the MP week 52. The data did not show any relevant changes in sex hormone levels or change from baseline in semen parameters across treatment groups. However, given that there are filgotinib-treated patients in whom reversibility of decreased sperm concentration has not been confirmed, it is recommended for clinicians to assess the appropriateness of use of the drug while taking into consideration individual patient's factors.

Animal studies did not indicate effects with respect to fertility in females.

4.7 Effects on ability to drive and use machines

Filgotinib has no or negligible influence on the ability to drive and use machines. However, patients should be advised that dizziness has been reported during treatment with Jyseleca (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Rheumatoid arthritis
The most frequently reported adverse reactions are nausea (3.5%), upper respiratory tract infection (URTI, 3.3%), urinary tract infection (UTI, 1.7%), dizziness (1.2%) and lymphopenia (1.0%).

Ulcerative colitis
In general, the overall safety profile observed in filgotinib-treated patients with ulcerative colitis was generally consistent with the safety profile observed in patients with rheumatoid arthritis.

Tabulated list of adverse reactions

The following adverse reactions are based on clinical studies (Table 2). The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 2: Adverse reactions

Frequency [a]	Adverse reaction
Infections and infestations	
Common	Urinary tract infection (UTI) Upper respiratory tract infection (URTI)
Uncommon	Herpes zoster Pneumonia Sepsis
Blood and lymphatic system disorders	
Common	Lymphopenia
Uncommon	Neutropenia
Metabolism and nutrition disorders	
Uncommon	Hypercholesterolaemia
Nervous system disorders	
Common	Dizziness
Gastrointestinal disorders	
Common	Nausea
Investigations	
Uncommon	Blood creatine phosphokinase increased

a Frequency based on placebo-controlled pre-rescue period (week 12) pooled across FINCH 1 and 2, and DARWIN 1 and 2, for patients with rheumatoid arthritis who received filgotinib 200 mg. Frequencies reported in the SELECTION study

in patients with ulcerative colitis who received filgotinib 200 mg were generally consistent with those reported in the rheumatoid arthritis studies.

Laboratory changes

Creatinine
An increase in serum creatinine occurred with filgotinib treatment. At week 24 in the Phase 3 studies (FINCH 1, 2, and 3), the mean (SD) increase from baseline in serum creatinine was 0.07 (0.12) and 0.04 (0.11) mg/dL for filgotinib 200 mg and 100 mg, respectively. Mean creatinine values remained within the normal range.

Lipids
Treatment with filgotinib was associated with dose-dependent increases in total cholesterol and HDL levels, while LDL levels were slightly increased. LDL/HDL ratios were generally unchanged. Lipid changes were observed within the first 12 weeks of filgotinib treatment and remained stable thereafter.

Serum phosphate
Generally mild, transient or intermittent, and dose-dependent decreases in serum phosphate levels occurred during treatment with filgotinib and resolved without discontinuation of treatment. At week 24 in the Phase 3 studies (FINCH 1, 2, and 3), serum phosphate values of less than 2.2 mg/dL (the lower limit of normal) were reported in 5.3% and 3.8% of subjects receiving filgotinib 200 mg and 100 mg, respectively; no values below 1.0 mg/dL were reported.

In placebo-controlled Phase 3 studies with background DMARDs (FINCH 1 and FINCH 2) through 12 weeks, serum phosphate levels of less than 2.2 mg/dL were reported in 1.6%, 3.1%, and 2.4% in the placebo, filgotinib 200 mg, and filgotinib 100 mg groups, respectively.

Description of selected adverse reactions

Infections
Rheumatoid arthritis
In placebo-controlled studies with background DMARDs (FINCH 1, FINCH 2, DARWIN 1, and DARWIN 2), the frequency of infection over 12 weeks in the filgotinib 200 mg group was 18.1% compared to 13.3% in the placebo group. In the MTX-controlled study FINCH 3, the frequency of infection over 24 weeks in the filgotinib 200 mg monotherapy and filgotinib 200 mg plus MTX groups was 25.2% and 23.1%, respectively, compared to 24.5% in the MTX group. The overall exposure-adjusted incidence rate (EAIR) of infections for the filgotinib 200 mg group across all seven Phase 2 and 3 clinical studies (2,267 patients) was 26.5 per 100 patient-years of exposure (PYE).

In placebo-controlled studies with background DMARDs, the frequency of serious infection over 12 weeks in the filgotinib 200 mg group was 1.0% compared to 0.6% in the placebo group. In the MTX-controlled study FINCH 3, the frequency of serious infection over 24 weeks in the filgotinib 200 mg monotherapy and filgotinib 200 mg plus MTX groups was 1.4% and 1.0%, respectively, compared to 1.0% in the MTX group. The overall EAIR of serious infections for the filgotinib 200 mg group across all seven Phase 2 and 3 clinical studies (2,267 patients) was 1.7 per 100 PYE. The most common serious infection was pneumonia. The EAIR of serious infections remained stable with long-term exposure.

In rheumatoid arthritis clinical studies, there was a higher incidence of serious infections in patients aged 65 years and older.

In placebo-controlled studies with background DMARDs, the frequencies of infectious ADRs over 12 weeks for filgotinib 200 mg compared to placebo were: URTI (3.3% *versus* 1.8%), UTI (1.7% *versus* 0.9%), pneumonia (0.6% *versus* 0.4%), and herpes zoster (0.1% *versus* 0.3%). Most of the herpes zoster events involved a single dermatome and were non-serious. The overall EAIR of herpes zoster across all seven Phase 2 and 3 clinical studies (2,267 and 1,647 total patients for 200 mg and

100 mg, respectively) was 1.6 and 1.1 per 100 PYE in the 200 mg group and 100 mg group, respectively.

Ulcerative colitis
The types of serious infections in the ulcerative colitis clinical studies were generally similar to those reported in the rheumatoid arthritis clinical studies with filgotinib monotherapy treatment groups.

Across the two placebo-controlled induction studies, the frequency of serious infections was 0.6% in the filgotinib 200 mg group, 1.1% in the filgotinib 100 mg group, and 1.1% in the placebo group. In the placebo-controlled maintenance study, the frequency of serious infections in the filgotinib 200 mg group was 1%, compared to 0% in the respective placebo group. In the maintenance study filgotinib 100 mg group, the frequency of serious infections was 1.7%, compared with 2.2% in the respective placebo group.

Opportunistic infections (excluding TB)
In rheumatoid arthritis placebo-controlled studies with background DMARDs, there were no opportunistic infections over 12 weeks in the filgotinib 200 mg group or the placebo group. In the MTX-controlled study FINCH 3, the frequency of opportunistic infections over 24 weeks was 0, 0.2%, and 0 in the filgotinib 200 mg monotherapy, filgotinib 200 mg plus MTX, and MTX groups, respectively. The overall EAIR of opportunistic infections for the filgotinib 200 mg group across all seven Phase 2 and 3 rheumatoid arthritis clinical studies (2,267 patients) was 0.1 per 100 PYE.

Nausea
Nausea was generally transient and reported during the first 24 weeks of filgotinib treatment.

Creatine phosphokinase
Dose-dependent increases in creatine phosphokinase (CPK) occurred within the first 12 weeks of filgotinib treatment and remained stable thereafter. At week 24 in the Phase 3 studies (FINCH 1, 2, and 3), the mean (SD) increase from baseline in CPK was -16 (449), 61 (260), and 33 (80) U/L for placebo, filgotinib 200 mg and 100 mg, respectively.

In placebo-controlled Phase 3 studies with background DMARDs (FINCH 1 and FINCH 2) through 12 weeks, CPK elevations > 5 × upper limit of normal (ULN) were reported in 0.5%, 0.3%, and 0.3% of patients in the placebo, filgotinib 200 mg, and filgotinib 100 mg groups, respectively. Most elevations > 5 × ULN did not require treatment discontinuation.

Experience from long-term extension studies

Rheumatoid arthritis
In the long-term extension study DARWIN 3, among patients enrolled from DARWIN 1 (N = 497), 238 patients received filgotinib 200 mg once a day for a median duration of 4.4 years; among patients enrolled from DARWIN 2 (N = 242), 234 patients received filgotinib 200 mg once a day for a median duration of 4.4 years. In the longterm extension study FINCH 4, 1,530 patients received filgotinib 200 mg once daily and 1,199 patients received filgotinib 100 mg once daily for a median duration of 1.5 years. The safety profile of filgotinib was similar to that in the Phase 2 and Phase 3 studies.

Ulcerative colitis
In the long-term extension study (SELECTION LTE) in patients who participated in the SELECTION study, patients received filgotinib 200 mg (N = 871), filgotinib 100 mg (N = 157), or placebo (N = 133) for median durations of 55, 36, and 32 weeks, respectively. The safety profile of filgotinib was similar to that in the SELECTION induction and maintenance studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Filgotinib has been administered in clinical studies following single and once daily administration up to 450 mg without dose-limiting toxicity. Adverse reactions were comparable to those seen at lower doses and no specific toxicities were identified. Pharmacokinetic data following a single dose of 100 mg filgotinib in healthy subjects indicate that approximately 50% of the administered dose is eliminated within 24 hours of dosing and 90% of the dose is eliminated within 72 hours. In case of an overdose, it is recommended that a patient be monitored for signs and symptoms of adverse reactions. Treatment of overdose with filgotinib consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. It is unknown whether filgotinib can be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA45

Mechanism of action

Filgotinib is an adenosine triphosphate (ATP)-competitive and reversible inhibitor of the JAK family. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane. JAK1 is important in mediating inflammatory cytokine signals, JAK2 in mediating myelopoiesis and erythropoiesis and JAK3 plays critical roles in immune homeostasis and lymphopoiesis. Within the signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity including gene expression. Filgotinib modulates these signalling pathways by preventing the phosphorylation and activation of STATs. In biochemical assays, filgotinib preferentially inhibited the activity of JAK1 and showed > 5-fold higher potency of filgotinib for JAK1 over JAK2, JAK3 and TYK2. In human cellular assays, filgotinib preferentially inhibited JAK1/JAK3-mediated signalling downstream of the heterodimeric cytokine receptors for interleukin (IL)-2, IL-4 and IL-15, JAK1/2-mediated IL-6, and JAK1/TYK2-mediated type I interferons, with functional selectivity over cytokine receptors that signal via pairs of JAK2 or JAK2/TYK2. GS-829845, the primary metabolite of filgotinib, was approximately 10-fold less active than filgotinib in *in vitro* assays, while exhibiting a similar JAK1 preferential inhibitory activity. In an *in vivo* rat model, the overall pharmacodynamic effect was predominantly driven by the metabolite.

Pharmacodynamic effects

Inhibition of IL-6 induced STAT1 phosphorylation
Filgotinib administration resulted in a dose--dependent inhibition of IL-6 induced STAT1 phosphorylation in whole blood from healthy subjects. Filgotinib administration did not affect JAK2 -associated GM-CSF induced STAT5 phosphorylation.

Immunoglobulins
In FINCH 1, 2, and 3, the median and interquartile ranges for serum IgG, IgM, and IgA values remained largely within the normal reference ranges through 24 weeks of treatment with filgotinib in patients with rheumatoid arthritis and through 58 weeks of treatment in patients with ulcerative colitis.

Haematologic effects
In FINCH 1, 2, and 3 in patients with rheumatoid arthritis, treatment with filgotinib was associated with a small, transient increase in mean ALC that remained within normal reference ranges and gradually returned to at or near baseline levels with continued treatment by week 12. In FINCH 1, 2, and 3, median haemoglobin values remained stable within the normal range through 24 weeks of

filgotinib treatment. A slight decrease in median platelet counts occurred within the first 4 weeks of filgotinib treatment and remained stable thereafter through 24 weeks. Median platelet counts remained within the normal range.

In SELECTION, in patients with ulcerative colitis, median haemoglobin values remained stable through 58 weeks of filgotinib treatment.

C--reactive protein
Decreases in serum C--reactive protein (CRP) were observed as early as 2 weeks after starting treatment with filgotinib and were maintained through 24 weeks of treatment in patients with rheumatoid arthritis and through 58 weeks of treatment in patients with ulcerative colitis.

Clinical efficacy and safety

Rheumatoid arthritis
The efficacy and safety of filgotinib once daily were assessed in three Phase 3 studies (FINCH 1, 2, and 3). These were randomised, double--blind, multicentre studies in patients with moderate to severe active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria.

FINCH 1 was a 52--week study in 1,755 patients with rheumatoid arthritis who had an inadequate response to MTX. Patients received filgotinib 200 mg once daily, filgotinib 100 mg once daily, adalimumab every 2 weeks, or placebo, all added to stable background MTX. At week 24, patients receiving placebo were re--randomised to filgotinib 100 mg or 200 mg once daily through week 52. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12.

FINCH 2 was a 24--week study in 448 patients with rheumatoid arthritis who had an inadequate response to bDMARDs. Patients received filgotinib 200 mg once daily, filgotinib 100 mg once daily, or placebo, all with a continued stable background dose of conventional synthetic DMARD(s) (csDMARD[s]: MTX, hydroxychloroquine, sulfasalazine, or leflunomide). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12.

FINCH 3 was a 52--week study in 1,249 patients with rheumatoid arthritis who were naïve to MTX therapy. Patients received filgotinib 200 mg once daily plus MTX once weekly, filgotinib 100 mg once daily plus MTX once weekly, filgotinib 200 mg (monotherapy) once daily, or MTX (monotherapy) once weekly. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Clinical response
Higher response rates *versus* placebo or MTX were seen at week 2 for ACR20, and responses were maintained through week 52.

Treatment with filgotinib 200 mg resulted in improvements in all individual ACR components, including tender and swollen joint counts, patient and physician global assessments, Health Assessment Questionnaire Disability Index (HAQ-DI), pain assessment and high sensitivity CRP, compared to placebo or MTX. In two of the Phase 3 studies (FINCH 1 and FINCH 2), the comparison (*versus* placebo) was carried out on top of MTX or csDMARD(s) (see above).

Low disease activity and remission
Across the Phase 3 studies, a significantly higher proportion of patients treated with filgotinib 200 mg plus MTX or other csDMARD achieved low disease activity and/or remission (DAS28-CRP $\leq$ 3.2 and DAS28-CRP < 2.6) at weeks 12 and 24 as compared to placebo or MTX. Filgotinib 200 mg was non-inferior to adalimumab at week 12 for DAS28-CRP $\leq$ 3.2 in FINCH 1 (Table 3).

Table 3: Clinical response at weeks 12, 24 and 52 in FINCH 1, 2, and 3

	FINCH 1 MTX-IR				FINCH 2 bDMARD-IR			FINCH 3 MTX-naïve			
Treatment	**FIL 200 mg**	**FIL 100 mg**	**ADA**	**PBO**	**FIL 200 mg**	**FIL 100 mg**	**PBO**	**FIL 200 mg + MTX**	**FIL 100 mg + MTX**	**FIL 200 mg mono**	**MTX**
	+ MTX				**+ csDMARD**						
N	475	480	325	475	147	153	148	416	207	210	416
Week											
ACR20 (percent of patients)											
12	77***¶	70***	71	50	66***	58***	31	77†††	72††	71††	59
24	78†††	78†††	74	59	69†††	55†††	34	81***	80*	78	71
52	78	76	74	-	-	-	-	75†††	73††	75†††	62
ACR50 (percent of patients)											
12	47†††¶¶¶	36†††	35	20	43†††	32†††	15	53†††	44†††	46†††	28
24	58†††	53†††	52	33	46†††	35††	19	62†††	57††	58††	46
52	62	59	59	-	-	-	-	62†††	59††	61†††	48
ACR70 (percent of patients)											
12	26†††¶¶¶	19†††	14	7	22†††	14†	7	33†††	27†††	29†††	13
24	36†††¶	30†††	30	15	32†††	20††	8	44†††	40†††	40†††	26
52	44	38	39	-	-	-	-	48†††	40††	45†††	30
DAS28-CRP ≤ 3.2 (percent of patients)											
12	50$^{***###}$	39***	43	23	41***	37***	16	56†††	50†††	48†††	29
24	61†††§§§¶¶	53†††§§§	50	34	48†††	38†††	21	69†††	63†††	60†††	46
52	66¶	59	59	-	-	-	-	69†††	60††	66†††	48
DAS28-CRP < 2.6 (percent of patients)											
12	34†††§§§¶¶¶	24†††§§	24	9	22†††	25†††	8	40†††	32†††	30†††	17
24	48***§§§¶¶¶	35***§§§	36	16	31†††	26††	12	54***	43***	42†††	29
52	54¶	43	46	-	-	-	-	53†††	43††	46†††	31
CDAI, change from baseline (mean)											
12	-26.0†††	-23.3†††	-23.5	-20.3	-26.2†††	-23.8†††	-17.3	-27.8†††	-26.1†††	-27.5†††	-22.7
24	-30.6†††	-28.6†††	-28.4	-26.3	-30.9†††	-27.8††	-25.4	-31.3†††	-30.0†††	-31.3†††	-28.2
52	-32.9	-30.9	-31.6	-	-	-	-	-33.8†††	-31.9†	-33.6†††	-31.2

ADA: adalimumab; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying anti-rheumatic drug; FIL: filgotinib; IR: inadequate responder; mono: monotherapy; MTX: methotrexate; PBO: placebo.

* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ *versus* placebo (*versus* MTX for FINCH 3) (statistically significant difference with multiplicity adjustment).

† $p \leq 0.05$; †† $p \leq 0.01$; ††† $p \leq 0.001$ *versus* placebo (*versus* MTX for FINCH 3) (nominal p-value).

\# $p \leq 0.05$; ## $p \leq 0.01$; ### $p \leq 0.001$ *versus* adalimumab for FINCH 1 (non-inferiority test, statistically significant difference with multiplicity adjustment) (analysed for DAS28-CRP ≤ 3.2 and < 2.6 pairwise comparisons only).

§ $p \leq 0.05$; §§ $p \leq 0.01$; §§§ $p \leq 0.001$ *versus* adalimumab for FINCH 1 (non-inferiority test, nominal p-value) (analysed for DAS28-CRP ≤ 3.2 and < 2.6 pairwise comparisons only).

¶ $p \leq 0.05$; ¶¶ $p \leq 0.01$; ¶¶¶ $p \leq 0.001$ *versus* adalimumab for FINCH 1 (superiority test, nominal p-value) (analysed for ACR20/50/70, and DAS28-CRP ≤ 3.2 and < 2.6 pairwise comparisons only).

Note: Comparisons were carried out on top of a stable background of MTX (FINCH 1) or csDMARD(s) (FINCH 2).

Radiographic response

Inhibition of progression of structural joint damage was assessed using the modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score, at weeks 24 and 52 in FINCH 1 and FINCH 3.

In patients who had an inadequate response to MTX, treatment with filgotinib plus MTX resulted in statistically significant inhibition of progression of structural joint damage compared to placebo plus MTX at week 24 (Table 4). Analyses of erosion and joint space narrowing scores were consistent with the overall scores.

Table 4: Radiographic response at weeks 24 and 52 in FINCH 1 and 3

	FINCH 1 MTX-IR				FINCH 3 MTX naïve			
Treatment	**FIL 200 mg + MTX**	**FIL 100 mg + MTX**	**ADA + MTX**	**PBO + MTX**	**FIL 200 mg + MTX**	**FIL 100 mg + MTX**	**FIL 200 mg mono**	**MTX**
N	475	480	325	475	416	207	210	416
Week								
Modified Total Sharp Score (mTSS), mean (SD) change from baseline								
24	0.13 (0.94)***	0.17 (0.91)***	0.16 (0.95)	0.37 (1.42)	0.21 (1.68)	0.22 (1.53)	-0.04 (1.71)††	0.51 (2.89)
52	0.21 (1.43)	0.50 (2.10)	0.58 (3.62)	-	0.31 (1.81)†††	0.23 (1.11)††	0.33 (1.90)††	0.81 (3.09)
Proportion of patients with no radiographic progression [a]								
24	88%**	86%	86%	81%	81%†	77%	83%†	72%
52	88%	81%	82%	-	81%††	76%	77%	71%

ADA: adalimumab; FIL: filgotinib; IR: inadequate responder; mono: monotherapy; MTX: methotrexate; PBO: placebo.
a No progression defined as mTSS change ≤ 0.
* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 *versus* placebo (statistically significant difference with multiplicity adjustment).
† p ≤ 0.05; †† p ≤ 0.01; ††† p ≤ 0.001 *versus* placebo (*versus* MTX for FINCH 3) (nominal p-value).

Physical function response and health related outcomes
Treatment with filgotinib 200 mg resulted in a significant improvement in physical function, as measured by change from baseline in HAQ-DI (Table 5).

Table 5: Mean change from baseline in HAQ-DI at weeks 12, 24 and 52 in FINCH 1, 2, and 3

	Mean change from baseline										
	FINCH 1 MTX-IR				FINCH 2 bDMARD-IR			FINCH 3 MTX naïve			
Treatment	**FIL 200 mg + MTX**	**FIL 100 mg + MTX**	**ADA + MTX**	**PBO + MTX**	**FIL 200 mg + csDMARD**	**FIL 100 mg + csDMARD**	**PBO + csDMARD**	**FIL 200 mg + MTX**	**FIL 100 mg + MTX**	**FIL 200 mg mono**	**MTX**
N	475	480	325	475	147	153	148	416	207	210	416
Week											
Health Assessment Questionnaire Disability Index (HAQ-DI)											
Baseline score	1.59	1.55	1.59	1.63	1.70	1.64	1.65	1.52	1.56	1.56	1.60
12	-0.69***	-0.56***	-0.61	-0.42	-0.55***	-0.48***	-0.23	-0.85†††	-0.77†††	-0.76†††	-0.61
24	-0.82†††	-0.75†††	-0.78	-0.62	-0.75†††	-0.60††	-0.42	-0.94***	-0.90**	-0.89†	-0.79
52	-0.93	-0.85	-0.85	-	-	-	-	-1.00†††	-0.97	-0.95†	-0.88

ADA: adalimumab; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; FIL: filgotinib; IR: inadequate responder; mono: monotherapy; MTX: methotrexate; PBO: placebo.
* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001 *versus* placebo (statistically significant difference with multiplicity adjustment).
† p ≤ 0.05; †† p ≤ 0.01; ††† p ≤ 0.001 *versus* placebo (*versus* MTX for FINCH 3) (nominal p-value).

Health status outcomes were assessed by the Short Form health survey (SF-36). Patients treated with filgotinib 200 mg plus MTX or other csDMARD demonstrated numerically greater improvement from baseline in the physical component summary score of SF-36 as well as in the Functional Assessment of Chronic Illness Therapy -Fatigue score (FACIT-F) at weeks 12 and 24 compared to placebo plus MTX/csDMARD or MTX.

Long-term efficacy
In a long--term Phase 2 open--label extension study (DARWIN 3), continued and durable responses were observed, with ACR20/50/70 responses maintained for up to 3 years in patients who received filgotinib 200 mg as monotherapy or with MTX.

Ulcerative colitis

The efficacy and safety of filgotinib once daily were evaluated in a randomised, double-blind, placebo-controlled combined Phase 2b/3 study (SELECTION) in patients with moderately to severely active ulcerative colitis (Mayo Clinic Score 6 to 12; endoscopy subscore ≥ 2; rectal bleeding subscore ≥ 1; stool frequency subscore ≥ 1; and Physician's Global Assessment subscore ≥ 2). SELECTION included two induction studies (UC1 and UC2) followed by a maintenance study (UC3), with a total duration of 58 weeks of therapy. Patients were permitted to use stable doses of concomitant therapies for ulcerative colitis, including oral aminosalicylates, oral corticosteroids (prednisone equivalent dose up to 30 mg/day), and immunomodulators (azathioprine, 6MP, or methotrexate).

UC-1 was an 11-week induction study in 659 patients with ulcerative colitis who were naïve to biologic therapy and had an inadequate response, loss of response, or intolerance to corticosteroids or immunomodulators. Patients received filgotinib 200 mg once daily (N = 245), filgotinib 100 mg once daily (N = 277), or placebo (N = 137). At baseline, 56% of patients had an endoscopic subscore of 3; 24% were receiving oral corticosteroids only, 23% immunomodulators only, 7% corticosteroids and immunomodulators, and 47% neither corticosteroids nor immunomodulators.

UC2 was an 11week induction study in 689 patients with ulcerative colitis who were biologic-experienced and had an inadequate response, loss of response, or intolerance to a tumour necrosis factor (TNF) blocker or vedolizumab. Patients received filgotinib 200 mg once daily (N = 262), filgotinib 100 mg once daily (N = 285), or placebo (N = 142). At baseline, 78% of patients had an endoscopic subscore of 3; 85% had failed at least 1 prior TNF blocker, 52% had failed vedolizumab, and 43% had failed at least 1 TNF blocker and vedolizumab; 36% were receiving oral corticosteroids only, 13% immunomodulators only, 10% corticosteroids and immunomodulators, and 41% neither corticosteroids nor immunomodulators.

The primary endpoint for UC-1 and UC-2 was the proportion of patients who achieved clinical remission at week 10. Clinical remission was defined as MCS endoscopy subscore of 0 or 1 (endoscopy subscore of 0 defined as normal or inactive disease and subscore of 1 defined as presence of erythema, decreased vascular pattern, and no friability), rectal bleeding subscore of 0 (no rectal bleeding), and at least a one point decrease in stool frequency subscore from baseline to achieve 0 or 1. Key secondary efficacy endpoints included MCS remission, endoscopic remission, and histologic remission at week 10.

UC3 was a 47week maintenance study in 558 patients with ulcerative colitis who achieved clinical response or remission at week 10 from filgotinib in UC1 (N = 320) or UC2 (N = 238). Clinical response was defined as a decrease in MCS of ≥ 3 points and ≥ 30% decrease from baseline, with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1. Patients were re-randomised at week 11 to receive their induction dose of filgotinib or placebo through week 58. As in UC1 and UC2, patients were permitted to use stable doses of oral aminosalicylates or immunomodulators; however, corticosteroid tapering was required three weeks after entering this study. The primary endpoint was the proportion of patients who achieved clinical remission at week 58. Key secondary efficacy endpoints were MCS remission, sustained clinical remission, 6month corticosteroid-free clinical remission, endoscopic remission, and histologic remission at week 58.

Clinical outcomes

Across the UC1 and UC2 studies, a significantly greater proportion of patients receiving filgotinib 200 mg achieved clinical remission at week 10 as compared to placebo (Table 6). A significantly greater proportion of biologic-naïve patients (UC1) receiving filgotinib 200 mg achieved MCS remission, endoscopic remission, and histologic remission at week 10 as compared to placebo (Table 6).

Efficacy in the filgotinib 100 mg group as compared to placebo was not statistically significant at week 10 in either UC-1 or UC-2.

Table 6: Proportion of patients meeting efficacy endpoints at week 10 in induction studies UC-1 and UC-2

Endpoint n (%)	UC-1 Biologic naïve N = 659			UC-2 Biologic experienced [a] N = 689		
	FIL 200 mg N = 245	Placebo N = 137	Treatment difference and 95% CI	FIL 200 mg N = 262	Placebo N = 142	Treatment difference and 95% CI
Clinical remission [b]	64 (26.1%)	21 (15.3%)	10.8% (2.1%, 19.5%) p = 0.0157	30 (11.5%)	6 (4.2%)	7.2% (1.6%, 12.8%) p = 0.0103
Failure to both TNF and vedolizumab [c]	-	-	-	8/120 (6.7%)	1/64 (1.6%)	-
MCS remission [d]	60 (24.5%)	17 (12.4%)	12.1% (3.8%, 20.4%) p = 0.0053	25 (9.5%)	6 (4.2%)	5.3% (−0.1%, 10.7%)
Endoscopic remission [e]	30 (12.2%)	5 (3.6%)	8.6% (2.9%, 14.3%) p = 0.0047	9 (3.4%)	3 (2.1%)	1.3% (−2.5%, 5.1%)
Histologic remission [f]	86 (35.1%)	22 (16.1%)	19.0% (9.9%, 28.2%) p < 0.0001	52 (19.8%)	12 (8.5%)	11.4% (4.2%, 18.6%)

CI: Confidence interval; FIL: filgotinib; MCS: Mayo Clinic Score.

a Biologic experienced = Patients who previously demonstrated an inadequate response, loss of response to, or intolerance of a TNF blocker or vedolizumab.

b Primary endpoint. Clinical remission was defined as MCS endoscopy subscore of 0 or 1 (endoscopy subscore of 0 defined as normal or inactive disease and subscore of 1 defined as presence of erythema, decreased vascular pattern, and no friability), rectal bleeding subscore of 0 (no rectal bleeding), and at least a one point decrease in stool frequency subscore from baseline to achieve 0 or 1.

c Subgroup analysis based on patients with prior treatment failure to both a TNF blocker and vedolizumab.

d MCS remission was defined as MCS ≤ 2 with no individual subscore of > 1.

e Endoscopic remission was defined as MCS endoscopic subscore of 0.

f Histologic remission was assessed using Geboes histologic scores and defined as Grade 0 of ≤ 0.3, Grade 1 of ≤ 1.1, Grade 2a of ≤ 2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0.

The proportion of patients in UC-1 and UC-2 achieving a clinical response was 66.5% and 53.1%, respectively, for patients receiving filgotinib 200 mg compared with 46.7% and 17.6%, respectively, for patients receiving placebo at week 10.

In the maintenance study (UC3), a significantly greater proportion of patients receiving filgotinib 200 mg or filgotinib 100 mg achieved clinical remission at week 58 as compared to placebo. The proportion of patients achieving clinical remission is shown in Table 7. A significantly greater proportion of patients receiving filgotinib 200 mg achieved MCS remission, sustained clinical remission, 6month corticosteroid-free clinical remission, endoscopic remission, and histologic remission at week 58 as compared to placebo.

Key secondary efficacy outcomes for treatment with filgotinib 100 mg as compared to placebo were not statistically significant at week 58.

Table 7: Proportion of patients meeting efficacy endpoints at week 58 in maintenance study UC-3

Endpoint n (%)	Induction FIL 200 mg		
	FIL 200 mg N = 199	Placebo N = 98	Treatment difference and 95% CI
Clinical remission [a b]	74 (37.2%)	11 (11.2%)	26.0% (16.0%, 35.9%) p < 0.0001
Biologic naïve	52/107 (48.6%)	9/54 (16.7%)	-
Biologic experienced	22/92 (23.9%)	2/44 (4.5%)	-
MCS remission [c]	69 (34.7%)	9 (9.2%)	25.5% (16.0%, 35.0%) p < 0.0001
Sustained clinical remission [d b]	36 (18.1%)	5 (5.1%)	13.0% (5.3%, 20.6%) p = 0.0024
Biologic naïve	25/107 (23.4%)	4/54 (7.4%)	-
Biologic experienced	11/92 (12.0%)	1/44 (2.3%)	-
6month corticosteroid-free clinical remission [e b]	25/92 (27.2%)	3/47 (6.4%)	20.8% (7.7%, 33.9%) p = 0.0055
Biologic naïve	18/43 (41.9%)	2/22 (9.1%)	-
Biologic experienced	7/49 (14.3%)	1/25 (4.0%)	-
Endoscopic remission [f]	31 (15.6%)	6 (6.1%)	9.5% (1.8%, 17.1%) p = 0.0157
Histologic remission [g]	76 (38.2%)	13 (13.3%)	24.9% (14.6%, 35.2%) p < 0.0001

CI: Confidence interval; FIL: filgotinib; MCS: Mayo Clinic Score.

a Primary endpoint. Clinical remission was defined as MCS endoscopy subscore of 0 or 1 (endoscopy subscore of 0 defined as normal or inactive disease and subscore of 1 defined as presence of erythema, decreased vascular pattern, and no friability), rectal bleeding subscore of 0 (no rectal bleeding), and at least a one point decrease in stool frequency subscore from induction baseline to achieve 0 or 1.

b Subgroup analysis based on patient participation in UC-1 (biologic naïve) or UC-2 (biologic experienced; TNF blocker and/or vedolizumab).

c MCS remission was defined as MCS ≤ 2 with no individual subscore of > 1.

d Sustained clinical remission was defined as clinical remission at both week 10 and week 58.

e 6month corticosteroid-free clinical remission was defined as clinical remission at week 58 in patients who were on corticosteroid at UC3 baseline and who were not receiving corticosteroids for at least 6 months prior to week 58.

f Endoscopic remission was defined as MCS endoscopic subscore of 0.

g Histologic remission was assessed using Geboes histologic scores and defined as Grade 0 of ≤ 0.3, Grade 1 of ≤ 1.1, Grade 2a of ≤ 2A.3, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0.

Endoscopic response

Endoscopic response was defined as an endoscopic subscore of 0 or 1. The proportion of patients in UC-1 and UC-2 achieving an endoscopic response was 33.9% and 17.2%, respectively, for patients receiving filgotinib 200 mg compared with 20.4% and 7.7%, respectively, for patients receiving placebo, at week 10. In UC-3, 40.7% of patients receiving filgotinib 200 mg *versus* 15.3% of patients receiving placebo achieved endoscopic response at week 58.

Health-related quality of life (HRQoL) outcomes

Patients receiving filgotinib 200 mg reported increases (improvements) in the total and all four domain scores of the Inflammatory Bowel Disease Questionnaire ([IBDQ] bowel symptoms, systemic

function, emotional function, and social function) at week 10 in UC-1 and UC-2, and at week 58 in UC-3.

Long-term extension study
Patients who did not achieve clinical response or remission at week 10 in UC1 or UC2 had the option to receive open-label filgotinib 200 mg in the SELECTION LTE study. After 12 weeks of additional treatment with filgotinib 200 mg in the SELECTION LTE study, the proportion of patients from UC1 and UC2 achieving partial MCS remission was 17.1% (12/70) and 16.7% (15/90), respectively and partial MCS response was achieved by 65.7% (46/70) and 62.2% (56/90), respectively. Partial MCS remission was defined as partial MCS ≤ 1 and partial MCS response was defined as a reduction of ≥ 2 in partial MCS and at least 30% reduction from the induction baseline score, with an accompanying decrease of ≥ 1 in the rectal bleeding subscore or an absolute rectal bleeding subscore of 0 or 1.

Other clinical safety studies
The effect of filgotinib 200 mg on spermatogenesis in men with inflammatory diseases were assessed in two randomized, double-blind, placebo-controlled, parallel-group, phase 2 studies; the MANTA study for active inflammatory bowel disease and the MANTA-RAy study for rheumatic diseases. Both studies had the same design and endpoint assessments through week 13. The patients who met a prespecified semen parameters (sperm concentration, total motility, and morphology) decrease threshold discontinued blinded study drug and entered the Monitoring Phase (MP) for up to 52 weeks or until reversibility was observed, whichever occurred first. The primary endpoint in both studies was the proportion of patients with a 50% or more decrease from baseline in sperm concentration at week 13. Across both studies, 248 patients were randomised to filgotinib or placebo. A total of 240 patients (filgotinib, n=120; placebo, n=120) took at least one dose of study drug, had two evaluable semen samples at baseline and at week 13, and were included in the semen analysis set.

The data from these two dedicated studies showed a similar proportion of patients who had a 50% or more decrease from baseline in semen parameters at week 13 pooled primary endpoint: 8 patients in the filgotinib group (6.7%), 10 patients in the placebo group (8.3%) (Table 8). All 10 patients in the placebo group who experienced a ≥50% decrease from baseline in sperm concentration achieved reversibility by the MP week 52 whereas 2 out of 8 patients in the filgotinib group did not achieve reversibility. One patient did not reverse by the MP week 52, and the other patient did not demonstrate reversibility at the MP week 13 and discontinued the study (patient withdrawal). The data did not show any relevant changes in sex hormone levels or change from baseline in semen parameters across treatment groups.

Table 8: Subjects Meeting Sperm Decrease Thresholds at Week 13 on Double-Blind Study Drug (Semen Analysis Set [Combined Data])

	FIL (N=120)	**PBO (N=120)**
Sperm Decrease Threshold Criteria	n/N (%)	n/N (%)
≥50% Decrease in Sperm Concentration (M/mL)	8/120 (6.7%)	10/120 (8.3%)
≥50% Decrease in Sperm Total Motility (%)	0/120	1/119 (0.8%)
≥50% Decrease in Sperm Morphology (% Normal)	0/120	1/120 (0.8%)
≥50% Decrease in Sperm Concentration (M/mL) and (≥50%Decrease in Total Motility and/or Morphology)	0/120	1/120 (0.8%)

FIL = filgotinib; PBO = placebo
Subjects in the Semen Analysis Set took study drug and had 2 evaluable semen samples at screening and at the Week 13 analysis visit.
Sperm decrease threshold defined as a decrease from baseline of at least 50% in sperm concentration and/or total motility and/ormorphology.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, filgotinib was absorbed quickly and its median peak plasma concentration was observed 2 to 3 hours post-dose after multiple dosing; the median peak plasma concentrations of its primary metabolite GS-829845 were observed 5 hours post-dose after multiple dosing. Filgotinib and GS-829845 exposures (AUC) and C_{max} were similar in healthy adult subjects and patients with rheumatoid arthritis and ulcerative colitis. Filgotinib and GS-829845 exposures (AUC) and C_{max} are dose--proportional over the therapeutic dose range. Steady-state concentrations of filgotinib are achieved in 2 - 3 days with negligible accumulation after once daily administration. Steady-state concentrations of GS-829845 are achieved in 4 days with approximately 2-fold accumulation after once daily dosing of filgotinib.

There were no clinically relevant differences in exposures when filgotinib was administered with a high-fat or low-fat meal as compared to a fasted state. Filgotinib can be administered with or without food.

Steadystate- exposures of filgotinib and GS-829845 are provided in Table 9.

Table 9: Multiple dose pharmacokinetic parameters of filgotinib and GS-829845 following oral administration of filgotinib 200 mg with or without food in patient populations

	Rheumatoid arthritis [a]		**Ulcerative colitis [b]**	
Parameter Mean (%CV)	**Filgotinib [c]**	**GS-829845 [d]**	**Filgotinib**	**GS-829845**
C_{max} (µg/mL)	2.15 (48.1)	4.43 (29.3)	2.12 (50.3) [e]	4.02 (30.5) [e]
AUC_{tau} (µg•h/mL)	6.77 (43.7)	83.2 (27.3)	6.15 (28.1) [f]	72.1 (33.9) [g]

CV: coefficient of variation.

a From intensive PK analyses of studies FINCH 1, FINCH 2, and FINCH 3 in rheumatoid arthritis patients receiving 200 mg filgotinib once daily.

b From intensive PK analysis of SELECTION study in ulcerative colitis patients receiving 200 mg filgotinib once daily.

c N = 37

d N = 33

e N = 13

f N = 12

g N = 11

Distribution

Filgotinib and GS-829845 binding to human plasma proteins is low (55 - 59% and 39 - 44% bound, respectively). The blood-to-plasma ratio of filgotinib ranged from 0.85 to 1.1 indicating no preferential distribution of filgotinib and GS-829845 into blood cells. Filgotinib and GS-829845 are substrates of the P-gp transporter.

Biotransformation

Filgotinib is extensively metabolised with approximately 9.4% and 4.5% of an orally administered dose recovered as unchanged filgotinib in urine and faeces, respectively. Filgotinib is primarily metabolised by CES2, and to a lesser extent by CES1. Both CES2 and CES1 form GS-829845, an active circulating metabolite that is approximately 10-fold less potent than the parent compound. In a clinical pharmacology study, filgotinib and GS-829845 accounted for the majority of radioactivity circulating in plasma (2.9% and 92%, respectively). No other major metabolites were identified.

As both filgotinib and GS-829845 contribute to efficacy, their exposures were combined into a single parameter, AUC_{eff}. AUC_{eff} is the sum of the AUC of filgotinib and GS-829845, corrected for their respective molecular weights and potencies.

Elimination

Approximately 87% of the administered dose was eliminated in the urine as filgotinib and its metabolites, while about 15% of the dose was eliminated in the faeces. GS-829845 accounted for approximately 54% and 8.9% of dose recovered in urine and faeces, respectively. The mean terminal half--lives of filgotinib and GS-829845 were approximately 7 and 19 hours, respectively.

Other special populations

Weight, gender, race, and age
Bodyweight, gender, race, and age did not have a clinically relevant effect on the pharmacokinetics (AUC) of filgotinib or GS-829845.

Elderly
There were no clinically relevant differences in mean filgotinib and GS-829845 exposures (AUC and C_{max}) between older patients aged ≥ 65 years relative to adult patients aged < 65 years.

Renal impairment
The pharmacokinetics of filgotinib and GS-829845 were unaffected in subjects with mild renal impairment (CrCl 60 to < 90 mL/min). Increases in exposures (AUC) of filgotinib, GS-829845, and combined AUC_{eff} (≤ 2-fold), were observed in subjects with moderate renal impairment (CrCl 30 to < 60 mL/min). In subjects with severe renal impairment (CrCl 15 to < 30 mL/min), filgotinib exposure (AUC) increased by 2.2-fold and GS-829845 exposure significantly increased by 3.5-fold leading to a 3-fold increase in AUC_{eff}. The pharmacokinetics of filgotinib has not been studied in subjects with end stage renal disease (CrCl < 15 mL/min).

Hepatic impairment
No clinically relevant changes in the exposures (AUC) of filgotinib and GS-829845 individually, or their combined exposure (AUC_{eff}), were observed in subjects with moderate hepatic impairment (Child-Pugh B). The pharmacokinetics of filgotinib has not been studied in subjects with severe hepatic impairment (Child-Pugh C).

Effect of filgotinib on other medicinal products

Potential interactions between filgotinib and co-administered medicinal products are listed in Table 10 below (increase is indicated as "↑", decrease as "↓", and no change as "↔"; no effect boundaries are 70 - 143% unless otherwise indicated).

Table 10: Interaction studies with filgotinib [1]

Medicinal product by therapeutic areas/Possible mechanism of interaction	Effects on medicinal product levels. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with filgotinib
ANTI-INFECTIVES		
Antimycobacterials		
Rifampicin (600 mg once daily) [2] (P-gp induction)	Filgotinib: AUC: ↓ 27% C_{max}: ↓ 26% GS-829845: AUC: ↓ 38% C_{max}: ↓ 19% AUC_{eff} [6]: ↓ 33%	No dose adjustment is required upon co-administration.

Medicinal product by therapeutic areas/Possible mechanism of interaction	Effects on medicinal product levels. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with filgotinib
Antifungals		
Itraconazole (200 mg single dose) [3] (P-gp inhibition)	Filgotinib: AUC: ↑ 45% C_{max}: ↑ 64% GS-829845: AUC: ↔ C_{max}: ↔ AUC_{eff}: ↑ 21%	No dose adjustment is required upon co-administration.
GASTRIC ACID REDUCING AGENTS		
Famotidine (40 mg twice daily) [2] (Increases gastric pH)	Filgotinib: AUC: ↔ C_{max}: ↔ GS-829845: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.
Omeprazole (40 mg once daily) [2] (Increases gastric pH)	Filgotinib: AUC: ↔ C_{max}: ↓ 27% GS-829845: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.
HMG-CoA REDUCTASE INHIBITORS		
Atorvastatin (40 mg single dose) [4] (Inhibition of CYP3A4/ OATP/BCRP)	Atorvastatin: AUC: ↔ C_{max}: ↓ 18% 2-hydroxy-atorvastatin: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.
Pravastatin (40 mg single dose) [4] (Inhibition of OATP)	Pravastatin: AUC: ↔ C_{max}: ↑ 25%	No dose adjustment is required upon co-administration.
Rosuvastatin (10 mg single dose) [4] (Inhibition of OATP and BCRP)	Rosuvastatin: AUC: ↑ 42% C_{max}: ↑ 68%	No dose adjustment is required upon co-administration.
ORAL ANTI-DIABETICS		
Metformin (850 mg single dose) [4] (Inhibition of OCT2, MATE1, and MATE-2K)	Metformin: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.
ORAL CONTRACEPTIVES		
Ethinyl estradiol (0.03 mg single dose)/Levonorgestrel (0.15 mg single dose) [4]	Ethinyl estradiol: AUC: ↔ C_{max}: ↔ Levonorgestrel: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.

Medicinal product by therapeutic areas/Possible mechanism of interaction	Effects on medicinal product levels. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with filgotinib
SEDATIVES/HYPNOTICS		
Midazolam (2 mg single dose) [4,5] (Inhibition of CYP3A4)	Midazolam: AUC: ↔ C_{max}: ↔ 1'OH-midazolam: AUC: ↔ C_{max}: ↔	No dose adjustment is required upon co-administration.

GS-829845: primary metabolite of filgotinib.

1 All interaction studies conducted in healthy volunteers.
2 Study conducted with filgotinib 200 mg single dose.
3 Study conducted with filgotinib 100 mg single dose.
4 Study conducted with filgotinib 200 mg once daily.
5 Bioequivalence boundaries are 80 - 125% for midazolam and 1'OH-midazolam.
6 As both filgotinib and GS-829845 contribute to efficacy, their exposures were combined into a single parameter, AUC_{eff}. AUC_{eff} is the combined AUC of filgotinib and GS-829845, adjusted for their respective molecular weights and potencies.

Potential for filgotinib to affect other medicinal products
In vitro data indicate that filgotinib and GS-829845 do not inhibit the activity of the following: CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 at clinically relevant concentrations. The potential for filgotinib to induce CYP2B6 constitutive androstane receptor (CAR) mediated metabolism *in vivo* is unknown. No conclusion can be drawn from the *in vitro* data regarding the potential of filgotinib to inhibit or induce CYP1A2. *In vivo* data demonstrated no inhibition or induction of CYP3A4 mediated metabolism.

In vitro studies indicate that filgotinib and GS-829845 are not inhibitors of P-gp, BCRP, OCT1, BSEP, OAT1, OAT3 or OAT4 at clinically relevant concentrations.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology.

The carcinogenic potential of filgotinib was evaluated in a 6-month rasH2 transgenic mouse study and a 2-year rat study. Filgotinib was not carcinogenic in mice at up to 150 mg/kg/day, which resulted in exposures of approximately 25 and 12 times the exposures in humans at the 100 mg and 200 mg once daily doses, respectively. In the 2-year rat study, filgotinib treatment resulted in an increase in incidence and decrease in latency of benign Leydig cell tumours at the highest dose of 45 mg/kg/day (exposures of approximately 4.2 times exposures in humans at the 200 mg once daily dose); the clinical relevance of this finding is low.

Filgotinib was not mutagenic or clastogenic in the *in vitro* bacterial reverse mutation assay, *in vitro* chromosome aberration assay, and *in vivo* rat micronucleus assay.

Adverse findings of degeneration/necrosis of incisor ameloblasts were observed in rats at exposures 21- to 28-fold greater than clinical exposures at the 200 mg filgotinib dose, with exposure margins at the no observed- adverse- effect- -level (NOAEL) ranging from 3.5- to 8-fold. The human relevance of these dental findings is considered low since in contrast to adult patients, ameloblasts in rats persist into adulthood to support lifelong continuous incisor growth.

Impaired spermatogenesis and histopathological effects on male reproductive organs (testes and epididymis) were observed with filgotinib in rats and dogs. The findings include lesions in testis which consisted of germ cell depletion/degeneration and/or tubular vacuolation with corresponding changes in epididymitis, such as reduced sperm content and/or increased cell debris. At the NOAELs in dogs (the most sensitive species), the exposure margin is 0.97- to 2.72-fold at the 200 mg once daily dose in

humans. The severity of the histological effects was dose--dependent. Spermatogenic and histopathological effects were not fully reversible at exposure margins of approximately 7- to 9-fold the exposure at the 200 mg once daily dose in humans.

Embryo-foetal development studies in rats and rabbits demonstrated embryolethality and teratogenicity at exposures comparable to 200 mg filgotinib once daily dosing in humans. Visceral and skeletal malformations and/or variations were observed at all dose levels of filgotinib.

Filgotinib was administered to pregnant rats at doses of 25, 50, and 100 mg/kg/day. Dos--related increases in the incidence of internal hydrocephaly, dilated ureters, and multiple vertebral anomalies were seen at all dose levels. At 100 mg/kg/day, an increased number of early and late resorptions were noted together with a decreased number of viable foetuses. In addition, foetal body weights were decreased.

In rabbits, filgotinib caused visceral malformations mainly in the lungs and cardiovascular system, at a dose level of 60 mg/kg/day. Filgotinib caused skeletal malformations affecting the vertebral column region at dose levels of 25 and 60 mg/kg/day, mainly in vertebra, ribs and sternebrae. Fused sternebrae also occurred at 10 mg/kg/day filgotinib. Retarded skeletal ossification was evidenced at 60 mg/kg/day.

No adverse effects on pre-/postnatal development were observed in rats in a pre- and postnatal development study of filgotinib and GS-829845. Filgotinib and GS-829845 were detected in nursing rat pups after administration of filgotinib to lactating female rats from gestation day 6 through 10 days post-partum at dose levels of 2, 5, and 15 mg/kg/day, likely due to the presence of filgotinib in milk. At the highest tested dose, maternal systemic exposure (AUC) to filgotinib in rats was approximately 2 times the exposure in humans at the 200 mg once daily dose; exposures in nursing pups were less than 6% that of maternal exposure on day 10 post-partum. Due to the low exposure of the animals, the pre-/postnatal development study was considered inconclusive.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Lactose monohydrate
Pregelatinized starch
Colloidal silicon dioxide
Fumaric acid
Magnesium stearate

Film coating

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30°C. Protect from moisture after opening the pouch.

6.5 Nature and contents of container

14 film-coated tablets
[PVC/PCTFE/aluminium foil blister, 14 tablets per sheet × 1 sheet in an aluminium pouch with silica gel desiccant]

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRANT

Eisai (Singapore) Pte. Ltd.
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Singapore 189721

8. DATE OF REVISION OF THE TEXT

March 2024

9. OTHERS

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