

## Efficacy and safety of filgotinib in patients with rheumatoid arthritis and

# inadequate response to disease-modifying antirheumatic drugs (DMARDs): A

# meta-analysis of randomized controlled trials

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#### Abstract

Background: Filgotinib has been approved for the treatment of rheumatoid arthritis (RA) in adults who respond inadequately to disease-modifying anti-rheumatic drugs (DMARDs) in Europe and Japan. Several randomized controlled trials (RCTs) have investigated its efficacy and safety in adult patients with RA. This meta-analysis aimed to study the efficacy and safety of filgotinib in patients with RA with an inadequate response to methotrexate or other DMARDs.

Methods: A systematic literature search was conducted to identify articles in PubMed, MEDLINE, EMBASE, and Cochrane Library from inception to December 1, 2021. Outcomes of interest included ACR20/50/70 responses, DAS28-CRP  $\leq$  3.2, SF-36 PCS Score, FACIT-fatigue, SDAI,CDAI, and HAQ-DI, which were assessed after treatment. The safety outcomes included treatment-emergent adverse events (TEAEs) and serious TEAEs. Odds ratios (ORs) with 95% confidence intervals (CI) were pooled for categorical variables, and the mean difference with 95%CI were pooled for continuous variables. We used Review Manager 5.3 for the standard meta-analysis. This study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Results: Four RCTs comparing filgotinib (200 and 100 mg once daily) with placebo were identified. Compared with placebo, 200 and 100 mg filgotinib was more effective in achieving ACR20/50/70 responses and other outcomes at weeks 12 and 24 (P < 0.05), with no significant difference in safety outcomes (P > 0.05). Filgotinib 200 mg performed better than filgotinib 100 mg in terms of ACR20/50 responses, DAS28-CRP  $\leq$  3.2, SDAI, and CDAI at weeks 12 and 24, and caused fewer serious TEAEs than the 100 mg dose.

Conclusions: Filgotinib is effective in the treatment of RA, and the 200 mg dose has a more beneficial profile than the 100 mg dose.

Keywords: Filgotinib; Rheumatoid arthritis; Meta-analysis; Efficacy



#### Introduction

Rheumatoid arthritis (RA) is a progressive inflammatory disease that is associated with long-term pain and significant disability. RA occurs in approximately 5 per 1000 people<sup>1</sup>.There are more than five million patients with RA in China, of whom 80.46% are women<sup>2</sup>. The direct cost of RA in China is \$1917.21 ± \$2559.06 per patient per year, which is a great economic burden<sup>3</sup>. The target of treatment for RA is to achieve low disease activity or remission. Methotrexate (MTX) is the first-line of therapy, and 40–50% of patients achieve remission or at least low disease activity with a dose of 25 mg weekly in combination with glucocorticoids<sup>1</sup>. However, not all patients respond to MTX. It has been reported that 30% of patients discontinue therapy within 1 year because of a lack of efficacy or undesirable adverse effects<sup>4</sup>.

The American College of Rheumatology (ACR) Guideline (2021) recommends that for patients for whom MTX monotherapy fails to achieve the goal treatment, biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) should be added to their treatment<sup>5</sup>. Janus kinases (JAKs: JAK1, JAK2, JAK3) inhibitors are an important class of tsDMARDs; JAKs are part of the intracellular signaling pathway activated by pro-inflammatory cytokines and participate in the pathogenesis of RA<sup>6</sup>. Filgotinib (Jyseleca<sup>®</sup>) is an oral ATP-competitive, reversible JAK1 preferential inhibitor used for the treatment of inflammatory diseases. A 4-year open-label extension study of phase II AR programs showed that filgotinib was well tolerated and safely administered in combination with MTX or as monotherapy<sup>7</sup>. Filgotinib has been approved for the treatment of RA in adults who have responded inadequately to, or are intolerant to, one or more DMARDs in Europe and Japan<sup>8</sup>. Three JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) have been approved by the United States Food and Drug Administration (FDA). More safety data is required for filgotinib<sup>9</sup>. The aim of this meta-analysis was to evaluate the safety and efficacy of filgotinib in patients with RA with an inadequate response to conventional synthetic DMARDs (csDMARDs), including MTX.

#### **Material and Methods**

#### Types of studies

All published and unpublished RCTs were included. We also would have included cluster-randomized controlled trials and crossover trials, but we found none. There were no language restrictions, and we did not exclude studies based on the date of publication.



## **Types of participants**

We included enrolled patients who were  $\geq$  18 years of age, (1) had a diagnosis of RA (2010 ACR/European League Against Rheumatism (EULAR) criteria) and ACR functional class I–III, and (2) had an inadequate response or intolerance to one or more bDMARDs. The key exclusion criterion was previous treatment with a JAK inhibitor.

### Types of outcome measures

The primary outcome was the proportion of subjects who achieved an ACR20 response at week 12. The secondary outcomes were (1) the proportion of patients with ACR20 responses at week 24; (2) the proportion of patients with ACR50/70 responses at weeks 12 and 24; (3) the proportion of patients with Disease Activity Score 28 - CRP (DAS28-CRP)  $\leq$  3.2 at weeks 12 and 24, higher values indicate higher disease activity; (4) change from baseline in Short Form-36 (SF-36) Physical Component Summary (PCS) score at weeks 12 and 24, positive change in value indicates improvement and better quality of life; (5) change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at weeks 12 and 24, positive change in value indicates improvement; (6) change from baseline in Simplified Disease Activity Index (SDAI)/Clinical Disease Activity Index (CDAI) at weeks 12 and 24, a negative change from baseline indicates improvement; (7) change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at weeks 12 and 24, a negative change from baseline indicates improvement. For safety outcomes, we analyzed treatment-emergent adverse events (TEAEs) and serious TEAEs.

## Information sources and search strategy

A literature review was conducted in the PubMed, Ovid MEDLINE, Ovid EMBASE, and Cochrane Library databases to identify eligible publications (up to December 1, 2021). The following keywords were used in the search: "filgotinib," "GLPG0634," "GS-6034," and "rheumatoid arthritis." We also manually searched the references of relevant reviews, systematic reviews, and included studies to identify other potentially eligible studies.

#### Selection process

Two researchers (YL W and L Y) independently reviewed titles and abstracts. The researchers then independently screened the titles and abstracts of all retrieved articles in pairs. In cases of



disagreement, consensus on which articles to screen for full-text was reached by discussion. If necessary, a third researcher (DM M) was consulted to make a final decision. After this, two researchers (LJ L and B L) independently screened the full-text articles for inclusion. Again, in cases of disagreement, a consensus was reached on inclusion or exclusion by discussion, and if necessary, a third researcher (LM P) was consulted.

#### **Data extraction**

Two investigators (ZG L and JY R) independently extracted data from the studies. The following details were derived from each study: (1) study characteristics: first author, year of publication, region, number of patients, study design, drug doses and frequency, follow-up duration, and inclusion/exclusion criteria; (2) patient characteristics: age, disease duration, and disease severity at baseline; (3) the primary outcome: ACR20 response at week 12; (4) the secondary outcomes: ACR20 response at week 24; ACR50/ACR70 responses and DAS28-CRP  $\leq$  3.2 at weeks 12 and 24, change from baseline in SF-36 PCS Score/FACIT-Fatigue/SDAI/CDAI/HAQ-DI at weeks 12 and 24; (5) Safety outcomes: TEAEs and serious TEAEs.

#### **Statistical analysis**

The Review Manager (RevMan 5.3) was used for the meta-analysis. Odds ratios (OR) with 95% confidence intervals (*CI*) were pooled for categorical variables. The mean difference (MD) with 95% *CI* were pooled for continuous variables. The significance level was set at 0.05, with a 2-tailed test used. *I*<sup>2</sup> statistic was used to evaluate heterogeneity between studies, and a value of > 50 was indicated significant heterogeneity. Because of the small number of studies, we did not test publication bias because any test would have had a low power to distinguish between chance and real asymmetry. We assessed the risk of bias in individual studies using the Cochrane Collaboration tool. The GRADE approach was used to assess the quality of the body of evidence for each individual efficacy outcome using within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias<sup>10</sup>. We performed this meta-analysis in compliance with the guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)<sup>11</sup>.



#### Results

#### **Description of studies**

We retrieved 55 citations from the electronic databases and manual search, as shown in Figure 1. After duplicates were removed, 41 articles were screened and the full text of 10 articles were reviewed for eligibility. Four studies met the eligibility criteria and were included in the final analysis (12-15). Meta-analysis for efficacy and safety outcome measures was performed using data from the end of the study period (timeframe: 12 and 24 weeks).

A total of 2346 patients (777 in the filgotinib 200 mg group, 788 in the filgotinib 100 mg group, and 781 in the placebo group) were included in the meta-analysis of the four included studies. There were 1269 (81%) women in the filgotinib groups (200 and 100 mg groups combined) and 638 (81.7%) in the placebo group. The baseline characteristics of the studies were comparable across all groups. The baseline characteristics of the studies are presented in Table I.

#### Filgotinib 200 mg versus placebo at week 12

Compared to placebo, 200 mg of filgotinib was more effective in achieving ACR20 [*OR* 3.60; 95% *Cl* 2.90 – 4.46; *P* < 0.001; *l*<sup>2</sup>=24%], ACR50 [*OR* 3.95; 95% *Cl* 3.13 – 4.98; *P* < 0.001; *l*<sup>2</sup>=0%], ACR70 responses [*OR* 4.35; 95% *Cl* 3.20 – 5.93; *P* < 0.001; *l*<sup>2</sup>=0%], and DAS28-CRP  $\leq$  3.2 [*OR* 3.34; 95% *Cl* 2.60 – 4.28; *P* < 0.001; *l*<sup>2</sup>=0%]at week 12 as shown in Figure 2A. The filgotinib 200 mg group had higher SF-36 PCS [*MD* 4.25; 95% *Cl* 3.12 – 5.38; *P* < 0.001; *l*<sup>2</sup>=38%] and FACIT-Fatigue [*MD* 4.76; 95% Cl 2.42 – 7.10; *P* < 0.001; *l*<sup>2</sup>=71%] and lower SDAI [*MD* -9.90; 95% Cl -13.32 to -6.49; *P* < 0.001; *l*<sup>2</sup>=73%] and CDAI [*MD* -8.68; 95% *Cl* -11.88 to -5.48; *P* < 0.001; *l*<sup>2</sup>=71%] than the placebo group (Figure 2B). Similarly, 100 mg of filgotinib was more effective than placebo in achieving ACR20/50/70 responses and DAS28-CRP  $\leq$  3.2 (Supplementary file 1) and other outcomes (Supplementary file 2).

#### Filgotinib 200 mg versus placebo at week 24

Compared to placebo, 200 mg of filgotinib was more effective in achieving ACR20 [*OR* 2.84; 95% *Cl* 1.90 – 4.23; *P*< 0.001;  $l^2 = 61\%$ ], ACR50 [*OR* 3.28; 95% *Cl* 2.38 – 4.53; *P* < 0.001;  $l^2 = 33\%$ ], ACR70 responses [*OR* 3.57; 95% *Cl* 2.72 – 4.68; *P* < 0.001;  $l^2 = 0\%$ ], and DAS28-CRP ≤ 3.2 [*OR* 3.16; 95% *Cl* 2.49 – 3.99; *P* < 0.001;  $l^2 = 0\%$ ] at week 24 as shown in Figure 3A. There was no significant difference in



safety outcomes between the two groups (*P*>0.05). The filgotinib 200 mg group had higher SF-36 PCS [*MD* 4.94; 95% *Cl* 2.20 – 7.67; *P* < 0.001;  $l^2 = 82\%$ ] and FACIT-Fatigue [*MD* 3.66; 95% *Cl* 1.28 – 6.04; *P* = 0.003;  $l^2 = 58\%$ ] and lower SDAI [*MD* –8.86; 95% *Cl* -14.57 to -3.14; *P* = 0.002;  $l^2 = 86\%$ ] and CDAI [*MD* -7.41; 95% *Cl* -12.63 to -2.19; *P* =0.005;  $l^2 = 84\%$ ] (Figure 3B) at 24 weeks than the placebo group. The result of HAQ-DI can be seen in Supplementary file 3. Similarly, 100 mg of filgotinib was more effective than placebo in achieving ACR20/50/70 responses, DAS28-CRP ≤ 3.2 (Supplementary file 4), and other outcomes (Supplementary file 5).

#### Filgotinib 200 mg versus filgotinib 100 mg at week 12

Compared to filgotinib 100 mg, 200 mg of filgotinib was more effective in achieving ACR20 [*OR* 1.40; 95% *Cl* 1.12 – 1.74; *P* = 0.003; *l*<sup>2</sup> = 0%], ACR50 [*OR* 1.50; 95% *Cl* 1.23 – 1.84; *P* < 0.001; *l*<sup>2</sup> = 0%], ACR70 responses [*OR* 1.47; 95% *Cl* 1.16 – 1.87; *P* = 0.002; *l*<sup>2</sup> = 0%], and DAS28-CRP  $\leq$  3.2 [*OR* 1.46; 95% *Cl* 1.16 – 1.82; *P*=0.001; *l*<sup>2</sup> = 16%] at week 12 as shown in Figure 4A. There was no significant difference in SF-36 PCS and FACIT-Fatigue between the two groups (*P* > 0.05). Compared to filgotinib 100 mg, SDAI [*MD* –2.75; 95% *Cl* -4.09 to -1.41; *P*< 0.001; *l*<sup>2</sup> = 0%] and CDAI [*MD* -2.46; 95% *Cl* -3.76 to -1.15; *P* < 0.001; *l*<sup>2</sup> = 0%] were marginally better improved by filgotinib 200 mg (Figure 4B).

#### Filgotinib 200 mg versus filgotinib 100 mg at week 24

Compared to 100 mg of filgotinib, 200 mg of filgotinib was more effective in achieving ACR20 [*OR* 2.75; 95% *Cl* 2.22 – 3.42; *P* < 0.001; *l*<sup>2</sup> = 61%], ACR50 [*OR* 1.26; 95% *Cl* 1.03 – 1.54; *P* = 0.03; *l*<sup>2</sup> = 0%], and DAS28-CRP  $\leq$  3.2 [*OR* 1.36; 95% *Cl* 1.08 – 1.70; *P* = 0.008; *l*<sup>2</sup> = 0%] at week 24. There were no significant differences in ACR70 responses, TEAEs, and SF-36 PCS scores between the two groups (*P*>0.05). The filgotinib 200 mg group had higher FACIT-Fatigue [*MD* 1.92; 95% Cl 0.86 – 2.99; *P* < 0.001; *l*<sup>2</sup> = 0%] and lower SDAI [*MD* -3.11; 95% *Cl* -4.37 to -1.85; *P* < 0.001; *l*<sup>2</sup> = 0%] and CDAI [*MD* -1.86; 95% Cl -3.10 – 0.62; *P* = 0.003; *l*<sup>2</sup> = 0%] than the filgotinib 100 mg group. There was no significant difference in TEAEs between the two groups (*P*>0.05), and the risk of serious TEAEs at the 200 mg dose was 0.3 times that with filgotinib 100 mg[*OR* 0.30; 95% *Cl* 0.15 – 0.61; *P* < 0.001; *l*<sup>2</sup> = 70%] (Figure 5A and Figure 5B).The results of the HAQ-Dlare shown in Supplementary file 6.



#### Risk of bias and quality of evidence

One of the criteria for including a study in the statistical analysis was the study quality. The Cochrane evaluation tool was used to assess the quality of the studies. These studies had an unclear risk of bias. We considered all studies that were used for the statistical analysis high-quality studies. The results of this assessment showed that the researchers followed the criteria for obtaining high-quality studies.

#### Discussion

This meta-analysis is the first to comprehensively evaluate the safety and efficacy of filgotinib inpatients with RA with an inadequate response to csDMARDs, including MTX. We retrieved four RCTs and extracted the efficacy and safety data of two doses of filgotinib (200 and 100 mg) and placebo. After pooling, once-daily doses of both 200 and 100 mg filgotinib significantly improved signs, symptoms, and physical function in patients with RA who had an inadequate response to csDMARDs compared to placebo, and there was no significant difference in safety outcomes (P > 0.05). The results at 12 and 24 weeks showed that filgotinib 200 mg was more beneficial than filgotinib 100 mg.

Treat-to-target (T2T) therapy is currently the mainstay of therapy for patients with early RA. MTX combined with glucocorticoid bridging is the mainstay of T2T therapy<sup>16</sup>. In 2019, EULAR suggested adopting MTX as the first choice of csDMARDs, regardless of disease activity<sup>17</sup>. The 2021 ACR Guideline for the treatment of RA recommends MTX as the first choice of DMARDs for patients with medium and high disease activity. Despite treatment with csDMARDs and bDMARDs, 30-40% of patients undergoing MTX treatment do not achieve ideal therapeutic effects and are prone to tolerance (18). JAK inhibitors (JAKs: JAK1, JAK2, and JAK3 inhibitors) are an important class of tsDMARDs. They selectively interfere with the ATP-binding site of JAKs, resulting in the suppression of downstream signaling pathways, which can have immunomodulatory effects on a wide range of pathological processes<sup>19</sup>. Small-molecule JAK inhibitors have been clinically developed for the treatment of RA. Assessment of drug-drug interaction potential suggests that to facitinib, baricitinib, and upadacitinib were generally beneficial with no perpetrator activity<sup>20</sup>. New JAK inhibitors may alter treatment paradigms through rapid dose-dependent action<sup>21</sup>. Filgotinib, a new JAK inhibitor, has been engineered to confer greater selectivity for JAK1 than for JAK2, JAK3, or Tyk2<sup>22</sup>. Filgotinib is generally well tolerated when administered alone or in combination with other drugs. Clinical studies have confirmed that filgotinib has a low risk of drug-drug interactions<sup>23</sup>. A systematic review indicated that



no dose changes were required when P-gp modulators and OCT2, MATE1, and MATE2K substrates were used in combination with filgotinib<sup>24</sup>. Another study showed that filgotinib has no clinically meaningful effect on exposure to atorvastatin, pravastatin, or rosuvastatin<sup>25</sup>.

Song et al.<sup>26</sup> reported that 100 mg and 200 mg filgotinib administered once daily in combination with MTX was the most efficacious intervention for active RA. Our research revealed that the efficacy of the 200 mg dose was better than that of the 100 mg dose in achieving ACR20/50/70 and DAS28-CRP  $\leq$  3.2 at week 12, with better improvement in SDAI and CDAI. At week 24, the efficacy of the 200 mg dose was also better in achieving ACR20/50, DAS28-CRP ≤ 3.2, FACIT-Fatigue, SDAI, and CDAI. There was no significant difference in TEAEs between 100 and 200 mg filgotinib (P > 0.05); however, the 200 mg dose had fewer serious TEAEs (3.86%, 30/777) than the 100 mg dose. This is consistent with the results of the latest pharmacokinetic study, which confirmed that filgotinib produced more robust therapeutic effects when administered at 200 mg once daily dosing than when administered at lower doses<sup>27</sup>. Lee et al. compared the efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib, and peficitinib as monotherapy for active rheumatoid arthritis; filgotinib 200 mg was superior to filgotinib 100 mg, tofatinib 5 mg, upadacitinib 15 mg, baricitinib 4 mg, and placebo<sup>28</sup>. In addition to being effective in patients with RA with an inadequate response to DMARDs, several RCTs on DMARDnaive RA patients showed that JAK inhibitors were more effective than MTX<sup>29-31</sup>. However, whether tsDMARDs are superior to MTX as first-line treatment for patients with moderate to high disease activity is still debated by the ACR panel<sup>5</sup>.

#### Conclusion

In conclusion, we conducted a meta-analysis involving four RCTs and found that filgotinib 200 and 100 mg can improve ACR20, ACR50, ACR70, DAS28-CRP  $\leq$  3.2, SF-36 PCS score, FACIT-Fatigue, HAQ-DI, SDAI, and CDAI in patients with RA with inadequate response to csDMARDs, including MTX. Compared with the 100 mg dose, 200 mg of filgotinib has a more beneficial profile. The goal of this study is to provide evidence for filgotinib as a new option for the treatment of refractory rheumatoid arthritis. However, further studies on the long-term efficacy and pharmacovigilance studies are required to support its long-term use.



## Author contribution

YLW, LY, and LMP conducted the studies, participated in collecting data, and drafted the manuscript. DM M, LJ L, and B L performed the statistical analyses and participated in the design. ZG L, JY R, and TY C participated in the acquisition, analysis, and interpretation of data and drafted the manuscript.





### Figure 2A

	filgotinib 20	)0mg	Place	to		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
2.1.1 ACR20							
Combe 2021	364	475	237	475	62.5%	3.29 [2.49, 4.35]	<b>∎</b>
Genovese 2019	97	147	46	148	17.6%	4.30 [2.64, 7.00]	_ <b>_</b>
Kavanaugh 2018	50	69	21	72	6.4%	6.39 [3.07, 13.30]	
Westhovens 2017	59	86	38	86	13.5%	2.76 [1.48, 5.15]	
Subtotal (95% CI)		777		781	<b>100.0</b> %	3.60 [2.90, 4.46]	•
Total events	570		342				
Heterogeneity: Chi <sup>z</sup> =	3.96, df = 3 (ł	P = 0.27	'); I <sup>z</sup> = 249	%			
Test for overall effect:	Z=11.67 (P	< 0.000	01)				
2.1.2 ACR50							
Combe 2021	224	475	94	475	67.1%	3.62 [2.71, 4.83]	
Genovese 2019	63	147	22	148	16.9%	4.30 [2.46, 7.51]	
Kavanaugh 2018	30	69	8	72	6.0%	6.15 [2.56, 14.77]	
Westhovens 2017	37	86	13	86	10.0%	4.24 [2.05, 8.78]	
Subtotal (95% CI)		777		781	100.0%	3.95 [3.13, 4.98]	
Total events	354		137				
Heterogeneity: Chi <sup>2</sup> =	1.46, df = 3 (ł	P = 0.69	l); l² = 0%				
Test for overall effect:	Z=11.56 (P	< 0.000	01)				
2.1.3 ACR70							
Combe 2021	124	475	32	475	54.3%	4.89 [3.24, 7.39]	
Genovese 2019	32	147	10	148	17.9%	3.84 [1.81, 8.15]	
Kavanaugh 2018	29	69	12	72	15.6%	3.63 [1.66, 7.93]	
Westhovens 2017	21	86	7	86	12.2%	3.65 [1.46, 9.11]	
Subtotal (95% CI)		777		781	100.0%	4.35 [3.20, 5.93]	•
Total events	206		61				
Heterogeneity: Chi <sup>2</sup> =	0.77, df = 3 (f	P = 0.86	i); l² = 0%				
Test for overall effect:	Z= 9.34 (P <	0.0000	1)				
2.1.4 DAS28-CRP ≤ 3	3.2			- b.		/ 1	
Combe 2021	236	475	111	475	80.5%	3.24 [2.45, 4.28]	∎
Genovese 2019	60	147	23	148	19.5%	3.75 [2.16, 6.52]	
Subtotal (95% CI)		622		623	100.0%	3.34 [2.60, 4.28]	● ●
Total events	296		134		• •		
Heterogeneity: Chi <sup>2</sup> =	0.21, df = 1 (i	P = 0.64	); l <sup>2</sup> = 0%				
Test for overall effect:	Z = 9.50 (P <	0.0000	1)				
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		/m \		/			U.U1 U.1 I IU 100
Test for subaroup diffe	erences: Chi <sup>a</sup>	<sup>2</sup> = 2.06.	df = 3 (P	= 0.56	). I <sup>z</sup> = 0%		Favours (experimental) Favours (control)
			/				
		r					



### Figure 2B

	filgotiı	filgotinib 200mg Placeto						Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.2.1 SF-36 PCS									
Combe 2021	9.2	8.1	475	5.8	7.1	480	44.2%	3.40 [2.43, 4.37]	•
Genovese 2019	7.6	7.68	147	3.6	8.16	153	24.7%	4.00 [2.21, 5.79]	
Kavanaugh 2018	8.6	9.05	69	3	7.55	70	13.3%	5.60 [2.83, 8.37]	
Westhovens 2017	8.9	8.35	86	3.2	6.86	85	17.8%	5.70 [3.41, 7.99]	
Subtotal (95% CI)			777			788	100.0%	4.25 [3.12, 5.38]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	2 = 7.36	ii² = 4.85 (P ≤ 0.0	5, df = 3 0001)	(P = 0.1	8); I² = (	38%			
2.2.2 FACIT-Fatigue									_
Combe 2021	9.2	9.8	475	6.8	9.9	480	33.6%	2.40 [1.15, 3.65]	
Genovese 2019	9.6	11.24	147	4.5	10.37	153	26.4%	5.10 [2.65, 7.55]	
Kavanaugh 2018	11.2	11.96	69	3.9	10.44	70	19.1%	7.30 [3.57, 11.03]	
Vvestnovens 2017	11.4	12.7	86	5.6	9.83	85 700	20.8%	5.80 [2.40, 9.20]	
Hotorogonoity: Tou? -	- 201. Ch	u <b>≅</b> – 10 3	05 df-	2 /D – N	02118-	7106	100.0%	4.70 [2.42, 7.10]	-
Test for overall effect:	Z = 3.98	(P < 0.0	001)	3 (F – U.	02),1 -	7170			
2.2.3 SDAI									
Combe 2021	-27.1	12.69	475	-20.6	13.85	480	33.1%	-6.50 [-8.18, -4.82]	- N
Genovese 2019	-27.6	15.54	147	-17.2	15.52	153	26.1%	-10.40 [-13.92, -6.88]	
Kavanaugh 2018	-26.5	14.57	69	-12.57	16.84	70	19.5%	-13.93 [-19.16, -8.70]	
Westhovens 2017	-27.2	14.37	86	-16.3	17.06	85	21.3%	-10.90 [-15.63, -6.17]	
Subtotal (95% CI)			777			788	100.0%	-9.90 [-13.32, -6.49]	
Heterogeneity: Tau* = Test for overall effect:	2 = 5.69	u² = 11.2 (P ≤ 0.0	21, df = 0001)	3 (P = 0.	01); F=	73%			$\sim$
2.2.4 CDAI									
Combe 2021	-26	12.41	475	-20.3	13.3	480	33.9%	-5.70 [-7.33, -4.07]	+
Genovese 2019	-26.2	15.04	147	-17.3	15.22	153	26.1%	-8.90 [-12.32, -5.48]	
Kavanaugh 2018	-25.07	14.47	69	-11.7	15.91	70	19.3%	-13.37 [-18.42, -8.32]	
Westhovens 2017	-25.5	13.91	86	-16.6	17.06	85	20.7%	-8.90 [-13.57, -4.23]	
Subtotal (95% CI)			777			788	100.0%	-8.68 [-11.88, -5.48]	-
Heterogeneity: I auf =	7.16; Ch	(n= 10.3 (n= 0.0	36, at =	3 (P = 0.	02); 1*=	71%			
l est for overall effect.	Z = 5.321	(P < 0.0	0001)						
									-20 -10 0 10 20
Test for subaroup diff	ferences:	Chi <sup>2</sup> = 1	09.90.	df = 3 (P	< 0.00	001), I <sup>z</sup>	= 97.3%		Favours (experimentai) Favours (control)
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## Figure 3A

	filgotinib 20	Omg	Place	to		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.1.1 ACR20							
Combe 2021	371	475	281	475	34.9%	2.46 [1.85, 3.27]	
Genovese 2019	102	147	51	148	26.0%	4.31 [2.65, 7.02]	
Kavanaugh 2018	46	69	41	72	18.9%	1.51 [0.76, 3.00]	
Westhovens 2017	63	86	36	86	20.3%	3.80 [2.00, 7.23]	
Subtotal (95% CI)		111		781	100.0%	2.84 [1.90, 4.23]	
l otal events	582	70.46	409				
Test for everall effect:	0.10; Chif = 7 7 = 5.11 /D 21	./b,ui= 0.00004	:3(P=L \	J.US); IT	= 61%		
restion overall ellect.	Z = 0.11 (F < 1	0.00001	/				
3.1.2 ACR50							
Combe 2021	275	475	158	475	56.6%	2 76 (2 1 2 3 59)	
Genovese 2019	67	147	28	148	26.7%	3.59 [2.13, 6.06]	_ <b>_</b> _
Westhovens 2017	43	86	14	86	16.7%	5.14 [2.52, 10.48]	
Subtotal (95% CI)		708		709	100.0%	3.28 [2.38, 4.53]	• • • • • • • • • • • • • • • • • • •
Total events	385		200				
Heterogeneity: Tau² =	0.03; Chi <sup>2</sup> = 2	.99, df=	= 2 (P = 0	).22); lª	= 33%		
Test for overall effect:	Z=7.25 (P ≺ I	0.00001	)				
3.1.3 ACR70							A [ A2
Combe 2021	172	475	71	475	/4.5%	3.23 [2.36, 4.42]	
Genovese 2019 Woothouses 2017	47	147	12	148	15.7%	5.33 [2.69, 10.56]	
vvestnovens 2017 Subtotal (95% CI)	25	80 709	8	80 700	9.8%	4.00 [1.68, 9.48]	
Total events	244	700	01	709	100.0%	5.57 [2.72, 4.00]	
Hotorogeneity: Tou <sup>2</sup> –	 	77 df-	ອາ - 2 (P – 1	1/11/17	- 0%		
Test for overall effect:	7 = 9 20 (P < 1	.,,, ui - 0.00001	· 2 () - ( )	.417,1	- 0 /0		
	2 - 0.20 ()	0.00001	<i>′</i>				
3.1.4 HAQ-DI							
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not applicable	е					
3.1.5 DAS28-CRP ≤ 3	3.2						
Combe 2021	288	475	160	475	79.1%	3.03 [2.33, 3.95]	
Genovese 2019 Subtetel (05% CD	71	14/	30	148	20.9%	3.67 [2.20, 6.15]	
Subtotal (95% CI)	250	022	400	023	100.0%	5.10 [2.49, 5.99]	•
Hotorogeneity: Tou <sup>2</sup> -	309 0.00:⊂bi≇–0	12 df-	190 - 170 – 1	1.621-18	- 0%		
Test for overall effect:	7 = 9.57 (P < 1	0.42, UI - 0.00001	· i (r – t		- 0 %		
restion overall enect.	2= 0.01 (1 - 1	0.00001	′				
3.1.6 Treatment-eme	rgent advers	e events	s (TEAE)		_		
Combe 2021	287	475	252	475	30.8%	1.35 [1.04, 1.75]	
Genovese 2019	82	147	100	148	25.8%	0.61 [0.38, 0.97]	
Kavanaugh 2018	30	69	28	72	21.0%	1.21 [0.62, 2.37]	- <b> -</b>
Westhovens 2017	50	86	32	86	22.4%	2.34 [1.27, 4.32]	
Subtotal (95% CI)		777		781	100.0%	1.21 [0.73, 2.00]	
Total events	449		412				
Heterogeneity: Tau <sup>2</sup> =	0.20; Chi <sup>2</sup> = 1	3.37, df	'= 3 (P =	0.004)	i; l² = 78%		
l est for overall effect:	Z = 0.76 (P = 1	0.45)					
3.1.7 Serious TEAE							
Combo 2021	21	475	20	475	70.1%	1.05/0.56/1.071	
Genovese 2021	4	470	20	470	15.4%	0.80 (0.00, 1.87)	<b>_</b>
Kavanaugh 2018	4	147 60	1	72	5.4%	3 23 [0 33 31 80]	
Westhovens 2017	2	86	4	86	9.2%	0.49 (0.09, 01.00)	
Subtotal (95% CI)	-	777	-1	781	100.0%	1.00 [0.59, 1.68]	<b>•</b>
Total events	30		30				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> = 1	.81, df=	= 3 (P = 0	).61); l <sup>a</sup>	= 0%		
Test for overall effect:	Z = 0.01 (P = )	0.99)					
<b></b>	<b>.</b>					~~ ~~	Favours [experimental] Favours [control]
Lect for subgroup diff	oronnos: Chiž	= 30.60	idt=5.0	P < D 0	UU11\ I₹—	83796	· · · · ·

Test for subaroup differences: Chi² = 30.59, df = 5 (P < 0.0001), l² = 83.7%



## Figure 3B

	filgoti	inib 200	mg	Р	laceto			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
3.2.1 SF-36 PCS									
Combe 2021	10.5	8.5	475	7.7	7.97	475	39.1%	2.80 [1.75, 3.85]	
Genuvese 2019 Waathavana 2017	9.4	0.23	09	3.3	202.1	21	29.7%	0.10[3.43, 8.77] 6.60[4.07:002]	
Subtotal (95% CI)	9.7	9.2	630	3.2	0.00	633	100.0%	4.94 [2.20, 7.67]	•
Heterogeneity: Tau <sup>2</sup> =	4.70; CI	hi² = 11.	05. df =	2 (P = (	0.004); I	<b>r</b> = 829	8		-
Test for overall effect:	Z = 3.54	(P = 0.0	0004)						
3.2.2 FACIT-Fatigue									
Combe 2021	10.5	10.63	475	8.4	10.48	475	48.3%	2.10 [0.76, 3.44]	<b>■</b>
Genovese 2019	11.6	11.67	69	7	10.23	72	24.5%	4.60 [0.97, 8.23]	
Vvestnovens 2017 Subtotal (95% CI)	11.6	12.33	630	б	9.64	633	27.2%	5.60 [2.29, 8.91]	•
Heterogeneity: Tau <sup>2</sup> =	2.58; CI	hi² = 4.7	4, df = 2	! (P = 0.	09); I <b>²</b> =	58%	100.070	5.00 [ 1.20, 0.04]	
Test for overall effect:	Z = 3.02	! (P = 0.0	JO3)						
3.2.3 SDAI	24.0	1240	175	26.6	12.04	175	20 500	5201600 260	
Compeizozi Genevece 2019	-31.8	12.18	4/5 60	-20.0	12.91	4/5	38.5%	-5.20 [-6.80, -3.60]	
Westhovens 2017	-32.1	15.02	86	-15.8	18.55	86	30.3%	-15 20 [-20 24 -10 16]	
Subtotal (95% CI)			630			633	100.0%	-8.86 [-14.57, -3.14]	
Heterogeneity: Tau² =	21.37; 0	Chi² = 13	3.90, df	= 2 (P =	0.0010	)); <b> </b> ² = 8	36%		X
Test for overall effect:	Z = 3.04	(P = 0.0	002)						
3.2.4.00.04									
Comba 2021	-30.6	11 99	475	- 26 2	12.20	475	20.2%	-4 20 1.5 94 -2 781	-
Genovese 2019	-30.9	13.77	69	-25.4	14.4	72	30.7%	-5.50 [-10.15, -0.85]	
Westhovens 2017	-29.4	13.91	86	-16	18.08	86	30.1%	-13.40 [-18.22, -8.58]	
Subtotal (95% CI)			630			633	<b>100.0</b> %	-7.41 [-12.63, -2.19]	→
Heterogeneity: Tau² =	: 17.52; (	Chi² = 12	2.43, df	= 2 (P =	0.002)	; <b> </b> ² = 84	1%		
Test for overall effect:	Z = 2.78	(P = 0.0	005)						
									-20 -10 0 10 20
Test for subaroup dif	ferences	: Chi²=	32.65. (	if = 3 (P	< 0.00	001). I <sup>z</sup>	= 90.8%		Favours [experimental] Favours [control]
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## Figure 4A

	filgotinib 2	00mg	filgotinib	100mg		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
4.1.1 ACR20							_
Combe 2021	364	475	335	480	56.9%	1.42 [1.06, 1.89]	
Genovese 2019	97	147	88	153	21.4%	1.43 [0.90, 2.29]	<b>+</b> ■
Kavanaugh 2018	50	69	46	70	9.2%	1.37 [0.67, 2.83]	
Westhovens 2017	59	86	54	85	12.5%	1.25 [0.67, 2.37]	
Subtotal (95% CI)		777		788	<b>100.0</b> %	1.40 [1.12, 1.74]	◆
Total events	570		523				
Heterogeneity: Chi² =	0.14, df = 3 (	(P = 0.99	); I² = 0%				
Test for overall effect:	Z = 3.01 (P =	: 0.003)					
4.1.2 ACR50							
Combe 2021	224	475	175	480	60.4%	1.56 [1.20, 2.01]	+
Genovese 2019	63	147	49	153	18.0%	1.59 [0.99, 2.55]	
Kavanaugh 2018	30	69	26	70	9.6%	1.30 [0.66, 2.57]	
Westhovens 2017	37	86	32	85	12.0%	1.25 [0.68, 2.31]	
Subtotal (95% CI)		777		788	100.0%	1.50 [1.23, 1.84]	•
Total events	354		282				
Heterogeneity: Chi <sup>2</sup> =	0.64. df = 3 (	P = 0.89	);   <sup>2</sup> = 0%				
Test for overall effect:	Z = 3.92 (P =	0.0001	)				
	,	,					
4.1.3 ACR70							
Combe 2021	124	475	89	480	58.7%	1.55 [1.14, 2.11]	
Genovese 2019	32	147	22	153	15.1%	1.66 [0.91, 3.01]	
Kavanaugh 2018	29	69	27	70	13.9%	1.15 [0.59, 2.28]	
Westhovens 2017	21	86	18	85	12.3%	1.20 [0.59, 2.46]	
Subtotal (95% CI)		777		788	100.0%	1.47 [1.16, 1.87]	✓ ★
Total events	206		156				
Heterogeneity: Chi <sup>2</sup> =	1.06, df = 3 (	(P = 0.79	); I² = 0%				
Test for overall effect:	Z = 3.16 (P =	: 0.002)					
44404000 000 < 2							
4.1.4 DAS28-CRP ≤ 3	5.2		400	400	70.00		
Compe 2021	236	4/5	186	480	73.8%	1.56 [1.21, 2.02]	
Genovese 2019 Subtetel (05% CI)	60	147	57	153	20.2%	1.16 [0.73, 1.85]	
Subtotal (95% CI)	206	022	242	033	100.0%	1.40 [1.10, 1.82]	•
Lotaregeneity: Chiž-	290 4 40 df = 47	m = 0.00	∠43 \\B160/				
Test for everall effect:	1.19, ut = 1 ( 7 = 2.20 / D =	(F = 0.20 - 0.004)	), 11 = 10 %				
restion overall ellect.	д — 3.20 (F –	- 0.001)					
				. 1			F F F F F F F F F F F F F F F F F F F
					/		0.01 0.1 1 10 100
Test for subaroun diffe	erences: Chi	i <sup>z</sup> = 0.23	df = 3 (P =	= 0.97) I <sup>2</sup> -	- 0%		Favours [experimental] Favours [control]
	crences. on	1 - 0.23.	ui - 5 (i -	- 0.517.1 -	- 0 /0		
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## Figure 4B

	filgoti	nib 200ı	mg	filgoti	nib 100r	ng		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
4.2.1 SF-36 PCS									
Combe 2021	9.2	8.1	475	8.5	7.7	480	63.2%	0.70 [-0.30, 1.70]	
Genovese 2019	7.6	7.68	147	6.8	8.22	153	19.6%	0.80 [-1.00, 2.60]	
Kavanaugh 2018	8.6	9.05	69	7.8	8.7	70	7.3%	0.80 [-2.15, 3.75]	_ <del></del>
Westhovens 2017	8.9	8.35	86	8.4	8.57	85	9.9%	0.50 [-2.04, 3.04]	
Subtotal (95% CI)			777			788	100.0%	0.71 [-0.09, 1.50]	◆
Heterogeneity: Chi <sup>2</sup> =	0.04, df=	= 3 (P =	1.00); P	²= 0%					
Test for overall effect:	Z=1.74	(P = 0.0	8)						
4.2.2 FACIT-Fatigue									
Combe 2021	9.2	9.8	475	9.1	10.2	480	66.6%	0.10 [-1.17, 1.37]	+
Genovese 2019	9.6	11.24	147	8.3	10.8	153	17.2%	1.30 [-1.20, 3.80]	+
Kavanaugh 2018	11.2	11.96	69	10.2	10.12	70	7.9%	1.00 [-2.69, 4.69]	
Westhovens 2017	11.4	12.7	86	9.5	11.16	85	8.3%	1.90 [-1.68, 5.48]	
Subtotal (95% CI)			777			788	100.0%	0.53 [-0.51, 1.56]	
Heterogeneity: Chi <sup>2</sup> =	1.43, df=	= 3 (P =	0.70); P	²= 0%					
Test for overall effect:	Z=1.00	(P = 0.3	2)						
4.2.3 SDAI									
Combe 2021	-27.1	12.69	475	-24.1	12.54	480	69.6%	-3.00 [-4.60, -1.40]	
Genovese 2019	-27.6	15.54	147	-24.9	15.01	153	14.9%	-2.70 [-6.16, 0.76]	
Kavanaugh 2018	-26.5	14.57	69	-25.27	16.61	70	6.6%	-1.23 [-6.42, 3.96]	
Westhovens 2017	-27.2	14.37	86	-25.2	15.58	85	8.8%	-2.00 [-6.49, 2.49]	
Subtotal (95% CI)			777			788	100.0%	-2.75 [-4.09, -1.41]	★
Heterogeneity: Chi <sup>2</sup> =	0.53, df=	= 3 (P =	0.91); P	'= 0%					
Test for overall effect:	Z=4.04	(P < 0.0	001)						
			-						
4.2.4 CDAI									
Combe 2021	-26	12.41	475	-23.3	12.32	480	69.3%	-2.70 [-4.27, -1.13]	✓
Genovese 2019	-26.2	15.04	147	-23.8	14.33	153	15.4%	-2.40 [-5.73, 0.93]	
Kavanaugh 2018	-25.07	14.47	69	-24.04	16.45	70	6.4%	-1.03 [-6.18, 4.12]	
Westhovens 2017	-25.5	13.91	86	-23.8	15.3	85	8.9%	-1.70 [-6.08, 2.68]	
Subtotal (95% CI)			777			788	100.0%	-2.46 [-3.76, -1.15]	•
Heterogeneity: Chi <sup>2</sup> =	0.50, df=	= 3 (P =	0.92); P	'= 0%					
Test for overall effect:	Z = 3.69	(P = 0.0	002)						
						<b>~</b> `			
					_				-10 -5 0 5 10 Eavoure (control)
Test for subaroup diff	erences:	$Chi^2 = 3$	31.92. d	f= 3 (P -	< 0.0000	01), I <sup>2</sup> =	90.6%		ravouis (experimental) ravouis (control)
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## Figure 5A

	filgotinib 20	00mg	filgotinib 1	00mg		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
5.1.1 ACR20							
Westhovens 2017	63	86	36	86	9.6%	3.80 [2.00, 7.23]	<b>_</b> _
Kavanaugh 2018	46	69	41	72	13.4%	1.51 [0.76, 3.00]	
Genovese 2019	102	147	51	148	15.5%	4.31 [2.65, 7.02]	
Combe 2021	371	475	281	475	61.5%	2.46 [1.85, 3.27]	<b>≢</b>
Subtotal (95% CI)		777		781	<b>100.0</b> %	2.75 [2.22, 3.42]	•
Total events	582		409				
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	7.76, df = 3 ( Z = 9.17 (P <	P = 0.05	); I≊ = 61 % 1)				
5.1.2 ACR50							
Westhovens 2017	43	86	40	86	11 7%	1 15 00 63 2 001	
Kavanaugh 2018	31	69	27	72	8.5%	1.36 [0.69, 2.66]	
Genovese 2019	67	147	54	148	17.2%	1 46 [0.91 2.32]	
Combe 2021	275	475	253	475	62.5%	1 21 [0 93 1 56]	
Subtotal (95% CI)	2.0	777	200	781	100.0%	1.26 [1.03, 1.54]	•
Total events	416		374				
Heterogeneity: Chi <sup>2</sup> =	0.62 df = 3.0	P = 0.89	): IZ = 0%				
Test for overall effect:	7 = 2.23 (P =	0.03)	/1 = 0 /0				
	2 - 2.20 () -	0.00)					
5.1.3 ACR70							
Westhovens 2017	25	86	28	86	13.0%	0.85 (0.44, 1.62)	
Kavanaugh 2018	17	69	29	72	14.0%	0.48 [0.24 1.00]	
Genovese 2019	47	147	31	148	13.8%	1 77 [1 05 3 00]	
Combe 2021	172	475	142	475	59.3%	1 33 [1 01 1 75]	
Subtotal (95% CI)		777	142	781	100.0%	1.21 [0.98, 1.50]	· · · · · · · · · · · · · · · · · · ·
Total events	261		230				
Heterogeneity: Chi <sup>2</sup> =	9.82 df = 3.0	P = 0.02	): I <sup>2</sup> = 69%				
Test for overall effect:	Z = 1.75 (P =	0.08)	,,,				
5 1 4 DAS20 CDD < 1	3.2						
0.1.4 DA320-CRP ≤ .	J.Z 71	147	50	140	22.0%	1 45 10 04 0 001	
Combo 2021	200	147	266	140	22.370	1.40 [0.91, 2.30]	
Subtotal (95% Cl)	200	622	200	623	100.0%	1.33 [1.03, 1.72]	
Total avanta	250	022	212	025	100.070	1.50 [ 1.00, 1.70]	•
Hotorogonoity: Chiž-	0 10 df = 1 /	0 - 0 76	010 \\I≊=004	- 74			
Tect for everall effect:	0.10, ut = 1 ( 7 = 2.66 /P =	F = 0.75	), 17 = 0.%	_			
restior overall ellect.	Z = 2.00 (P =	0.008)			$\sim$		
5.1.5 Treatment-eme	rgent advers	se event	s (TEAE)				
Westhovens 2017	50	86	37	85	8.9%	1.80 (0.98, 3.30)	
Kavanaugh 2018	30	69	23	70	7.4%	1.57 [0.79, 3.13]	<b></b>
Genovese 2019	82	147	77	153	19.1%	1.25 [0.79, 1.96]	_ <b>_</b>
Combe 2021	287	475	287	480	64.6%	1.03 [0.79, 1.33]	<b>+</b>
Subtotal (95% CI)		777		788	100.0%	1.18 [0.96, 1.44]	◆
Total events	449		424				
Heterogeneity: Chi <sup>2</sup> =	3.70. df = 3 (	P = 0.30	); <b>I</b> <sup>2</sup> = 19%				
Test for overall effect:	Z = 1.59 (P =	0.11)					
5.1.6 Serious TEAF							
Westhovens 2017	2	88	4	85	11.6%	0.48 (0.09.2.70)	<b>_</b>
Kayanaugh 2018	2	00 60	- 0	70	1 4 %	7 42 [0 38 146 41]	<b>_</b>
Genovese 2019	4	147	6	152	16.9%	0.69 [0.19.7.49]	
Combe 2021	1	475	24	480	70.3%	0.03 [0.13, 2.40]	
Subtotal (95% Cl)	1	777	24	789	100.0%	0.30 [0.15, 0.61]	- ◆
Total events	10		34	100	100.070	0.00 [0.10, 0.01]	-
Heterogeneity Chi2-	1016 df= 2	(P = 0.0	ייינ 2)∙ ו≅ = 70%				
Test for overall effect:	7 = 3.37 (P =	0 0008°					
Contor overall ellett.	2 - 0.07 (r	5.5000,	r				
							0.02 0.1 1 10 50
Test for subgroup diff	oroncos: Chi	z – 61 Q(	) df = 6 (P -	- 0 00001	I) IZ – Q1	0%	Favours [experimental] Favours [control]

Test for subaroup differences: Chi<sup>2</sup> = 61.90, df = 5 (P < 0.00001), l<sup>2</sup> = 91.9%



## Figure 5B

	filgoti	nib 200	ib 200mg filgotinib 100mg				Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
5.2.1 SF-36 PCS									
Westhovens 2017	9.7	9.18	86	9.9	10.04	85	8.9%	-0.20 [-3.08, 2.68]	
Kavanaugh 2018	9.7	9.05	69	10	9.79	70	7.5%	-0.30 [-3.43, 2.83]	
Genovese 2019	9.4	8.23	147	9	8.44	153	20.8%	0.40 [-1.49, 2.29]	+
Combe 2021	10.4	8.49	475	10.3	8.64	480	62.7%	0.10 [-0.99, 1.19]	•
Subtotal (95% CI)			777			788	<b>100.0</b> %	0.11 [-0.76, 0.97]	•
Heterogeneity: Tau <sup>2</sup> =	: 0.00; Cł	ni² = 0.20	0, df = 3	(P = 0.)	98); I <sup>z</sup> =	0%			
Test for overall effect:	Z=0.24	(P = 0.8	1)						
5.2.2 FACIT-Fatigue									
Westhovens 2017	11.6	12.33	86	11.1	11.06	85	9.3%	0.50 [-3.01, 4.01]	
Kavanaugh 2018	13.7	11.46	69	11.3	10.04	70	8.9%	2.40 [-1.18, 5.98]	
Genovese 2019	11.6	11.67	147	9.8	10.39	153	18.2%	1.80 [-0.70, 4.30]	. +
Combe 2021	10.5	10.63	475	8.4	10.48	480	63.7%	2.10 [0.76, 3.44]	
Subtotal (95% CI)			777			788	<b>100.0</b> %	1.92 [0.86, 2.99]	•
Heterogeneity: Tau² =	: 0.00; Cł	ni <b>z</b> = 0.78	3, df = 3	(P = 0.)	86); I² =	0%			
Test for overall effect:	Z = 3.53	(P = 0.0)	1004)						
5.2.3 SDAI									
Westhovens 2017	-31	15.02	86	-28.6	15.03	85	7.8%	-2.40 [-6.90, 2.10]	
Kavanaugh 2018	-29.56	15.44	69	-29.5	14.16	70	6.5%	-0.06 [-4.99, 4.87]	
Genovese 2019	-32.1	14.41	147	-27.8	13.54	153	15.8%	-4.30 [-7.47, -1.13]	
Combe 2021	-31.8	12.18	475	-28.6	11.57	480	69.8%	-3.20 [-4.71, -1.69]	
Subtotal (95% CI)			777			788	<b>100.0</b> %	-3.11 [-4.37, -1.85]	•
Heterogeneity: Tau² =	: 0.00; Cł	ni² = 2.10	2, df = 3	(P = 0.3)	55); I² =	0%			
Test for overall effect:	Z=4.83	(P ≤ 0.0	0001)						
5.2.4 CDAI									
Westhovens 2017	-29.4	13.91	86	-28.6	15.02	85	8.1%	-0.80 [-5.14, 3.54]	
Kavanaugh 2018	-28.1	15.1	69	-29.5	14.14	70	6.5%	1.40 [-3.46, 6.26]	
Genovese 2019	-30.9	13.77	147	-27.8	13.54	153	16.0%	-3.10 [-6.19, -0.01]	
Combe 2021	-30.6	11.88	475	-28.6	11.57	480	69.3%	-2.00 [-3.49, -0.51]	<b>T</b>
Subtotal (95% CI)			777			788	100.0%	-1.86 [-3.10, -0.62]	•
Heterogeneity: Tau² =	: 0.00; Cł	ni² = 2.61	1, df = 3	(P = 0)	46); I² =	0%			
Test for overall effect:	Z = 2.94	(P = 0.0	103)						
						<b>X</b>			
									-20 -10 0 10 20
					100				Favours (experimental) Favours (control)
Test for subaroup dif	ferences:	Chi <sup>2</sup> = 4	42.57.0	lf = 3 (P	< 0.000	101). I <sup>2</sup> =	: 93.0%		
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	filgotinib	100mg	Place	to		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
2.3.1 ACR20							
Combe 2021	335	480	237	475	63.9%	2.32 [1.78, 3.02]	<b>∎</b>
Genovese 2019	88	153	46	148	17.6%	3.00 [1.87, 4.82]	
Kavanaugh 2018	46	70	21	72	6.3%	4.65 [2.29, 9.45]	
Westhovens 2017	54	85	38	86	12.2%	2.20 [1.19, 4.06]	
Subtotal (95% CI)		788		781	<b>100.0</b> %	2.57 [2.09, 3.16]	•
Total events	523		342				
Heterogeneity: Chi <sup>2</sup> =	3.93, df = 3	(P = 0.27	'); <b>I</b> ² = 249	%			
Test for overall effect:	Z=8.97 (P	< 0.0000	1)				
232 000							
Combo 2021	175	400	0.4	475	20 0 0 2	2 2 2 1 7 4 2 4 2 1	-
Compension 2010	170	400	34	470	17.0%	2.33 [1.74, 3.12]	
Keyeneyeh 2019	49	100	22	140	17.2% 5.6%	2.70 [1.00, 4.70] A 70 [1.06, 44, 40]	
Navanauyn 2010 Waathayana 2017	20	70	10	72	0.0%	4.75[1.90,11.40]	
Subtatal (05% CI)	32	80 700	13	80 704	9.1%	3.39[1.03,7.07]	
Subtotal (95% CI)		/88	407	781	100.0%	2.02 [2.07, 3.32]	
i otal events	282		137				
Heterogeneity: Chif =	2.85, df = 3	P = 0.42	!); I* = U%				
l est for overall effect:	Z = 8.03 (P	< 0.0000	1)				
0.0.0.80070							
2.3.3 ACR/U							
Combe 2021	89	480	32	475	55.0%	3.15 [2.06, 4.83]	
Genovese 2019	22	153	10	148	18.3%	2.32 [1.06, 5.08]	
Kavanaugh 2018	27	70	12	72	15.2%	3.14 [1.43, 6.88]	
Westhovens 2017	18	85	7	86	11.5%	3.03 [1.19, 7.70]	
Subtotal (95% CI)		788		781	100.0%	2.98 [2.17, 4.10]	· · · · · · · · · · · · · · · · · · ·
Total events	156		61				
Heterogeneity: Chi <sup>2</sup> =	0.48, df = 3	(P = 0.92	!); I² = 0%				-
Test for overall effect:	Z=6.74 (P	< 0.0000	1)				
2.3.4 DAS28-CRP 🧠	3.2						
Combe 2021	186	480	111	475	82.3%	2.07 [1.57, 2.75]	
Genovese 2019	57	153	23	148	17.7%	3.23 [1.86, 5.61]	
Subtotal (95% CI)		633		623	100.0%	2.28 [1.77, 2.92]	
Total events	243		134				
Heterogeneity: Chi <sup>2</sup> =	1.95, df = 1	(P = 0.16	i); I² = 499	%		b.	
Test for overall effect:	Z= 6.46 (P	< 0.0000	1)		<u> </u>		
					/		0.01 0.1 1 10 100
							Favours [experimental] Favours [control]
Test for subaroup diff	erences: C	hi <sup>z</sup> = 1.77.	. df = 3 (P	= 0.62	). I <sup>2</sup> = 0%		
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	filgotinib 100mg Placeto						Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl		
2.4.1 SF-36 PCS											
Combe 2021	8.5	7.7	480	5.8	7.1	475	42.8%	2.70 [1.76, 3.64]			
Genovese 2019	6.8	8.22	153	3.6	8.16	148	24.3%	3.20 [1.35, 5.05]	-		
Kavanaugh 2018	7.8	8.7	70	3	7.55	72	14.8%	4.80 [2.12, 7.48]	-		
Westhovens 2017	8.4	8.57	85	3.2	6.86	86	18.1%	5.20 [2.87, 7.53]			
Subtotal (95% CI)			788			781	<b>100.0</b> %	3.58 [2.39, 4.78]	•		
Heterogeneity: Tau² =	: 0.64; Ch	ni <b>≈</b> = 5.29	9, df = 3	(P = 0.1	15); I <sup>z</sup> =	43%					
Test for overall effect:	Z = 5.88	(P < 0.0	0001)								
2.4.2 FACIT-Fatigue											
Combe 2021	9.1	10.2	480	6.8	9.9	475	41.2%	2.30 [1.03, 3.57]			
Genovese 2019	8.3	10.8	153	4.5	10.37	148	25.0%	3.80 [1.41, 6.19]	-		
Kavanaugh 2018	10.2	10.12	70	3.9	10.44	72	16.1%	6.30 [2.92, 9.68]	-		
Westhovens 2017	9.5	11.16	85	5.6	9.83	86	17.7%	3.90 [0.75, 7.05]			
Subtotal (95% CI)			788			781	100.0%	3.60 [1.99, 5.21]	•		
Heterogeneity: Tau <sup>2</sup> = 1.22; Chi <sup>2</sup> = 5.53, df = 3 (P = 0.14); i <sup>2</sup> = 46%											
reation overall effect.	2 - 4.50	(1 ~ 0.0	001)								
2.4.3 SDAI											
Combe 2021	-24.1	12.54	480	-20.6	13.85	475	31.0%	-3.50 [-5.18, -1.82]			
Genovese 2019	-24.9	15.01	153	-17.2	15.52	148	26.5%	-7.70 [-11.15, -4.25]			
Kavanaugh 2018	-25.27	16.61	70	-12.5	16.84	72	20.4%	-12.77 [-18.27, -7.27]			
Westhovens 2017	-25.2	15.58	85	-16.3	17.06	86	22.1%	-8.90 [-13.80, -4.00]			
Subtotal (95% CI)			788			781	100.0%	-7.70 [-11.74, -3.65]			
Heterogeneity: Tau <sup>2</sup> =	: 12.98; C	°hi² = 15	.43, df:	= 3 (P =	0.001);	I <sup>2</sup> = 81	%				
Test for overall effect:	Z = 3.73	(P = 0.0	002)								
2.4.4 CDAI											
Combe 2021	-23.3	12.32	480	-20.3	13.3	475	31.6%	-3.00 [-4.63, -1.37]	-		
Genovese 2019	-23.8	14.33	153	-17.3	15.22	148	26.6%	-6.50 [-9.84, -3.16]			
Kavanaugh 2018	-24.04	16.45	70	-11.7	15.91	72	20.1%	-12.34 [-17.66, -7.02]			
Westhovens 2017	-23.8	15.3	85	-16.6	17.06	86	21.6%	-7.20 [-12.06, -2.34]			
Subtotal (95% CI)			788	_		781	100.0%	-6.72 [-10.50, -2.94]	•		
Heterogeneity: Tau <sup>2</sup> =	: 11.05; C	:hi²=14 /⊡00	.16, df:	= 3 (P =	0.003);	I <sup>2</sup> = 79	%				
Test for overall effect:	Z= 3.49	(P = 0.0	005)								
To at fay out avour diff		062-4		K_ 0.00	- 0.000	043 17	04.00		Favours (experimental) Favours (control)		
rest for subdroup diff	ierences.	Cni-= :	02.28. U	11 = 3 (P	< 0.000	UD. F:	= 94.3%	)			
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	filgotir	nib 200mg	g pl	aceto		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD T	otal Mean	SD Tot	al Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
3.3.1 12 week							
Westhovens 2017	-0.75	0.6	86 -0.38	0.61	35 16.3%	-0.37 [-0.55, -0.19]	
Kavanaugh 2018	-0.74	0.67	69 -0.24	0.59	70 12.9%	-0.50 [-0.71, -0.29]	
Genovese 2019	-0.55	0.59	147 -0.23	0.55 1	53 26.0%	-0.32 [-0.45, -0.19]	
Combe 2021	-0.69	0.61	475 -0.42	0.54 4	30 44.8%	-0.27 [-0.34, -0.20]	
Subtotal (95% CI)			(()	7	se 100.0%	-0.33 [-0.41, -0.25]	▼
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	U.00; Ch Z = 7.68	rf = 4.73, i (P ≤ 0.000	dt = 3 (P = 0. 001)	19); I <sup>z</sup> = 37	%		
3.3.2 24 week							
Westhovens 2017	-0.818	0.63	86 -0.37	0.62	36 29.1%	-0.45 [-0.63, -0.26]	
Genovese 2019	-0.75	0.62	69 -0.42	0.6	72 27.3%	-0.33 [-0.53, -0.13]	
Combe 2021	-0.82	0.63	475 -0.62	0.6 4	75 43.6%	-0.20 [-0.28, -0.12]	
Subtotal (95% CI)			630	6	33 100.0%	-0.31 [-0.47, -0.15]	
Heterogeneity: Tau² =	0.01; Ch	i² = 6.48, i	df = 2 (P = 0.	04); I² = 69	%		
Test for overall effect:	Z = 3.80	(P = 0.000	01)				
							-2 -1 0 1 2
Tact for cubarous diff	oroncoc	Chiž – 0 c	16 df - 1 /P -	- 0 92\ 12-	0%		Favours (experimental) Favours (control)
restion suburoup UIII	erentes.	om = 0.0	55. ur≓ i trª =	- 0.02), 11=	070		
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w.							



	filgotinib 10	)0mg	Place	to		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
3.4.1 ACR20							
Combe 2021	373	480	281	475	10.7%	2.41 [1.81, 3.19]	
Genovese 2019	84	153	51	148	4.0%	2.32 [1.45, 3.69]	
Kavanaugh 2018	55	70	41	72	1.5%	2.77 [1.33, 5.79]	
Westhovens 2017	52	85	36	86	2.4%	2.19 [1.19, 4.03]	
Subtotal (95% CI)		788		781	18.5%	2.39 [1.93, 2.96]	•
Total events	564		409				
Heterogeneity: Chi <sup>2</sup> =	0.26, df = 3 (	P = 0.97	); I² = 0%				
Test for overall effect: .	Z = 7.95 (P <	0.0000	1)				
3.4.2 ACR50							
Combe 2021	253	480	158	475	12.8%	2.24 [1.72, 2.91]	
Genovese 2019	54	153	28	148	3.1%	2.34 [1.38, 3.96]	
Westhovens 2017	40	85	14	86	1.3%	4.57 [2.24, 9.33]	
Subtotal (95% CI)		/18		709	17.2%	2.43 [1.94, 3.03]	
Total events	347		200				
Heterogeneity: Chi* =	3.42, df = 2 (	P = 0.18	); I* = 429	ю			
lest for overall effect: .	Z = 7.82 (P <	0.0000	1)				
3 / 3 / 0 0 70							
J.4.J ACK/U	4.40	400	74	175	0.50	0.00 14 74 0.001	
Compe 2021	142	480	71	4/5	8.5% 4.70	2.39 [1.74, 3.29]	
Genovese 2019 Westhewers 2017	31	153	12	148	1.7%	2.88 [1.42, 5.86]	
Subtotal (95% CI)	28	60 719	0	700	0.9%	4.79 [2.03, 11.28]	
Total quanta	204	/ 10	01	709	11.170	2.00 [2.02, 5.50]	
Hotorogonoity: Chiž -	201 200 df = 27	0 - 0 22	91 \\IZ= 100	v.			
Tect for overall effect:	2.29, ui – 2 (i 7 – 6 00 /D ~	0.02	), I — I 35 1)	10			
restion overall ellect.	Z = 0.90 (F <	0.0000	0				
$3.4.5$ DAS28.CRP $\leq 3$	12						
Combe 2021	255	490	160	475	17.9%	2 22 11 72 2 001	
Genovece 2021	200	163	31	1/1.9	2 2 96	2.20 [1.72, 2.30]	
Subtotal (95% CI)	50	633	51	623	16.1%	2.25 [1.78, 2.84]	●
Total events	313	000	191				
Heterogeneity: Chi <sup>2</sup> =	0.01 df=1.0	P = 0.91	):I≊ = 0%	•	~ V		
Test for overall effect:	Z = 6.81 (P <	0.0000	1)	- 4			
			.,			h	
3.4.6 Treatment-eme	rgent advers	se event	s (TEAE)			· · · · · · · · · · · · · · · · · · ·	
Combe 2021	287	480	252	475	17.3%	1.32 [1.02, 1.70]	
Genovese 2019	77	153	100	148	8.6%	0.49 [0.30, 0.78]	- <b>-</b>
Kavanaugh 2018	23	70	28	72	3.2%	0.77 [0.39, 1.53]	+ <u>+</u>
Westhovens 2017	37	85	32	86	3.1%	1.30 [0.71, 2.40]	_ <del></del>
Subtotal (95% CI)		788		781	32.1%	1.04 [0.85, 1.27]	◆
Total events	424		412				
Heterogeneity: Chi <sup>2</sup> =	14.63, df = 3	(P = 0.0	02); I² = 7	'9%			
Test for overall effect: .	Z = 0.38 (P =	0.71)	/				
	<b>(</b> 4	-					
3.4.7 Serious TEAE							
Combe 2021	24	480	20	475	3.2%	1.20 [0.65, 2.20]	
Genovese 2019	6	153	5	148	0.8%	1.17 [0.35, 3.91]	
Kavanaugh 2018	0	70	1	72	0.2%	0.34 [0.01, 8.44]	
Westhovens 2017	4	85	4	86	0.6%	1.01 [0.24, 4.19]	
Subtotal (95% CI)		788		781	5.0%	1.13 [0.68, 1.85]	
Total events	34		30				
Heterogeneity: Chi <sup>2</sup> =	0.60, df = 3 (	P = 0.90	); I²=0%				
Test for overall effect: .	Z = 0.46 (P =	0.64)					
Total (05%) ch		1100		4204	400.04	4 04 [4 79 9 49]	
i otal (95% CI)	4000	4433	4000	4384	100.0%	1.91 [1.73, 2.10]	•
i otal events	1883	0.00.00	1333		,		
Heterogeneity: Chif =	7 0.00, 01 = 11 7 = 10.04 /0	ສ(⊢<ປ. ∠0.000	00001);1 043	-= / 59	0		0.01 0.1 i 10 100
Test for overall effect.	∠ = 12.94 (P pronocci Obi	~ 0.0000 8 - 50 04	01) 2 df - 5 1	<b>.</b>	00043 12	- 01 104	Favours [experimental] Favours [control]
Test for subaroup diffe	erences: Chi	= 50.00	5. ui = 5 (i	г ۹ О.О	00010.1**	- 31.170	



	filgot	tinib 100	mg	Placeto				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
3.5.1 SF-36 PCS									
Combe 2021	9.9	10.04	85	3.2	6.86	86	26.9%	6.70 [4.12, 9.28]	
Genovese 2019	40.0	8.44	153	5.5 77	7.95	148	33.2%	2.40 [0.55, 4.25]	
Subtotal (95% CI)	10.5	0.04	718	1.1	1.97	709	39.9%	2.60 [1.55, 3.65] 3.64 [1.49, 5.78]	•
Heterogeneity: Tau <sup>2</sup> :	= 2.71 0	:hi² = 8.8	5 df=1	2 (P = 0	01): 17 =	: 77%	100.070	5.04 [ 1.45, 5.10]	•
Test for overall effect $Z = 3.3$ ( $P = 0.0009$ )									
3.5.2 FACIT-Fatigue									
Combe 2021	11.1	11.06	85	6	9.64	86	28.5%	5.10 [1.99, 8.21]	
Genovese 2019	9.8	10.39	153	7	10.23	148	33.1%	2.80 [0.47, 5.13]	
Westhovens 2017	8.4	10.48	480	8.4	10.48	475	38.4%	0.00 [-1.33, 1.33]	
Subtotal (95% CI)	- 5 40.0	- 	/18 00.df=	2/0-	0.0043	709	100.0%	2.38 [-0.58, 5.34]	
neterogeneny, nau = 3,43, cm = 1,030, un = 2 (r = 0.004), r = 62.26 Teactfor workall affact 7 = 1.52 (P = 0.10)									
reactor overall energy 2 = 1.30 (( = 0.12)									
3.5.3 SDAI									
Combe 2021	-28.6	15.03	85	-15.8	18.55	86	28.0%	-12.80 [-17.86, -7.74]	
Genovese 2019	-27.8	13.54	153	-24.9	14.4	148	34.0%	-2.90 [-6.06, 0.26]	A [ -■-] A <sup>¬</sup>
Westhovens 2017	-28.6	11.57	480	-26.6	12.91	475	38.0%	-2.00 [-3.56, -0.44]	
Subtotal (95% CI)			718			709	100.0%	-5.33 [-10.31, -0.35]	
Heterogeneity: 1auf=16.38; Chif=16.00, df=2 (P = 0.0003); F=88%									
l est for overall effect	: Z = 2.10	U (P = U.I	U4)						
3.5.4 CDAI									
Combe 2021	-28.6	15.03	85	-16	18.08	86	26.5%	-12.60 [-17.58, -7.62]	(
Genovese 2019	-27.8	13.54	153	-25.4	14.4	148	33.9%	-2.40 [-5.56, 0.76]	
Westhovens 2017	-30.9	11.7	480	-26.3	12.38	475	39.6%	-4.60 [-6.13, -3.07]	
Subtotal (95% CI)			718			709	100.0%	-5.97 [-10.21, -1.74]	-
Heterogeneity: Tau <sup>2</sup> = 11.19; Chi <sup>2</sup> = 11.70, df = 2 (P = 0.003); l <sup>2</sup> = 83%									
Test for overall effect	: Z = 2.76	6 (P = 0.0	006)						
									-20 -10 Ó 10 20
Test for subgroup differences: Chi <sup>2</sup> = 23.19, df = 3 (P < 0.0001), l <sup>2</sup> = 87.1% Favours [experimental] Favours [control]									
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**Figure Legends** 

Figure 1 - Flow diagram of study selection

Figure 2A - Meta-analysis of filgotinib 200 mg versus placebo at week 12 (categorical) Figure 2B - Meta-analysis of filgotinib 200 mg versus placebo at week 12 (continuous) Figure 3A - Meta-analysis of filgotinib 200 mg versus placebo at week 24 (categorical) Figure 3B - Meta-analysis of filgotinib 200 mg versus placebo at week 24 (continuous) Figure 4A - Meta-analysis of filgotinib 200 mg versus 100 mg at week 12 (categorical) Figure 4B - Meta-analysis of filgotinib 200 mg versus 100 mg at week 12 (continuous) Figure 5A - Meta-analysis of filgotinib 200 mg versus 100 mg at week 24 (continuous) Figure 5B - Meta-analysis of filgotinib 200 mg versus 100 mg at week 24 (categorical)

Supplementary file 1: Meta-analysis of filgotinib 100 mg versus placebo at week 12 (categorical) Supplementary file 2: Meta-analysis of filgotinib 100 mg versus placebo at week 12 (continuous) Supplementary file 3 Meta-analysis of filgotinib 200 mg versus placebo (HAQ-DI) Supplementary file 4 Meta-analysis of filgotinib 100 mg versus placebo at week 24 (categorical) Supplementary file 5 Meta-analysis of filgotinib 100 mg versus placebo at week 24 (categorical) Supplementary file 6 Meta-analysis of filgotinib 200 mg versus placebo at week 24 (continuous)



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