

## **REVIEW ARTICLES**

# 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  $1917.21 \pm 2559.06$  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-

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Submitted: 09/02/2022 Accepted: 28/04/2022 Correspondence to: Liming Pan E-mail: 278753262@qq.com 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®) 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 (FAC-IT)-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.  $I^2$  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% *CI* 2.90 – 4.46; *P*<0.001; *I*<sup>2</sup>=24%], ACR50 [*OR* 3.95; 95% *CI* 3.13 – 4.98; *P*<0.001; *I*<sup>2</sup>= 0%], ACR70 responses [*OR* 4.35; 95% *CI* 3.20 – 5.93; *P*<0.001; *I*<sup>2</sup>=0%], and DAS28-CRP ≤ 3.2 [*OR* 3.34; 95% *CI* 2.60 – 4.28; *P*<0.001; *I*<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% *CI* 3.12 – 5.38; *P*<0.001; *I*<sup>2</sup>=38%] and FAC-IT-Fatigue [*MD* 4.76; 95% *CI* 2.42 – 7.10; *P*<0.001; *I*<sup>2</sup>=71%] and lower SDAI [*MD* -9.90; 95% *CI* -13.32 to



Figure 1. Flow diagram of study selection

or 1 o 1	riigotinib 2	00mg	Place	bo		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]	
Genovese 2019	97	147	46	148	17.6%	4.30 [2.64, 7.00]	
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>2</sup> =	= 3.96, df = 3 (	P = 0.27)	); <b>I</b> ≊ = 249	%			
Test for overall effect:	:: Z = 11.67 (P	< 0.0000	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		72	6.0%	6 15 [2 56 14 77]	
Westhovens 2017	37	86	13	88	10.0%	4 24 [2:05, 14:77]	
Subtotal (95% CI)		777	10	781	100.0%	3.95 [3.13, 4.98]	•
Total events	354		137		1001070	oloo loulo, liool	-
Heterogeneity Chiž =	-146 df = 3/	P = 0.69	:E= 0%				
Test for overall effect:	: Z = 11.56 (P	< 0.0000	)1)				
2 1 3 ACR70							
2.110 Held 0	101	475	32	475	6/ 3%	A 90 13 24 7 301	
Combe 2021	1/4				04.070	4.00 0.24, 1.00	
Combe 2021 Genovese 2019	124	147	10	148	17 9%	3 84 [1 81 8 15]	
Combe 2021 Genovese 2019 Kavanauch 2018	124 32 29	147 69	10	148	17.9% 15.6%	3.84 [1.81, 8.15]	
Compe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017	124 32 29 21	147 69	10 12 7	148 72	17.9% 15.6% 12.2%	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11]	
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% CI)	124 32 29 21	147 69 86 777	10 12 7	148 72 86 781	17.9% 15.6% 12.2% 100.0%	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] 4.35 [3.20, 5.93]	
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% CI) Total events	124 32 29 21	147 69 86 777	10 12 7 61	148 72 86 <b>781</b>	17.9% 15.6% 12.2% <b>100.0</b> %	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] <b>4.35 [3.20, 5.93]</b>	
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Cl) Total events	124 32 29 21 206 : 0.77 df = 3 (	147 69 86 777 P = 0.86	10 12 7 61	148 72 86 <b>781</b>	17.9% 15.6% 12.2% <b>100.0</b> %	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] <b>4.35 [3.20, 5.93]</b>	•
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>#</sup> = Test for overall effect:	124 32 29 21 206 = 0.77, df = 3 ( : Z = 9.34 (P <	147 69 86 777 P = 0.86)	02 10 12 7 61 ); I <sup>≠</sup> = 0%	148 72 86 781	17.9% 15.6% 12.2% <b>100.0</b> %	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] 4 <b>.35 [3.20, 5.93]</b>	
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: 214 DAS28 CPD <	124 32 29 21 206 = 0.77, df = 3 ( :: Z = 9.34 (P <	147 69 86 <b>777</b> P = 0.86; 0.00001	10 12 7 61 ); I <sup>2</sup> = 0%	148 72 86 781	17.9% 15.6% 12.2% <b>100.0%</b>	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] <b>4.35 [3.20, 5.93]</b>	•
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>#</sup> = Test for overall effect: 2.1.4 DAS28-CRP ≤ Combe 2021	124 32 29 21 206 : 0.77, df = 3 ( :: Z = 9.34 (P < 3.2	147 69 86 777 P = 0.86) 0.00001	10 12 7 61 ); I <sup>2</sup> = 0%	148 72 86 <b>781</b>	17.9% 15.6% 12.2% <b>100.0%</b>	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] <b>4.35 [3.20, 5.93]</b>	•
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: 2.1.4 DAS28-CRP ≤ Combe 2021 Cencercea 2010	124 32 29 21 206 : 0.77, df = 3 ( : Z = 9.34 (P < 3.2 236 60	475 147 69 86 <b>777</b> P = 0.86)	10 12 7 61 ); I <sup>2</sup> = 0% I) 111	148 72 86 <b>781</b> 475	17.9% 15.6% 12.2% <b>100.0%</b> 80.5%	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] <b>4.35 [3.20, 5.93]</b> 3.24 [2.46, 4.28]	•
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: 2.1.4 DAS28-CRP $\leq$ Combe 2021 Genovese 2019 Subtotal (05% CP)	124 32 29 21 206 = 0.77, df = 3 ( : Z = 9.34 (P = 3.2 236 60	147 69 86 777 P = 0.86) 0.00001 475 147 622	10 12 7 61 ); I*= 0% )) 111 23	148 72 86 <b>781</b> 475 148	17.9% 15.6% 12.2% 100.0% 80.5% 19.5%	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] <b>4.35 [3.20, 5.93]</b> 3.24 [2.45, 4.28] 3.75 [2.16, 6.52]	•
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: 2.1.4 DAS28-CRP $\leq$ Combe 2021 Genovese 2019 Subtotal (95% CI) Total events	124 32 29 21 206 = 0.77, df = 3 ( : Z = 9.34 (P = 3.2 236 60	473 147 69 86 <b>777</b> P = 0.86) 0.00001 475 147 <b>622</b>	10 12 7 61 );   <sup>2</sup> = 0%  ) 111 23	148 72 86 <b>781</b> 475 148 <b>623</b>	17.9% 15.6% 12.2% 100.0% 80.5% 19.5% 100.0%	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] <b>4.35 [3.20, 5.93]</b> 3.24 [2.45, 4.28] 3.75 [2.16, 6.52] <b>3.34 [2.60, 4.28]</b>	•
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>#</sup> = Test for overall effect: 2.1.4 DAS28-CRP $\leq$ Combe 2021 Genovese 2019 Subtotal (95% Cl) Total events	124 32 29 21 206 = 0.77, df = 3 ( ± Z = 9.34 (P = 236 60 296	147 69 86 777 P = 0.86) 0.00001 475 147 622	10 12 7 61 );   <sup>2</sup> = 0%  ) 111 23 134	148 72 86 <b>781</b> 475 148 <b>623</b>	17.9% 15.6% 12.2% 100.0% 80.5% 19.5% 100.0%	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] <b>4.35 [3.20, 5.93]</b> 3.24 [2.45, 4.28] 3.75 [2.16, 6.52] <b>3.34 [2.60, 4.28]</b>	•
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: 2.1.4 DAS28-CRP $\leq$ Combe 2021 Genovese 2019 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = Teactfor events	124 32 29 21 206 = 0.77, df = 3 ( t Z = 9.34 (P = 3.2 236 60 296 : 0.21, df = 1 ( 7 = 0 (2) (f = 1 (	475 147 86 777 P = 0.86; 0.00001 475 147 622 P = 0.64;	10 12 7 61 ); I <sup>=</sup> = 0% )) 1111 23 134 ); I <sup>=</sup> = 0%	148 72 86 <b>781</b> 475 148 <b>623</b>	17.9% 15.6% 12.2% 100.0% 80.5% 19.5% 100.0%	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] <b>4.35 [3.20, 5.93]</b> 3.24 [2.45, 4.28] 3.75 [2.16, 6.52] <b>3.34 [2.60, 4.28]</b>	•
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>#</sup> = Test for overall effect: <b>2.1.4 DAS28-CRP</b> $\leq$ Combe 2021 Genovese 2019 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>#</sup> = Test for overall effect:	124 32 29 21 206 = 0.77, df = 3 ( t Z = 9.34 (P = 3.2 236 60 296 = 0.21, df = 1 ( : Z = 9.50 (P =	473 147 69 86 <b>777</b> P = 0.86) : 0.00001 475 147 <b>622</b> P = 0.64) : 0.00001	10 12 7 61 );   <sup>2</sup> = 0%  ) 111 23 134 );   <sup>2</sup> = 0%	148 72 86 <b>781</b> 475 148 <b>623</b>	17.9% 15.6% 12.2% 100.0% 80.5% 19.5% 100.0%	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] <b>4.35 [3.20, 5.93]</b> 3.24 [2.45, 4.28] 3.75 [2.16, 6.52] <b>3.34 [2.60, 4.28]</b>	•
Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>#</sup> = Test for overall effect: <b>2.1.4 DAS28-CRP</b> $\leq$ Combe 2021 Genovese 2019 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>#</sup> = Test for overall effect:	124 32 29 21 206 = 0.77, df = 3 ( t Z = 9.34 (P = 3.2 236 60 296 = 0.21, df = 1 ( : Z = 9.50 (P =	475 69 86 <b>777</b> P = 0.86; 0.00001 475 147 <b>622</b> P = 0.64; 0.00001	10 10 12 7 61 );   <sup>p</sup> = 0% )) 1111 23 134 );   <sup>p</sup> = 0% ))	148 72 86 781 475 148 623	17.9% 15.6% 12.2% 100.0% 80.5% 19.5% 100.0%	3.84 [1.81, 8.15] 3.63 [1.66, 7.93] 3.65 [1.46, 9.11] <b>4.35 [3.20, 5.93]</b> 3.24 [2.45, 4.28] 3.75 [2.16, 6.52] <b>3.34 [2.60, 4.28]</b>	

Figure 2A. Meta-analysis of filgotinib 200 mg versus placebo at week 12 (categorical outcomes)

	filgoti	nib 200	mg	PI	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	fotal	Mean	SD	rotal	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> :	= 0.51; Ch	ni² = 4.8	5, df = 3	(P = 0.1	8); I² = 3	38%			
Test for overall effect	: Z = 7.36	(P < 0.0	10001)						
2.2.2 FACIT-Fatique									
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]	
Westhovens 2017	11.4	12.7	86	5.6	9.83	85	20.8%	5 80 [2 40 9 20]	
Subtotal (95% CI)			777			788	100.0%	4.76 [2.42, 7,10]	•
Heterogeneity: Tau <sup>2</sup> :	= 3.84: Ch	ni² = 10 :	35 df=	3 (P = 0.)	02): I <b>P</b> =	71%			
Test for overall effect	: Z = 3.98	(P < 0.0	1001)	- (	,, .				
2.2.3 SDAI									_
Combe 2021	-27.1	12.69	475	-20.6	13.85	480	33.1%	-6.50 [-8.18, -4.82]	
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)						788	100.0%	-9.90 [-13.32, -6.49]	-
Heterogeneity: Tau <sup>2</sup>	= 8.42; Ch	11 <sup>2</sup> = 11.3	21, df =	3 (P = 0.	01); I <sup>z</sup> =	73%			
Test for overall effect	: Z = 5.69	(P < 0.0	10001)						
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: Tau <sup>2</sup> :	= 7.16; Ch	ni² = 10.3	36, df=	3 (P = 0.)	02); I <b>²</b> =	71%			
Test for overall effect	: Z = 5.32	(P < 0.0	10001)						
								_	
									-20 -10 0 10 20
-	~								Favours (control) Favours (experimental)
<ul> <li>Loct for subgroup dif</li> </ul>	Terences:	Chi <sup>2</sup> = 1	109.90.	at = 3 (P	< 0.001	JU1). 🖻	= 97.3%		

Figure 2B. Meta-analysis of filgotinib 200 mg versus placebo at week 12 (continuous outcomes)

-6.49; P<0.001;  $I^2$ =73%] and CDAI [*MD* -8.68; 95% *CI* -11.88 to -5.48; P<0.001;  $I^2$ =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% *CI* 1.90 – 4.23; *P*<0.001; *I*<sup>2</sup> = 61%], ACR50 [*OR* 3.28; 95% *CI* 2.38 – 4.53; *P*<0.001; *I*<sup>2</sup> = 33%], ACR70 responses [*OR* 3.57; 95% *CI* 2.72 – 4.68; *P*<0.001; *I*<sup>2</sup> = 0%], and DAS28-CRP ≤ 3.2 [*OR* 3.16; 95% *CI* 2.49 – 3.99; *P*<0.001; *I*<sup>2</sup> = 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% *CI* 

Study or Subgroup	filgotinib 2 Events	00mg Total	Place Events	bo Total	Weight	Odds Ratio M-H, Random, 95% Cl	Odds Ratio 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)		777		781	100.0%	2.84 [1.90, 4.23]	•
Total events	582		409				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	: 0.10; Chi² = Z = 5.11 (P ∘	7.76, df= 0.00001	= 3 (P = 0 )	).05); I <sup>z</sup>	= 61%		
3.1.2 ACR50							
Combe 2021	275	475	158	475	56.6%	2.76 [2.12, 3.59]	
Genovese 2019	67	147	28	148	26.7%	3.59 [2.13, 6.06]	
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: Tau <sup>2</sup> = Test for overall effect:	: 0.03; Chi <sup>2</sup> = Z = 7.25 (P <	2.99, df= 0.00001	= 2 (P = 0 )	).22); I <del>*</del>	= 33%		
3.1.3 ACR70							
Combe 2021	172	475	71	475	74.5%	3.23 [2.36, 4.42]	<del>-</del>
Genovese 2019	47	147	12	148	15.7%	5.33 [2.69, 10.56]	_ <b>−</b>
Westhovens 2017	25	86	8	86	9.8%	4.00 [1.68, 9.48]	·
Subtotal (95% CI)		708	-	709	100.0%	3.57 [2.72, 4.68]	◆
Total events	244		91				
Test for overall effect:	Z = 9.20 (P <	0.00001	)	.41),1	- 0 %		
Subtotal (95% CI)						Not optimable	
						NOLESUMADIE	
Total events	Ο	U	n	0		Notestimable	
Total events Heterogeneity: Not ap Test for overall effect:	0 plicable Not applicat	ile	0	U		Notestimable	
Total events Heterogeneity: Not ap Test for overall effect: 3.1.5 DAS28-CRP ≤	0 oplicable Not applicat 3.2	ile	0	U		NOTestimable	
Total events Heterogeneity: Not ap Test for overall effect: 3.1.5 DAS28-CRP ≤ Combe 2021	0 oplicable Not applicak 3.2 288	u 11e 475	0 160	475	79.1%	3.03 [2.33, 3.95]	-
Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≤ Combe 2021 Genovese 2019	0 oplicable Not applicab 3.2 288 71	ule 475 147	0 160 30	475 148	79.1% 20.9%	3.03 [2.33, 3.95] 3.67 [2.20, 6.15]	-
Total events Heterogeneity: Not ap Test for overall effect: 3.1.5 DAS28-CRP ≤ Combe 2021 Genovese 2019 Subtotal (95% CI)	0 pplicable Not applicab 3.2 288 71	ule 475 147 <b>622</b>	0 160 30	475 148 623	79.1% 20.9% <b>100.0</b> %	3.03 [2.33, 3.95] 3.67 [2.20, 6.15] <b>3.16 [2.49, 3.99]</b>	<b>≞</b> ◆
Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≪ Combe 2021 Genovese 2019 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0 pplicable Not applicat 288 71 359 0.00; Chi <sup>2</sup> = Z = 9.57 (P <	475 147 622 0.42, df=	0 160 30 190 :1 (P = ( )	475 148 <b>623</b> ).52);   <sup>2</sup>	79.1% 20.9% <b>100.0</b> % = 0%	3.03 [2.33, 3.95] 3.67 [2.20, 6.15] <b>3.16 [2.49, 3.99]</b>	•
Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≤ Combe 2021 Genovese 2019 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme	0 pplicable Not applicat 3.2 288 71 359 0.00; Chi <sup>2</sup> = Z = 9.57 (P • ergent advers	475 147 622 0.42, df = 0.00001 se events	0 160 30 :1 (P = ( ) s (TEAE)	475 148 <b>623</b> ).52); I <sup>2</sup>	79.1% 20.9% <b>100.0</b> % = 0%	3.03 [2.33, 3.95] 3.67 [2.20, 6.15] <b>3.16 [2.49, 3.99]</b>	•
Subtora (57% Ct) Total events Heterogeneity: Not ar Test for overall effect: <b>3.1.5 DAS28-CRP</b> $\leq$ Combe 2021 Genovese 2019 <b>Subtotal (95% Ct)</b> Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>3.1.6 Treatment-eme</b> Combe 2021	0 pplicable Not applicat 288 71 359 0.00; Chi <sup>2</sup> = Z = 9.57 (P < ergent adver: 287	475 147 622 0.42, df = 0.00001 se events 475	0 160 30 = 1 (P = ( ) s (TEAE) 252	475 148 <b>623</b> ).52); I <sup>2</sup> 475	79.1% 20.9% <b>100.0</b> % = 0% 30.8%	3.03 [2.33, 3.95] 3.67 [2.20, 6.15] <b>3.16 [2.49, 3.99]</b> 1.35 [1.04, 1.75]	•
Subtract (57% Ct) Total events Heterogeneity: Not ap Test for overall effect: <b>3.1.5 DAS28-CRP</b> $\leq$ Combe 2021 Genovese 2019 <b>Subtotal (95% Ct)</b> Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>3.1.6 Treatment-eme</b> Combe 2021 Genovese 2019	0 pplicable Not applicat 3.2 288 71 359 0.00; Chi <sup>2</sup> = Z = 9.57 (P • 287 82	475 147 622 0.42, df = 0.00001 se events 475 147	0 160 30 = 1 (P = ( ) s (TEAE) 252 100	475 148 <b>623</b> 0.52); I <sup>2</sup> 475 148	79.1% 20.9% <b>100.0</b> % = 0% 30.8% 25.8%	3.03 [2.33, 3.95] 3.67 [2.20, 6.15] 3.16 [2.49, 3.99] 1.35 [1.04, 1.75] 0.61 [0.38, 0.97]	*
Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≤ Combe 2021 Genovese 2019 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme Combe 2021 Genovese 2019 Kavanaugh 2018	0 pplicable Not applicat 288 71 359 0.00; Chi <sup>2</sup> = Z = 9.57 (P + 287 82 30	475 147 622 0.42, df = 0.00001 se events 475 147 69	0 160 30 = 1 (P = ( ) <b>s (TEAE)</b> 252 100 28	475 148 <b>623</b> 0.52);   <sup>2</sup> 475 148 72	79.1% 20.9% <b>100.0%</b> = 0% 30.8% 25.8% 21.0%	1.35 [1.04, 1.75] 0.61 [0.38, 0.97] 1.21 [0.62, 2.37]	* •
Combe 2021 Subtoal (55% Ct) Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≪ Combe 2021 Genovese 2019 Subtotal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017	0 pplicable Not applicat 288 71 359 0.00; Chi <sup>2</sup> = Z = 9.57 (P • ergent adver: 287 82 30 50	475 147 <b>622</b> 0.42, df = 0.00001 <b>se events</b> 475 147 69 86	0 160 30 190 1 (P = 0 ) 252 100 28 32	475 148 <b>623</b> 0.52);   <sup>2</sup> 475 148 72 86	79.1% 20.9% <b>100.0%</b> = 0% 30.8% 25.8% 21.0% 22.4%	3.03 [2.33, 3.95] 3.67 [2.20, 6.15] <b>3.16 [2.49, 3.99]</b> 1.35 [1.04, 1.75] 0.61 [0.38, 0.97] 1.21 [0.62, 2.37] 2.34 [1.27, 4.32]	* *
Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≪ Combe 2021 Genovese 2019 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% CI)	0 pplicable Not applicat 3.2 288 71 359 0.00; Chi <sup>2</sup> = Z = 9.57 (P ≪ 287 82 30 50	475 147 622 0.42, df= 0.00001 se events 475 147 69 86 777	0 160 30 190 1 (P = 0 ) <b>5 (TEAE)</b> 252 100 28 32	475 148 623 0.52); I <sup>2</sup> 475 148 72 86 781	79.1% 20.9% <b>100.0%</b> = 0% 30.8% 25.8% 21.0% 22.4% <b>100.0</b> %	1.35 [1.04, 1.75] 0.61 [0.38, 0.97] 1.21 [0.62, 2.37] 1.24 [0.73, 2.00]	
Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≤ Combe 2021 Genovese 2019 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0 pplicable Not applicat 3.2 288 71 359 0.00; Chi² = Z = 9.57 (P ≪ 287 82 30 50 449 0.20; Chi² = Z = 0.76 (P =	475 147 622 0.42, df = 0.00001 se events 475 147 69 86 777 13.37, df 13.37, df	0 160 30 190 1 (P = 0 ) 5 (TEAE) 260 28 32 412 5 3 (P =	475 148 623 0.52);   <sup>2</sup> 475 148 72 8 781 0.004)	79.1% 20.9% <b>100.0</b> % = 0% 30.8% 25.8% 21.0% 22.4% <b>100.0</b> % ;   <b>r</b> = 78%	3.03 [2.33, 3.95] 3.67 [2.20, 6.16] <b>3.16 [2.49, 3.99]</b> 1.35 [1.04, 1.75] 0.61 [0.38, 0.97] 1.21 [0.62, 2.37] 2.34 [1.27, 4.32] <b>1.21 [0.73, 2.00]</b>	
Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≤ Combe 2021 Genovese 2019 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.7 Serious TEAE	0 pplicable Not applicat 3.2 288 71 359 0.00; Chi <sup>2</sup> = Z = 9.57 (P - 287 82 30 50 449 0.20; Chi <sup>2</sup> = Z = 0.76 (P =	475 147 622 0.42, df = 0.00001 se events 475 147 69 86 777 13.37, df 13.37, df	0 160 30 190 1 (P = 0 ) 5 (TEAE) 28 32 412 '= 3 (P =	475 148 623 0.52); I <sup>2</sup> 475 148 72 86 781 0.004)	79.1% 20.9% <b>100.0</b> % = 0% 30.8% 25.8% 21.0% 22.4% <b>100.0</b> % ;   <sup>2</sup> = 78%	<ul> <li>3.03 [2.33, 3.95]</li> <li>3.67 [2.20, 6.16]</li> <li>3.16 [2.49, 3.99]</li> <li>1.35 [1.04, 1.75]</li> <li>0.61 [0.38, 0.97]</li> <li>1.21 [0.62, 2.37]</li> <li>2.34 [1.27, 4.32]</li> <li>1.21 [0.73, 2.00]</li> </ul>	
Subtoral (57/Ct) Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≪ Combe 2021 Genovese 2019 Subtotal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.7 Serious TEAE Combe 2021	0 pplicable Not applicat 3.2 288 71 359 : 0.00; Chi <sup>2</sup> = Z = 9.57 (P = 287 82 30 50 449 : 0.20; Chi <sup>2</sup> = Z = 0.76 (P = 21	475 147 622 0.42, df= 0.00001 se events 475 147 69 86 777 13.37, df 13.37, df 13.37, df	0 160 30 190 1 (P = 0 ) 5 (TEAE) 252 100 28 322 412 = 3 (P = 20	475 148 623 9.52);   <sup>2</sup> 475 148 72 86 781 0.004) 475	79.1% 20.9% <b>100.0</b> % = 0% 30.8% 21.0% 22.4% <b>100.0</b> % ;   <sup>2</sup> = 78%	3.03 [2.33, 3.95] 3.67 [2.20, 6.15] <b>3.16 [2.49, 3.99]</b> 1.35 [1.04, 1.75] 0.61 [0.38, 0.97] 1.21 [0.62, 2.37] 2.34 [1.27, 4.32] <b>1.21 [0.73, 2.00]</b>	
Subtotal (55% Ct) Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≤ Combe 2021 Genovese 2019 Subtotal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.7 Serious TEAE Combe 2021 Genovese 2019	0 pplicable Not applicat 3.2 288 71 359 0.00; Chi <sup>2</sup> = Z = 9.57 (P ergent adver: 287 82 30 	475 147 622 0.42, df = 0.00001 se events 475 147 69 86 777 13.37, df : 0.45) 475 147	0 160 30 190 192 252 100 28 32 412 27 3 (P=( ) 412 20 5	4755 148 623 1.52);   <sup>2</sup> 4755 148 72 866 781 0.004) 4755 148	79.1% 20.9% 100.0% = 0% 30.8% 21.0% 22.4% 100.0% ; I <sup>2</sup> = 78% 70.1% 15.4%	3.03 [2.33, 3.95] 3.67 [2.20, 6.15] <b>3.16 [2.49, 3.99]</b> 1.35 [1.04, 1.75] 0.61 [0.38, 0.97] 1.21 [0.62, 2.37] 2.34 [1.27, 4.32] <b>1.21 [0.73, 2.00]</b> 1.05 [0.56, 1.97] 0.80 [0.21, 3.04]	
Subtola (55% Ct) Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≪ Combe 2021 Genovese 2019 Subtola (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtola (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.7 Serious TEAE Combe 2021 Genovese 2019 Kavanaugh 2018	0 pplicable Not applicat 3.2 288 71 359 0.00; Chi <sup>2</sup> = 287 82 30 50 449 0.20; Chi <sup>2</sup> = Z = 0.76 (P = 21 4 3	475 147 622 0.42, df= 0.00001 se events 475 147 69 86 777 13.37, df 13.37, df : 0.45)	0 160 30 190 190 252 100 28 32 412 29 20 5 1	4755 148 623 0.52);   <sup>2</sup> 475 148 72 86 781 0.004) 475 148 72	79.1% 20.9% <b>100.0</b> % = 0% 30.8% 25.8% 21.0% 22.4% <b>100.0</b> % ;   <b>r</b> = 78% 70.1% 5.2%	1.05 [1.04, 1.75] 0.61 [0.38, 0.97] 1.21 [0.62, 2.37] 2.34 [1.27, 4.32] 1.21 [0.73, 2.00]	
Subtora (55% Ct) Total events Heterogeneity: Not ar Test for overall effect: <b>3.1.5 DAS28-CRP</b> $\leq$ Combe 2021 Genovese 2019 <b>Subtotal (95% Ct)</b> Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>3.1.6 Treatment-eme</b> Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 <b>Subtotal (95% Ct)</b> Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>3.1.7 Serious TEAE</b> Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017	0 pplicable Not applicat 3.2 288 71 359 0.00; Chi² = Z = 9.57 (P ≪ 287 82 30 50 449 0.20; Chi² = Z = 0.76 (P = 21 4 3 2	475 147 622 0.42, df= 0.00001 se events 475 147 69 86 777 13.37, df 13.37, df 13.37, df 147 69 86	0 160 30 190 252 100 28 32 412 20 5 1 4	475 148 623 9.52);   <sup>2</sup> 475 148 72 86 781 0.004) 475 148 72 86 781	79.1% 20.9% <b>100.0</b> % = 0% 30.8% 25.8% 21.0% 22.4% <b>100.0</b> % ;   <b>r</b> = 78% 70.1% 15.4% 5.2%	1.05 [0.56, 1.97] 0.80 [0.23, 0.34] 1.05 [0.56, 1.97] 0.80 [0.24, 3.04] 1.05 [0.56, 1.97] 0.80 [0.24, 3.04] 1.05 [0.56, 1.97] 0.80 [0.24, 3.04] 3.23 [0.33, 31.80] 0.49 [0.09, 2.74]	
Subtoral (5% Ct) Total events Heterogeneity: Not ar Test for overall effect: 3.1.5 DAS28-CRP ≪ Combe 2021 Genovese 2019 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Cl) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.7 Serious TEAE Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Cl)	0 pplicable Not applicat 3.2 288 71 359 0.00; Chi <sup>2</sup> = Z = 9.57 (P - 287 82 30 50 449 0.20; Chi <sup>2</sup> = Z = 0.76 (P = 21 4 3 2	475 147 622 0.42, df= 0.00001 se events 475 147 69 86 777 13.37, df 13.37, df 13.37, df 147 69 475 147 69 877	0 160 30 190 252 100 28 32 412 = 3 (P = 20 5 1 4	4755 148 623 0.52);   <sup>2</sup> 4755 148 72 86 781 0.004) 4755 148 72 781 0.004)	79.1% 20.9% <b>100.0</b> % = 0% 30.8% 25.8% 21.0% 22.4% <b>100.0</b> % ;   <sup>2</sup> = 78% 70.1% 15.4% 5.2% 9.2% 90.0%	<ul> <li>3.03 [2.33, 3.95]</li> <li>3.67 [2.20, 6.15]</li> <li>3.16 [2.49, 3.99]</li> <li>1.35 [1.04, 1.75]</li> <li>0.61 [0.38, 0.97]</li> <li>1.21 [0.62, 2.37]</li> <li>2.34 [1.27, 4.32]</li> <li>1.21 [0.73, 2.00]</li> <li>1.05 [0.56, 1.97]</li> <li>0.80 [0.21, 3.04]</li> <li>3.23 [0.33, 31.80]</li> <li>0.49 [0.99, 2.74]</li> <li>1.00 [0.59, 1.68]</li> </ul>	
Subtotal (55% Ct) Total events Heterogeneity: Not a; Test for overall effect: 3.1.5 DAS28-CRP ≪ Combe 2021 Genovese 2019 Subtotal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.7 Serious TEAE Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.7 Serious TEAE Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Ct) Total events	0 pplicable Not applicat 3.2 288 71 359 $0.00; Chi^2 = 287$ rgent adver: 287 82 30 50 449 $0.20; Chi^2 = 21$ 443 2 = 0.76 (P = 21 4 3 2 30 30	475 147 622 0.42, df= : 0.00001 se events 475 147 69 86 777 13.37, df : 0.45) 475 147 69 86 777 69 86 777	0 160 30 190 190 252 200 28 32 412 = 3 (P= 20 5 1 4 30	475 148 623 3.52);   <sup>2</sup> 475 148 72 8 781 0.004) 475 148 72 148 72 148 72 86 781	79.1% 20.9% 100.0% = 0% 30.8% 25.8% 21.0% 22.4% 100.0% ;   <sup>2</sup> = 78% 70.1% 15.4% 5.2% 9.2% 100.0%	1.35 [1.04, 1.75] 0.61 [0.38, 0.97] 1.21 [0.62, 2.37] 2.34 [1.27, 4.32] 1.21 [0.73, 2.00] 1.05 [0.56, 1.97] 0.80 [0.21, 3.04] 3.23 [0.33, 31.80] 0.49 [0.09, 2.74] 1.00 [0.59, 1.68]	
Subtoal (55% Ct) Total events Heterogeneity: Not a; Test for overall effect: 3.1.5 DAS28-CRP $\leq$ Combe 2021 Genovese 2019 Subtoal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.6 Treatment-eme Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtoal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.7 Serious TEAE Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtoal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.1.7 Serious TEAE Combe 2021 Genovese 2019 Kavanaugh 2018 Westhovens 2017 Subtotal (95% Ct) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0 pplicable Not applicat 3.2 288 71 359 $0.00; Chi^2 = Z^2 = 9.57 (P - 20^2)^2 + 20^2$ 30 50 449 $0.20; Chi^2 = Z^2 + 0.76 (P - 20^2)^2 + 20^2)^2 + 20^2$ 21 4 3 2 30 $0.00; Chi^2 = Z^2 + 20^2$ 30 $0.00; Chi^2 = Z^2 + 20^2)^2 + 20^2$ 30 $0.00; Chi^2 = Z^2 + 20^2)^2 + 20^2$	475 147 622 0.42, df = 0.00001 se events 475 147 69 86 777 13.37, df 13.37, df 13.37, df 147 89 86 777 1.81, df = 0.99)	0 160 30 190 190 252 100 28 32 412 20 5 1 4 30 20 5 1 4 30 20 5 1 4 20 5 1 4 20 20 20 20 20 20 20 20 20 20	475 148 623 0.52);  * 475 148 72 86 781 0.004) 475 148 72 86 781 72 86 781 0.61);  *	79.1% 20.9% 100.0% = 0% 30.8% 25.8% 21.0% 22.4% 100.0% ;  ² = 78% 70.1% 15.4% 5.2% 9.2% 100.0% = 0%	3.03 [2.33, 3.95]         3.67 [2.20, 6.15]         3.16 [2.49, 3.99]         1.35 [1.04, 1.75]         0.61 [0.38, 0.97]         1.21 [0.62, 2.37]         2.34 [1.27, 4.32]         1.21 [0.73, 2.00]         1.05 [0.56, 1.97]         0.80 [0.21, 3.04]         3.23 [0.33, 31.80]         0.49 [0.09, 2.74]         1.00 [0.59, 1.68]	

Figure 3A. Meta-analysis of filgotinib 200 mg versus placebo at week 24 (categorical outcomes)

Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% CI	IV. Random, 95% Cl
3.2.1 SE-36 PCS	moun		Total	moun	00	Tettai	i i o igiti		
Combe 2021	10.5	8.5	475	77	7 97	475	39.1%	2 80 [1 75 3 85]	
Genovese 2019	94	8 23	69	3.3	7.95	72	29.7%	6 10 [3 43 8 77]	
Westhovens 2017	97	9.20	86	3.2	6.86	86	31.3%	6 50 [4 07 8 93]	
Subtotal (95% CI)	0.1	0.2	630	0.2	0.00	633	100.0%	4.94 [2.20, 7.67]	•
Heterogeneity: Tau <sup>2</sup>	= 4.70; C	hi² = 11	.05. df=	= 2 (P =	0.004);	<b>=</b> 829	6		
Test for overall effec	t: Z = 3.54	4 (P = 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]	
Westhovens 2017	11.6	12.33	86	6	9.64	86	27.2%	5.60 [2.29, 8.91]	
Subtotal (95% CI)			630			633	100.0%	3.66 [1.28, 6.04]	◆
Heterogeneity: Tau <sup>2</sup>	= 2.58; C	hi² = 4.7	4, df =	2 (P = 0	.09); l² =	58%			
Test for overall effec	t: Z = 3.02	2 (P = 0.)	003)						
3.2.3 SDAI									
Combe 2021	-31.8	12.18	475	-26.6	12.91	475	38.5%	-5.20 [-6.80, -3.60]	÷
Genovese 2019	-32.1	14.41	69	-24.9	14.4	72	31.1%	-7.20 [-11.96, -2.44]	
Westhovens 2017	-31	15.02	86	-15.8	18.55	86	30.3%	-15.20 [-20.24, -10.16]	_ <b>_</b>
Subtotal (95% CI)			630			633	100.0%	-8.86 [-14.57, -3.14]	$\bullet$
Heterogeneity: Tau <sup>2</sup>	= 21.37; •	Chi² = 1	3.90, df	= 2 (P =	= 0.0010	l); l² = 8	6%		
Test for overall effec	t: Z = 3.04	4 (P = 0.	002)						
3.2.4 CDAI									
Combe 2021	-30.6	11.88	475	-26.3	12.38	475	39.2%	-4.30 [-5.84, -2.76]	* (
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	100.0%	-7.41 [-12.63, -2.19]	$\bullet$
Heterogeneity: Tau <sup>2</sup>	= 17.52;+	Chi <sup>z</sup> = 1	2.43, df	'= 2 (P =	= 0.002)	; I <b>²</b> = 84	%		
Tact for everall offer	t: Z = 2.78	3 (P = 0.)	005)						
restion overall ellec								_	
restion overall ellec									

Figure 3B. Meta-analysis of filgotinib 200 mg versus placebo at week 24 (continuous outcomes)

2.20 – 7.67; P < 0.001;  $I^2 = 82\%$ ] and FACIT-Fatigue [*MD* 3.66; 95% *CI* 1.28 – 6.04; P = 0.003;  $I^2 = 58\%$ ] and lower SDAI [*MD* –8.86; 95% *CI* -14.57 to -3.14; P = 0.002;  $I^2 = 86\%$ ] and CDAI [*MD* -7.41; 95% *CI* -12.63 to -2.19; P = 0.005;  $I^2 = 84\%$ ] (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  $\leq$  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% *CI* 1.12 – 1.74; *P* = 0.003; *I*<sup>2</sup> = 0%], ACR50 [*OR* 1.50; 95% *CI* 1.23 – 1.84; *P* < 0.001; *I*<sup>2</sup> = 0%], ACR70 responses [*OR* 1.47; 95% *CI* 1.16 – 1.87; *P* = 0.002; *I*<sup>2</sup> = 0%], and DAS28-CRP ≤ 3.2 [*OR* 1.46; 95% *CI* 1.16 – 1.82; *P*=0.001; *I*<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% *CI* -4.09 to -1.41; *P*<0.001; *I*<sup>2</sup> = 0%] and CDAI [*MD* -2.46; 95% *CI* -3.76 to -1.15; *P* < 0.001; *I*<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% *CI* 2.22 – 3.42; *P*<0.001; *I*<sup>2</sup> = 61%], ACR50 [*OR* 1.26; 95% CI 1.03 – 1.54; P = 0.03;  $I^2 = 0\%$ ], and DAS28- $\mathsf{CRP} \leq 3.2 \; [OR\; 1.36; 95\% \; CI\; 1.08 - 1.70; P = 0.008; I^2$ = 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% CI 0.86 - 2.99; P < 0.001;  $I^2 = 0\%$ ] and lower SDAI [MD] -3.11; 95% CI -4.37 to -1.85; P< 0.001; I<sup>2</sup> = 0%] and CDAI [MD -1.86; 95% CI -3.10 - -0.62; P = 0.003; I<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  $0.30; 95\% CI 0.15 - 0.61; P < 0.001; I^2 = 70\%$ ] (Figure 5A and Figure 5B). The results of the HAQ-DIare 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 consid-

	filaotinib 2	00ma	filaotinib 1	00ma		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]	+
Kavanaugh 2018	50	69	46	70	9.2%	1.37 [0.67, 2.83]	_ <del></del>
Westhovens 2017	59	86	54	85	12.5%	1.25 [0.67, 2.37]	_ <b>+</b>
Subtotal (95% CI)		777		788	100.0%	1.40 [1.12, 1.74]	◆
Total events	570		523				
Heterogeneity: Chi <sup>2</sup> =	= 0.14, df = 3	(P = 0.99	); <b> </b> <sup>2</sup> = 0%				
Test for overall effect	t: 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]	
Kayanaugh 2018	30	69	76	70	9.6%	1 30 [0 66 2 57]	_ <b>_</b>
Weethovene 2017	37	20	20	95	12.0%	1.26 [0.60, 2.37]	<b>_</b>
Subtotal (95% CI)	57	777	52	788	100.0%	150 [123 184]	◆
Total events	354		282		1001070	100 [ 1120, 110 1]	
Heterogeneity: Chi?=	-064 df=3i	(P = 0.89	): IF = 0%				
Test for overall effect	- 0.04, 01 – 0 / t 7 = 3 92 (P <	<pre>(i = 0.03 ≤ 0.0001)</pre>	), i = 0,0 )				
		. 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	t: Z = 3.16 (P =	= 0.002)					
4.1.4 DAS28-CRP ≤	3.2						
Combe 2021	236	475	186	480	73.8%	1.56 [1.21.2.02]	
Genovese 2019	60	147	57	153	26.2%	1 16 [0 73 1 85]	
Subtotal (95% CI)		622		633	100.0%	1.46 [1.16, 1.82]	◆
Total events	296	- LL	243		1001010		
Heterogeneity: Chi <sup>2</sup> =	=119 df=1	(P = 0.28	): F= 16%				
Test for overall effect	T = 3.28 (P =	0.20 = 0.001)	<u>, ,                                  </u>				
reaction over all effect		- 0.001)					
							· · · · · · ·
							0.01 0.1 1 10 100

Figure 4A. Meta-analysis of filgotinib 200 mg versus 100 mg at week 12 (categorical outcomes)



Figure 4B. Meta-analysis of filgotinib 200 mg versus 100 mg at week 12 (continuous outcomes)



Figure 5A. Meta-analysis of filgotinib 200 mg versus 100 mg at week 24 (categorical outcomes)

ered 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 main-



Figure 5B. Meta-analysis of filgotinib 200 mg versus 100 mg at week 24 (continuous outcomes)

stay 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 bD-MARDs, 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 drugdrug 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  $\leq$  3.2, FAC-IT-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 DMARD-naive 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**

YL W, L Y, and LM P 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.

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matoid Arthritis Based on Phase 2 and Phase 3 Studies. British journal of clinical pharmacology. 2022.

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#### SUPPLEMENTARY MATERIAL

Study of Subgroup Events for a Levents for a Vergan M-H, Fixed, 95% CI M-H, Fixed, 95% CI Combes 2021 335 400 237 475 63.9% 2.32 [1.78, 3.02] Genowse 2019 88 153 46 148 17.6% 3.00 [1.87, 4.92] Westhovens 2017 54 85 38 86 12.2% 2.20 [1.19, 4.06] Subtotal (95% CI) 788 781 100.0% 2.57 [2.09, 3.16] Total events 523 342 Heterogeneity, Ch <sup>2</sup> = 3.93, df = 3 (P = 0.77), P = 24% Test for overall effect Z = 8.97 (P < 0.00001) 2.3.2 ACR50 Combes 2019 49 153 22 148 17.2% 2.70 [1.53, 4.75] Kawanaugh 2018 26 70 8 72 5.6% 4.73 [1.96, 11.40] Westhovens 2017 32 85 13 66 9.1% 3.39 [1.63, 7.07] Subtotal (95% CI) 788 781 100.0% 2.62 [2.07, 3.32] Total events 222 137 Heterogeneity, Ch <sup>2</sup> = 2.8, 0.6 = 3 (P = 0.27), P = 0.% Test for overall effect Z = 8.03 (P < 0.00001) 2.3.3 ACR70 Combes 2019 22 153 10 146 11.83% 2.32 [1.06, 5.08] Kawanaugh 2018 27 70 12 72 152% 3.14 [1.43, 68.8] Westhovens 2017 18 85 7 86 11.5% 3.03 [1.19, 7.70] Subtotal (95% CI) 788 781 100.0% 2.29 [2.17, 4.10] Heterogeneity, Ch <sup>2</sup> = 0.46 (P < 0.00001) 2.3.4 DAS28-CRP $\leq$ 3.2 Combes 2019 57 153 23 148 1.17% 32.3[ 1.65, 7.61] Subtotal (95% CI) 78 71 102.8 2.17, 4.10] Total events 156 61 Heterogeneity, Ch <sup>2</sup> = 0.44 (P < 0.00001) 2.3.4 DAS28-CRP $\leq$ 3.2 Combes 2019 57 153 3 144 175 82.3% 2.07 [1.57, 2.75] Genoves 2019 57 153 4.76 11.7% 32.3[ 1.86, 5.61] Subtotal (95% CI) 78 78 100.0% 2.28 [1.77, 2.92] Total events 243 134 Heterogeneity, Ch <sup>2</sup> = 1.85, df = 1 (P = 0.16), P = 43% Test for overall effect Z = 6.46 (P < 0.00001) 2.3.4 DAS28-CRP $\leq$ 3.2 Combes 2019 57 153 23 148 17.7% 32.3 [1.86, 5.61] Subtotal (95% CI) 76 158 24.51 (P = 0.48) H1.1 475 82.3% 2.07 [1.57, 2.75] Genoves 2019 57 153 23 148 17.7% 32.3 [1.68, 5.61] Total events 243 134 H275 42.3% 1.00.0% 2.28 [1.77, 2.92] Total events 243 134 H275 42.3% 1.00.0% 2.28 [1.77, 2.92] Total events 243 134 H275 42.3% 1.00.0% 2.28 [1.77, 2.92] Total events 243 134 H275 42.3% 1.00.0% 2.28 [1.77, 2.92] Total events 243 134 H275 42.3% 1.00.0% 2.28 [1.77, 2.92] Total events 243 134 H275 42.3% 1.00.0% 2.28 [1.77, 2.92] Total	Study or Subgroup         Events         10           2.3.1 ACR20         2.3.1 ACR20         335         4           Combe 2021         335         4         5           Combe 2021         335         4         5           Senovese 2019         88         1           Kavanaugh 2018         46         6           Westhovens 2017         54         5           Subtotal (95% CI)         7         7           Total events         523         -           Heterogeneity: Chi <sup>2</sup> = 3.93, df = 3 (P = 0         0           2.3.2 ACR50         2         0           Combe 2021         175         4           Senovese 2019         49         1 <avanaugh 2018<="" td="">         26         ///esthovens 2017           Vesthovens 2017         32         -           Subtotal (95% CI)         7         7           Fotal events         282         -           Heterogeneity: Chi<sup>2</sup> = 2.85, df = 3 (P = 0         -           Combe 2021         89         4           Senovese 2019         22         1           <avanaugh 2018<="" td="">         27         -           Vesthovens 2017         18</avanaugh></avanaugh>	oral E 480 153 70 85 788 0.27); 1 00001) 480 153 70 85 0.420; 1 00001) 480 153 480 153	237 46 21 38 342 (I <sup>2</sup> = 24%) ) 94 22 8 13 137 (I <sup>2</sup> = 0%) )	475 148 72 86 <b>781</b> 6 475 148 72 86 <b>781</b>	63.9% 17.6% 6.3% 12.2% 100.0% 68.0% 17.2% 5.6% 9.1% 100.0%	м.н. нхед, 95% СГ 2.32 [1.78, 3.02] 3.00 [1.87, 4.82] 4.65 [2.29, 9.45] 2.20 [1.19, 4.06] <b>2.57 [2.09, 3.16]</b> 2.33 [1.74, 3.12] 2.70 [1.53, 4.75] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b>	M-H, Fixed, 9: 	2% LI
$\begin{array}{c} 2.31 \ ALX020 \\ Combe 2021 & 335 & 480 & 237 & 475 & 63.9\% & 2.32 [1.78, 3.02] \\ 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 & 68 & 12.2\% & 2.20 [1.19, 4.06] \\ Subtotal (95\% Ch) & 788 & 781 & 100.0\% & 2.57 [2.09, 3.16] \\ Total events & 523 & 342 \\ Heterogeneihy Chill2 = 3.93, df = 3 (P = 0.27); P = 24\% \\ Testfor overall effect Z = 8.97 (P < 0.00001) \\ 2.32 \ ACR50 \\ Combe 2021 & 175 & 480 & 94 & 475 & 68.0\% & 2.33 [1.74, 3.12] \\ Genovese 2019 & 49 & 153 & 22 & 148 & 17.2\% & 2.70 [1.53, 4.75] \\ Kavanaugh 2018 & 26 & 70 & 8 & 72 & 5.6\% & 4.73 [1.86, 11.40] \\ Westhovens 2017 & 32 & 85 & 13 & 86 & 9.1\% & 3.39 [1.63, 7.07] \\ Subtotal (95\% Ch) & 788 & 781 & 100.0\% & 2.62 [2.07, 3.32] \\ Total events & 262 & 137 \\ Heterogeneihy: Chil2 = 2.85, df = 3 (P = 0.42); P = 0\% \\ Total events & 262 & 137 \\ Heterogeneihy: Chil2 = 2.85, df = 3 (P = 0.42); P = 0\% \\ Total events & 156 & 61 \\ Westhovens 2017 & 18 & 85 7 & 786 & 11.5\% & 3.03 [1.9, 7.70] \\ Subtotal (95\% Ch) & 788 & 781 & 100.0\% & 2.98 [2.17, 4.10] \\ \hline \ Westhovens 2017 & 18 & 85 7 & 86 & 11.5\% & 3.03 [1.9, 7.70] \\ Subtotal (95\% Ch) & 788 & 781 & 100.0\% & 2.98 [2.17, 4.10] \\ \hline \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$	2.3.1 ACK20         Combe 2021       335       4         Genovese 2019       88       1         Kavanaugh 2018       46         Westhovens 2017       54         Subtotal (95% CI)       7         Fotal events       523         -teterogeneity: Chi <sup>P</sup> = 3.93, df = 3 (P = 0.01         2.3.2 ACR50         Combe 2021       175         Genovese 2019       49         Genovese 2019       49         Kavanaugh 2018       26         Westhovens 2017       32         Subtotal (95% CI)       7         Fotal events       282         -teterogeneity: Chi <sup>P</sup> = 2.85, df = 3 (P = 0.00         2.3.3 ACR70       20         Combe 2021       89         Senovese 2019       22         Cavanaugh 2018       27         Vesthovens 2017       18         Subtotal (95% CI)       7         Total events       156         vesthovens 2017       18         Subtotal (95% CI)       7         Total events       156         veents       156         veents       156         veents       156 <th>480 153 70 85 <b>788</b> :0.27); 1 00001) 480 153 70 85 <b>788</b> :0.42); 1 00001) 480 153</th> <th>237 46 21 38 342 (I<sup>2</sup> = 24%) ) 94 22 8 13 137 (I<sup>2</sup> = 0%) )</th> <th>475 148 72 86 <b>781</b> 6 475 148 72 86 <b>781</b></th> <th>63.9% 17.6% 6.3% 12.2% 100.0% 68.0% 17.2% 5.6% 9.1% 100.0%</th> <th>2.32 [1.78, 3.02] 3.00 [1.87, 4.82] 4.65 [2.29, 9.45] 2.20 [1.19, 4.06] <b>2.57 [2.09, 3.16]</b> 2.33 [1.74, 3.12] 2.70 [1.53, 4.76] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b></th> <th>-</th> <th></th>	480 153 70 85 <b>788</b> :0.27); 1 00001) 480 153 70 85 <b>788</b> :0.42); 1 00001) 480 153	237 46 21 38 342 (I <sup>2</sup> = 24%) ) 94 22 8 13 137 (I <sup>2</sup> = 0%) )	475 148 72 86 <b>781</b> 6 475 148 72 86 <b>781</b>	63.9% 17.6% 6.3% 12.2% 100.0% 68.0% 17.2% 5.6% 9.1% 100.0%	2.32 [1.78, 3.02] 3.00 [1.87, 4.82] 4.65 [2.29, 9.45] 2.20 [1.19, 4.06] <b>2.57 [2.09, 3.16]</b> 2.33 [1.74, 3.12] 2.70 [1.53, 4.76] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b>	-	
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Kavanaugh 2018       46       70       21       72       6.3%       4.65       (2.29, 9.46)         Westhovens 2017       54       85       38       86       12.2%       2.20       [1.9], 4.06]         Subtotal (95% CI)       788       781       100.0%       2.57       [2.09, 3.16]         Total events       523       342       445       [2.29, 3.16]         Heterogeneity: Chf <sup>2</sup> = 3.9, 7(P < 0.00001)       2.32       2.33       [1.74, 3.12] $\bullet$ Genovese 2019       49       153       22       148       17.2%       2.70 [1.53, 4.75]         Kavanaugh 2018       26       70       8       72       5.6%       4.73 [1.96, 11.40]         Westhovens 2017       32       85       13       86       9.1%       3.39 [1.63, 7.07]         Subtotal (95% CI)       788       781       100.0%       2.62 [2.07, 3.32] $\bullet$ Test for overall effect Z = 8.03 (P < 0.00001)       2.33       1.18       1.83%       2.32 [1.06, 5.08] $\star$ Kavanaugh 2018       27       70       12       72       55.0%       3.15 [2.06, 4.83] $\bullet$ $\bullet$ Genovese 2019       27       70       2.73	Kavanaugh 2018       46         Kavanaugh 2017       54         Westhovens 2017       54         Subtotal (95% CI)       7         Total events       523         Heterogeneity: Chi² = 3.93, df = 3 (P = 0         Fest for overall effect: Z = 8.97 (P < 0.01	70 85 <b>788</b> : 0.27); 1 00001) 480 153 70 85 <b>788</b> : 0.42); 1 00001) 480 153	21 38 342 ; I <sup>2</sup> = 24% ) 94 22 8 13 137 ; I <sup>2</sup> = 0% ) 32	72 86 <b>781</b> 6 475 148 72 86 <b>781</b>	6.3% 12.2% 100.0% 68.0% 17.2% 5.6% 9.1% 100.0%	4.66 [2.29, 9.46] 2.20 [1.19, 4.06] <b>2.57 [2.09, 3.16]</b> 2.33 [1.74, 3.12] 2.70 [1.53, 4.75] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b>		• • •
Westhovens 2017 54 85 38 86 12.2% 2.20[1.19, 4.06] Total events 523 342 Heterogeneity. ChF = 3.93, df = 3 (P = 0.27); P = 24% Test for overall effect Z = 8.97 (P < 0.00001) 2.3.2 ACR50 Combe 2021 175 480 94 475 68.0% 2.33 [1.74, 3.12] Genowese 2019 49 153 22 148 17.2% 2.70 [1.53, 4.75] Kavanaugh 2018 26 70 8 72 5.6% 4.73 [1.96, 11.40] Westhovens 2017 32 85 13 86 91% 3.39 [1.63, 7.07] Subtotal (95% Cl) 768 781 100.0% 2.62 [2.07, 3.32] Total events 282 137 Heterogeneity. ChF = 2.85, df = 3 (P = 0.42); P = 0% Test for overall effect Z = 8.03 (P < 0.0001) 2.3.3 ACR70 Combe 2021 89 480 32 475 55.0% 3.15 [2.06, 4.83] Genowese 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% Cl) 788 781 100.0% 2.98 [2.17, 4.10] Total events 156 61 Heterogeneity. ChF = 0.48, df = 3 (P = 0.92); P = 0% Test for overall effect Z = 6.74 (P < 0.00001) 2.3.4 DAS28-CRP $\leq$ 3.2 Combe 2021 186 480 111 475 82.3% 2.07 [1.57, 2.75] Genowese 2019 57 153 23 148 17.7% 3.23 [1.86, 5.61] Subtotal (95% Cl) 633 623 100.0% 2.28 [1.77, 2.92] Total events 243 134 Heterogeneity. ChF = 1.95, df = 1 (P = 0.16); P = 49% Test for overall effect Z = 6.46 (P < 0.00001) 4.01 0.1 100	Westhovens 2017       54         Subtotal (95% CI)       7         Total events       523         Heterogeneity: Chi <sup>a</sup> = 3.93, df = 3 (P = 0.01)         2.3.2 ACR50         Combe 2021       175         Combe 2021       175         Subtotal (95% CI)       7         Senovese 2019       49         Avanaugh 2018       26         Westhovens 2017       32         Subtotal (95% CI)       7         Total events       282         Heterogeneity: Chi <sup>a</sup> = 2.85, df = 3 (P = 0.00)         2.3.3 ACR70         Combe 2021       89         Senovese 2019       22         Combe 2021       89         Asenovese 2019       22         Combe 2021       89         Senovese 2019       22         Combe 2021       89         Asenovese 2019       22         Combourse 2017       18         Subtotal (95% CI)       7         Total events       156         Heterogeneity: Chi <sup>a</sup> = 0.48, df = 3 (P = 0.00)	85 788 : 0.27); 1 00001) 480 153 70 85 788 : 0.42); 1 00001) 480 153	38 342 ;  = 24% ) 94 22 8 13 13 ;  = 0% ) 32	86 <b>781</b> 6 475 148 72 86 <b>781</b>	12.2% 100.0% 68.0% 17.2% 5.6% 9.1% 100.0%	2.20 [1.19, 4.06] 2.57 [2.09, 3.16] 2.33 [1.74, 3.12] 2.70 [1.53, 4.75] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] 2.62 [2.07, 3.32]		<ul> <li>▲</li> <li>▲</li> <li>▲</li> <li>▲</li> <li>▲</li> <li>▲</li> <li>▲</li> </ul>
Subtotal (95% CI) 788 781 100.0% 2.57 [2.09, 3.16] Total events 523 342 Heterogeneity: Ch <sup>2</sup> = 3.93, df = 3 (P = 0.27); P = 24% Test for overall effect Z = 8.97 (P < 0.00001) 2.3.2 ACR50 Combe 2021 175 480 94 475 68.0% 2.33 [1.74, 3.12] Genovese 2019 49 153 22 148 17.2% 2.70 [1.53, 4.75] Kavanaugh 2018 26 70 8 72 56% 4.73 [1.96, 11.40] Westhovens 2017 32 95 13 86 9.1% 3.39 [1.63, 7.07] Subtotal (95% CI) 788 781 100.0% 2.62 [2.07, 3.32] Total events 282 137 Heterogeneity: Ch <sup>2</sup> = 2.8, 0(f = 3 (P = 0.12); P = 0% Test for overall effect Z = 8.03 (P < 0.00001) 2.3.3 ACR70 Combe 2021 89 480 32 475 55.0% 3.15 [2.06, 4.83] Genovese 2019 22 153 10 148 18.3% 2.23 [1.06, 5.08] Kavanaugh 2018 27 70 12 72 15.2% 3.03 [1.19, 7.70] Subtotal (95% CI) 768 781 100.0% 2.98 [2.17, 4.10] Total events 156 61 Heterogeneity: Ch <sup>2</sup> = 0.48, df = 3 (P = 0.92); P = 0% Test for overall effect Z = 6.74 (P < 0.00001) 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: Ch <sup>2</sup> = 1.95, df = 1 (P = 0.16); P = 49% Test for overall effect Z = 6.46 (P < 0.00001) 4.0.1 1 10 100	Subtotal (95% Cl)         7           Total events         523           Heterogeneity: Chi <sup>2</sup> = 3.93, df = 3 (P = 1           Test for overall effect: Z = 8.97 (P < 0.01	788 : 0.27); 1 00001) 480 153 70 85 788 : 0.42); 1 00001) 480 153	342 ;   <sup>2</sup> = 24% ) 94 22 8 13 137 ;   <sup>2</sup> = 0% ) 32	781 6 148 72 86 781	68.0% 17.2% 5.6% 9.1% <b>100.0</b> %	2.33 [1.74, 3.12] 2.70 [1.53, 4.75] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b>		<ul> <li>▼</li> <li>▼</li> <li>▼</li> </ul>
Total events 523 342 Heterogeneity: $ChF = 3.93$ , $df = 3(P = 0.27)$ ; $F = 24\%$ Test for overall effect Z = 8.97 (P < 0.00001) <b>2.3.2 ACR50</b> Combe 2021 175 480 94 475 68.0% 2.33 [1.74, 3.12] Genovese 2019 49 163 22 148 17.2% 2.70 [1.53, 4.75] Kavanaugh 2018 26 70 8 72 5.6% 4.73 [1.96, 11.40] Westhovens 2017 32 85 13 86 9.1% 3.39 [1.63, 7.07] Subtotal (95% CI) 788 781 100.0% 2.62 [2.07, 3.32] Total events 282 137 Heterogeneity: $ChF = 2.85$ , $df = 3$ ( $P = 0.42$ ); $P = 0.\%$ Test for overall effect Z = 8.03 (P < 0.00001) <b>2.3.3 ACR70</b> Combe 2011 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: $ChF = 0.48$ , $df = 3$ ( $P = 0.32$ ); $F = 0\%$ Test for overall effect Z = 6.74 ( $P < 0.00001$ ) <b>2.3.4 DAS28-CRP <math>\leq</math> 3.2</b> 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: $ChF = 1.95$ , $df = 1$ ( $P = 0.16$ ); $F = 43\%$ Test for overall effect Z = 6.46 ( $P < 0.00001$ )	Total events       523         Heterogeneity: Chi <sup>2</sup> = 3.93, df = 3 (P = (         Test for overall effect: Z = 8.97 (P < 0.0)	: 0.27); I 00001) 480 153 70 85 <b>788</b> : 0.42); I 00001) 480 153	342 ;  *= 24% ) 94 22 8 13 137 ;  *= 0% ) 32	475 148 72 86 <b>781</b>	68.0% 17.2% 5.6% 9.1% <b>100.0</b> %	2.33 [1.74, 3.12] 2.70 [1.53, 4.75] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b>	4	• •
Heterogeneity: $Ch^2 = 3.93$ , $df = 3 (P = 0.27)$ ; $F = 24\%$ Test for overall effect: $Z = 8.97 (P < 0.00001)$ <b>2.3.2 ACR50</b> Combe 2021 175 480 94 475 68.0% 2.33 [1.74, 3.12] Genovese 2019 49 153 22 148 17.2% 2.70 [1.53, 4.75] Kavanaugh 2018 26 70 8 72 5.6% 4.73 [1.96, 11.40] Westhovens 2017 32 85 13 86 9.1% 3.39 [1.53, 7.07] Subtotal (95% CI) 788 781 100.0% 2.62 [2.07, 3.32] Total events 282 137 Heterogeneity: $Ch^2 = 2.85, df = 3 (P = 0.42); F = 0\%$ Test for overall effect: $Z = 8.03 (P < 0.00001)$ <b>2.3.3 ACR70</b> 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: $Ch^2 = 0.48, df = 3 (P = 0.92); F = 0\%$ Test for overall effect: $Z = 6.46 (P < 0.00001)$ <b>2.3.4 DAS28-CRP ≤ 3.2</b> 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: $Ch^2 = 1.95, df = 1 (P = 0.16); F = 49\%$ Test for overall effect: $Z = 6.46 (P < 0.00001)$	Heterogeneity: Chi² = 3.93, df = 3 (P = 1)         Test for overall effect: Z = 8.97 (P < 0.0)	: 0.27); 1 00001) 480 153 70 85 <b>788</b> : 0.42); 1 00001) 480 153	94 22 8 13 137 ; I <sup>2</sup> = 0% )	475 148 72 86 <b>781</b>	68.0% 17.2% 5.6% 9.1% <b>100.0</b> %	2.33 (1.74, 3.12) 2.70 (1.53, 4.75) 4.73 (1.96, 11.40) 3.39 (1.63, 7.07) <b>2.62 (2.07, 3.32)</b>	4	• • • •
Test for overall effect $Z = 8.97$ (P < 0.00001) 2.3.2 ACR50 Combe 2021 175 480 94 475 68.0% 2.33 [1.74, 3.12] Genovese 2019 49 153 22 148 17.2% 2.70 [1.53, 4.75] Kavanaugh 2018 26 70 8 72 5.6% 4.73 [1.96, 11.40] Westhovens 2017 32 85 13 86 9.1% 3.39 [1.63, 7.07] Subtotal (95% CI) 788 781 100.0% 2.62 [2.07, 3.32] Total events 282 137 Heterogeneity: Chi <sup>2</sup> = 2.85, df = 3 (P = 0.42); P = 0% Test for overall effect $Z = 8.03$ (P = 0.42); P = 0% Test for overall effect $Z = 8.03$ (P = 0.42); P = 0% Test for overall effect $Z = 8.03$ (P = 0.00001) 2.3.3 ACR70 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> = 0.42; (F = 0.92); F = 0% Test for overall effect $Z = 6.74$ (P < 0.00001) 2.3.4 DAS28-CRP $\leq$ 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); P = 49% Test for overall effect $Z = 6.46$ (P < 0.00001)	Test for overall effect: $Z = 8.97$ (P < 0.01	480 153 70 85 <b>788</b> : 0.42); 1 00001) 480 153	) 94 22 8 13 137 ; I <sup>2</sup> =0% ) 32	475 148 72 86 <b>781</b>	68.0% 17.2% 5.6% 9.1% <b>100.0</b> %	2.33 [1.74, 3.12] 2.70 [1.53, 4.75] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b>	-	• •
2.3.2 ACR50         Combe 2021       175       480       94       475       68.0%       2.33 [1.74, 3.12]         Genovese 2019       49       153       22       148       17.2%       2.70 [1.53, 4.75]         Kavanaugh 2018       26       70       8       72       5.6%       4.73 [1.96, 11.40]         Westhovens 2017       32       85       13       86       9.1%       3.33 [1.74, 3.12]         Total events       282       137         Heterogeneity: Chi <sup>2</sup> 2.16, df = 3 (P = 0.42); P = 0%       781       100.0%       2.62 [2.07, 3.32]         Total events       282       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]       Image: Combe 2.021       8.6       6.1         Revenues 2019       57       15.6       61       61       Image: Combe 2.021       186       480       111       475       82.3%       2.07 [1.57, 2.75]       Image: Combe	2.3.2 ACR50         Combe 2021       175       4         Genovese 2019       49       1         Kavanaugh 2018       26       7         Subtotal (95% CI)       7       7         Total events       282       4         Heterogeneity: Chi <sup>a</sup> = 2.85, df = 3 (P = 0       7         Z.3.3 ACR70       20       9         Combe 2021       89       4         Senovese 2019       22       1         Kavanaugh 2018       27       7         Vesthovens 2017       18       5         Subtotal (95% CI)       7       7         Total events       156       156         Heterogeneity: Chi <sup>a</sup> = 0.48, df = 3 (P = 0       9       9	480 153 70 85 <b>788</b> : 0.42); 1 000001) 480 153	94 22 8 13 ; I <sup>2</sup> = 0% ) 32	475 148 72 86 <b>781</b>	68.0% 17.2% 5.6% 9.1% <b>100.0</b> %	2.33 [1.74, 3.12] 2.70 [1.53, 4.75] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b>		▲ 
2.3.2 ACR50 Combe 2021 175 480 94 475 68.0% 2.33 [1.74, 3.12] Genovese 2019 49 153 22 148 17.2% 2.70 [1.53, 4.75] Kavanaugh 2018 26 70 8 72 5.6% 4.73 [1.96, 11.40] Westhovens 2017 32 85 13 86 9.1% 3.39 [1.63, 7.07] Subtotal (95% CI) 788 781 100.0% 2.62 [2.07, 3.32] Total events 282 137 Heterogeneity: Chi <sup>2</sup> = 2.85, df = 3 (P = 0.42); P = 0% Test for overall effect Z = 8.03 (P < 0.00001) 2.3.3 ACR70 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 = 0.32); P = 0% Test for overall effect Z = 6.74 (P < 0.00001) 2.3.4 DAS28-CRP $\leq$ 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); P = 49% Test for overall effect Z = 6.46 (P < 0.00001)	2.3.2 ACR50         Combe 2021       175       4         Genovese 2019       49       1         Kavanaugh 2018       26         Westhovens 2017       32         Subtotal (95% CI)       7         Total events       282         -teterogeneity: Chi <sup>2</sup> = 2.85, df = 3 (P = 0         Fest for overall effect: Z = 8.03 (P < 0.01	480 153 70 85 <b>788</b> : 0.42); I 00001) 480 153	94 22 8 13 137 ; I <sup>z</sup> = 0% )	475 148 72 86 <b>781</b>	68.0% 17.2% 5.6% 9.1% <b>100.0</b> %	2.33 [1.74, 3.12] 2.70 [1.53, 4.75] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b>		• •
Combe 2021 175 480 94 475 68.0% 2.33 [1.74, 3.12] Genovese 2019 49 153 22 148 17.2% 2.70 [1.53, 4.75] Kavanaugh 2018 26 70 8 72 5.6% 4.73 [1.66, 11.40] Westhovens 2017 32 85 13 86 9.1% 3.39 [1.63, 7.07] Subtotal (95% CI) 788 781 100.0% 2.62 [2.07, 3.32] Total events 222 137 Heterogeneity. Chi <sup>2</sup> = 2.85, df = 3 (P = 0.42); P = 0% Test for overall effect Z = 8.03 (P < 0.00001) 2.3.3 ACR70 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, 5.88] 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> = 0.49, df = 3 (P = 0.92); P = 0% Test for overall effect Z = 6.74 (P < 0.00001) 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); P = 49% Test for overall effect Z = 6.46 (P < 0.00001) $\frac{1}{0.01} 0.1 1 100$	Combe 2021         175         4           Genovese 2019         49         1           Kavanaugh 2018         26           Westhovens 2017         32           Subtotal (95% Cl)         7           Fotal events         282           Heterogeneity: Chi² = 2.85, df = 3 (P = 0)           Cost for overall effect: Z = 8.03 (P < 0.01)	480 153 70 85 <b>788</b> : 0.42); I 00001) 480 153	94 22 8 13 137 ;   <sup>2</sup> = 0% ) 32	475 148 72 86 <b>781</b>	68.0% 17.2% 5.6% 9.1% <b>100.0</b> %	2.33 [1.74, 3.12] 2.70 [1.53, 4.75] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b>	-	• •
Genovese 2019 49 163 22 148 17.2% 2.70 [1.53, 4.75] Kavanaugh 2018 26 70 8 72 5.6% 4.73 [1.96, 11.40] Westhovens 2017 32 85 13 86 9.1% 3.39 [1.63, 7.07] Subtotal (95% CI) 788 781 100.0% 2.62 [2.07, 3.32] Total events 282 137 Heterogeneity: ChF = 2.85, df = 3 (P = 0.42); P = 0% Test for overall effect: $Z = 8.03$ (P < 0.00001) 2.3.3 ACR70 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, 8.88] Westhovens 2017 18 85 7 86 11.5% 3.03 [1.9, 7.70] Subtotal (95% CI) 788 781 100.0% 2.98 [2.17, 4.10] Total events 156 61 Heterogeneity: ChF = 0.48, df = 3 (P = 0.92); F = 0% Test for overall effect: $Z = 6.74$ (P < 0.00001) 2.3.4 DAS28-CRP $\leq 3.2$ 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: ChF = 1.95, df = 1 (P = 0.16); F = 49% Test for overall effect: $Z = 6.46$ (P < 0.00001) 0.01 0.1 1 10	Genovese 2019         49         1           Kavanaugh 2018         26           Westhovens 2017         32           Subtotal (95% Cl)         7           Total events         282           Heterogeneity: Chi² = 2.85, df = 3 (P = 0)           Fest for overall effect: Z = 8.03 (P < 0.01)	153 70 85 <b>788</b> : 0.42); 1 00001) 480 153	22 8 13 137 ;  ² = 0% ) 32	148 72 86 <b>781</b>	17.2% 5.6% 9.1% <b>100.0</b> %	2.70 [1.53, 4.75] 4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b>	-	→ → ◆
Kavanaugh 2018       26       70       8       72       5.6%       4.73 [1.96, 11.40]         Westhovens 2017       32       85       13       86       9.1%       3.39 [1.63, 7.07]         Subtotal (95% CI)       788       781       100.0%       2.62 [2.07, 3.32]         Total events       282       137         Heterogeneity: Chi <sup>P</sup> = 2.85, df = 3 (P = 0.42); P = 0%       281 (1.63, 7.07)         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]       Image: Chi <sup>P</sup> = 0.48, df = 3 (P = 0.92); P = 0%         Test for overall effect: Z = 6.74 (P < 0.00001)	Kavanaugh 2018         26           Westhovens 2017         32           Subtotal (95% CI)         7           Total events         282           Heterogeneity: Chi <sup>2</sup> = 2.85, df = 3 (P = 0           Fest for overall effect: Z = 8.03 (P < 0.01	70 85 <b>788</b> : 0.42); I 00001) 480 153	8 13 137 137 137 137 32	72 86 <b>781</b>	5.6% 9.1% <b>100.0</b> %	4.73 [1.96, 11.40] 3.39 [1.63, 7.07] <b>2.62 [2.07, 3.32]</b>	-	
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Subtotal (95% CI)       788       781       100.0%       2.62 [2.07, 3.32]         Total events       282       137         Heterogeneity: Chi <sup>2</sup> = 2.85, df = 3 (P = 0.42); P = 0%       781       100.0%       2.62 [2.07, 3.32]         Cambe 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); P = 0%       2.07 [1.57, 2.75]       •       •         Genovese 2019       57       153       23       100.0%       2.28 [1.77, 2.92]       •         Combe 2021       186       480       111       475       82.3%       2.07 [1.57, 2.75]       •       •         Genovese 2019       57       153       23 <t< td=""><td>Subtotal (95% CI)         7           Total events         282           Heterogeneity: Chi<sup>a</sup> = 2.85, df = 3 (P = 0           Fest for overall effect: Z = 8.03 (P &lt; 0.01</td>           2.3.3 ACR70           Combe 2021         89           Senovese 2019         22           Varianaugh 2018         27           Vesthovens 2017         18           Subtotal (95% CI)         7           Total events         156           Heterogeneity: Chi<sup>a</sup> = 0.48, df = 3 (P = 0</t<>	Subtotal (95% CI)         7           Total events         282           Heterogeneity: Chi <sup>a</sup> = 2.85, df = 3 (P = 0           Fest for overall effect: Z = 8.03 (P < 0.01	788 : 0.42); I 00001) 480 153	137 ;  ² = 0% ) 32	781	100.0%	2.62 [2.07, 3.32]		•
Total events 282 137 Heterogeneity: $Chi^{P} = 2.85$ , $df = 3$ ( $P = 0.42$ ); $P = 0\%$ Test for overall effect $Z = 8.03$ ( $P < 0.00001$ ) <b>2.3.3 ACR70</b> 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] <b>Subtotal (95% Cl)</b> 788 781 100.0% 2.98 [2.17, 4.10] Total events 156 61 Heterogeneity: $Chi^{P} = 0.48$ , $df = 3$ ( $P = 0.92$ ); $P = 0\%$ Test for overall effect $Z = 6.74$ ( $P < 0.00001$ ) <b>2.3.4 DAS28-CRP</b> $\leq$ <b>3.2</b> 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] <b>Subtotal (95% Cl)</b> 633 623 100.0% 2.28 [1.77, 2.92] Total events 243 134 Heterogeneity: $Chi^{P} = 1.95$ , $df = 1$ ( $P = 0.16$ ); $P = 49\%$ Test for overall effect $Z = 6.46$ ( $P < 0.00001$ )	Total events         282           Heterogeneity: Chi² = 2.85, df = 3 (P = 1)           Fest for overall effect: Z = 8.03 (P < 0.01)	: 0.42);   00001) 480 153	137 ; I² = 0% ) 32					
Heterogeneity: $Chi^2 = 2.85$ , $df = 3$ (P = 0.42); P = 0% Test for overall effect: Z = 8.03 (P < 0.00001) 2.3.3 ACR70 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: $Chi^2 = 0.48$ , $df = 3$ (P = 0.92); P = 0% Test for overall effect: Z = 6.74 (P < 0.00001) 2.3.4 DAS28-CRP $\leq$ 3.2 Combe 2021 186 480 111 475 82.3% 2.07 [1.57, 2.76] 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: $Chi^2 = 1.95$ , $df = 1$ (P = 0.16); P = 49% Test for overall effect: Z = 6.46 (P < 0.00001) 0.01 0.1 1 10 100	Heterogeneity: Chi <sup>≈</sup> = 2.85, df = 3 (P = 0         Test for overall effect: Z = 8.03 (P < 0.01	: 0.42);   00001) 480 153	;   <b>2</b> = 0% ) 32					
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2.3.3 ACR70         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]       Image: Chi P = 0.48, df = 3 (P = 0.92); P = 0%         Total events       156       61       114       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]       Image: Chi P = 1.95, df = 1 (P = 0.16); P = 49%         Test for overall effect Z = 6.46 (P < 0.00001)	2.3.3 ACR70           Combe 2021         89         4           Senovese 2019         22         1           Kavanaugh 2018         27         1           Kosthovens 2017         18         1           Subtotal (95% CI)         7         7           Total events         156         1           Heterogeneity: Chi <sup>2</sup> = 0.48, df = 3 (P = 0         1         1	480 153	32					
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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Genovese 2019         22         1 <avanaugh 2018<="" td="">         27           Mesthovens 2017         18           subtotal (95% Cl)         7           Fotal events         156           Heterogeneity: Chi<sup>a</sup> = 0.48, df = 3 (P = 0)</avanaugh>	153		475	55.0%	3.15 [2.06, 4.83]		
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Subtotal (95% Cl) 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); i <sup>2</sup> = 0% Test for overall effect Z = 6.74 (P < 0.00001) 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% Cl) 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 <sup>2</sup> = 49% Test for overall effect: Z = 6.46 (P < 0.00001) 0.01 0.1 1 10 100	Subtotal (95% Cl) 7 Fotal events 156 Heterogeneity: Chi² = 0.48, df = 3 (P = 0	85	7	86	11.5%	3.03 [1.19, 7.70]		
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Heterogeneity: Chi <sup>2</sup> = 0.48, df = 3 (P = 0.92); I <sup>2</sup> = 0% Test for overall effect: Z = 6.74 (P < 0.00001) 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% Cl) 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 <sup>2</sup> = 49% Test for overall effect: Z = 6.46 (P < 0.00001) 0.01 0.1 1 10 100	Heterogeneity: Chi² = 0.48, df = 3 (P = l		61					
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Lor bit 20 201       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% Cl)       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 <sup>2</sup> = 49%         Test for overall effect: Z = 6.46 (P < 0.00001)	$234$ DAS28.CRP $\leq 32$							
Connector       100       400       111       473       02.3 %       2.07 [1.37, 2.75]         Genovese 2019       57       153       23       148       17.7%       3.23 [1.86, 5.61]         Subtotal (95% Cl)       633       623       100.0%       2.28 [1.77, 2.92]         Total events       243       134         Heterogeneity: Chi² = 1.95, df = 1 (P = 0.16); l² = 49%         Test for overall effect: Z = 6.46 (P < 0.00001)	Combo 2021 106 /	480	111	475	82.306	2 07 (1 57 2 75)		-
Subtotal (95% Cl)         633         623         100.0%         2.28 [1.77, 2.92]           Total events         243         134           Heterogeneity: Chi² = 1.95, df = 1 (P = 0.16); l² = 49%           Test for overall effect: Z = 6.46 (P < 0.00001)	Sonovaca 2010 57 1	400	22	1/10	17 704	2.07 [1.07, 2.70]		-
Total events 243 134 Heterogeneity: Chi <sup>2</sup> = 1.95, df = 1 (P = 0.16); I <sup>2</sup> = 49% Test for overall effect: Z = 6.46 (P < 0.00001)	Subtotal (95% CI) 6	633	20	623	100.0%	2 28 [1 77 2 02]		•
Heterogeneity: Chi <sup>2</sup> = 1.95, df = 1 (P = 0.16); l <sup>2</sup> = 49% Test for overall effect: Z = 6.46 (P < 0.00001)	Fotol overte 242	033	124	023	100.0%	2.20[1.11, 2.92]		•
Heterogenetity. Chr = 1.35, di = 1 (r = 0.16), r = 49% Test for overall effect: Z = 6.46 (P < 0.00001) 	/utar events Z43	0.4 00.1	134					
I estitor overall enect: Z = 6.46 (P < 0.00001)	heterogeneity: Chine 1.95, di = 1 (P = t Talat fan avanal, affactu 7 - 0.40 (P - 0.90)	0.16)(1	,r≃=49% `	0				
	rest for overall effect: Z = 6.46 (P < 0.00	00001)	)					
0.01 0.1 1 10 100							<b>⊢</b> − − <b> </b>	
							0.01 0.1 İ	10 100

Supplementary figure 1. Meta-analysis of filgotinib 100 mg versus placebo at week 12 (categorical outcomes)



Supplementary figure 2. Meta-analysis of filgotinib 100 mg versus placebo at week 12 (continuous outcomes)

	filaotir	nib 200r	na	pla	acebo			Mean Difference	Mean Dir	ference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Rando	m. 95% Cl
3.3.1 12 week										
Westhovens 2017	-0.75	0.6	86	-0.38	0.61	85	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	153	26.0%	-0.32 [-0.45, -0.19]		
Combe 2021	-0.69	0.61	475	-0.42	0.54	480	44.8%	-0.27 [-0.34, -0.20]		
Subtotal (95% CI)			777			788	100.0%	-0.33 [-0.41, -0.25]	•	
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	i² = 4.73	), df = 3	(P = 0.1)	19); I <sup>z</sup> :	= 37%				
Test for overall effect:	Z=7.68 (	(P < 0.0	0001)							
3.3.2 24 week										
Westhovens 2017	-0.818	0.63	86	-0.37	0.62	86	29.1%	-0.45 [-0.63, -0.26]		
Concycco 2010	-0.75	0.62	69	-0.42	0.6	72	27.3%	-0.33 [-0.53, -0.13]		
Genovese zora			175	0.60	0.6	475	13.6%	0.001.0.00 0.401	<b>.</b>	
Combe 2021	-0.82	0.63	4/5	-0.02	0.0		40.070	-0.20 [-0.28, -0.12]		
Combe 2021 Subtotal (95% CI)	-0.82	0.63	475 630	-0.02	0.0	633	100.0%	-0.20 [-0.28, -0.12] -0.31 [-0.47, -0.15]	<b>•</b>	
Combe 2021 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> =	-0.82 0.01; Chi	0.63 i² = 6.48	475 630 (df=2	-0.02 (P = 0.0	0.0 04); I² :	<b>633</b> = 69%	100.0%	-0.20 [-0.28, -0.12] -0.31 [-0.47, -0.15]	*	
Combe 2021 Subtotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	-0.82 0.01; Chi Z = 3.80 (	0.63 i² = 6.48 (P = 0.0)	475 630 (df = 2 001)	-0.62 (P = 0.0	0.0 04); I²∶	<b>633</b> = 69%	43.0% 100.0%	-0.20 [-0.28, -0.12] - <b>0.31 [-0.47, -0.15]</b>	•	
Combe 2021 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	-0.82 0.01; Chi Z = 3.80 (	0.63 i² = 6.48 (P = 0.0)	475 630 (, df = 2 001)	-0.02 (P = 0.0	0.0 04); I² :	<b>633</b> = 69%	100.0%	-0.20 [-0.25, -0.12] -0.31 [-0.47, -0.15]	*	
Combe 2021 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	-0.82 0.01; Ch Z = 3.80 (	0.63 i <sup>2</sup> = 6.48 (P = 0.0)	475 630 (, df = 2 001)	-0.82 (P = 0.0	0.0 04); I² :	<b>633</b> = 69%	100.0%	-0.20 [-0.23, -0.12] -0.31 [-0.47, -0.15]	-2 -1 (	



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: Chiž -	-0.26 df = 3.	(P – 0 97)	-1≊ = 0%				
Test for overall effect	: Z = 7.95 (P <	< 0.00001	)				
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)		718		709	17.2%	2.43 [1.94, 3.03]	◆
Total events	347		200				
Heterogeneity: Chi <sup>2</sup> =	= 3.42. df = 2 (	(P = 0.18)	: <b> ²</b> = 429	ж			
Test for overall effect	: Z = 7.82 (P <	< 0.00001	)				
3.4.3 ACR70							
Combe 2021	142	480	71	475	8.5%	2.39 [1.74, 3.29]	
Genovese 2019	31	153	12	148	1.7%	2.88 [1.42, 5.86]	
Westhovens 2017	28	85	8	86	0.9%	4.79 [2.03, 11.28]	
Subtotal (95% CI)		718		709	11.1%	2.66 [2.02, 3.50]	•
Total events	201		91				
Heterogeneity: Chi² = Test for overall effect	= 2.29, df = 2 ( : Z = 6.98 (P <	(P = 0.32) < 0.00001	; I² = 139 )	%			
3.4.5 DAS28-CRP ≤	3.2						
Combe 2021	255	480	160	475	12.8%	2.23 [1.72, 2.90]	
Genovese 2019	58	153	31	148	3.3%	2.30 [1.38, 3.85]	
Subtotal (95% CI)		633		623	16.1%	2.25 [1.78, 2.84]	•
Total events	313		191				
Heterogeneity: Chi² = Test for overall effect	= 0.01, df = 1 ( : Z = 6.81 (P <	(P = 0.91) < 0.00001	; I² = 0% )				
3.4.6 Treatment-em	ergent adver	se events	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]	
Kavanaugh 2018	23	70	28	72	3.2%	0.77 [0.39, 1.53]	
Westhovens 2017	37	85	32	86	3.1%	1.30 [0.71, 2.40]	
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 = 0.00	)2): <b>I</b> <sup>2</sup> = 7	79%			
Test for overall effect	: Z = 0.38 (P =	= 0.71)	-,,				
3.4.7 Serious TEAE							
Combe 2021	24	480	20	475	3.2%	1.20 [0.65, 2.20]	- <del> </del>
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]	<b>•</b>
Total events	34		30				
Heterogeneity: Chi <sup>2</sup> =	= 0.60, df = 3 i	(P = 0.90)	;   <b>2</b> = 0%				
Test for overall effect	: Z = 0.46 (P =	= 0.64)					
Total (95% CI)		4433		4384	100.0%	1.91 [1.73, 2.10]	•
Total events	1883		1333				
rotal ovorito							
Heterogeneity: Chi² =	= 75.56. df = 1	9 (P < 0.0	00001); P	<sup>2</sup> = 759	6		

Supplementary figure 4. Meta-analysis of filgotinib 100 mg versus placebo at week 24 (categorical outcomes)

Study or Subgroup	Moan	SD	Total	Mean	SD	Total	Woight	N Random 95% Cl	M Bandom 95% Cl
	Mean	30	Total	Wean	30	Total	weight	IV, Nahuom, 55% Ci	IV, Nalidolli, 55% Cl
Combo 2024		10.04	05		0.00	06	20.00	0.70 (4.4.2, 0.20)	
Compuses 2021	9.9	0.44	450	0.2	2.00	440	20.970	0.70 [4.12, 9.20]	
Weethouse 2019	9 10 0	0.44	400	2.0	7.80	140	33.270	2.40 [0.00, 4.20]	
Subtotal (05% CI)	10.5	0.04	400 710	1.1	1.97	700	39.9%	2.00 [1.00, 5.00] 3.64 [4.40, 5.70]	▲
Hotorogonoity: Tou? -	- 2.71 - 01		710 5 df = 1	2 /P = 0	01\-18-	770	100.0%	5.04 [1.45, 5.76]	•
Test for overall effect:	Z = 3.33	(P = 0.0	0, ur = . 0009)	2 (1 - 0.	.01),1 =				
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]	<b>+</b>
Subtotal (95% CI)			718			709	100.0%	2.38 [-0.58, 5.34]	◆
			<i>,</i>						
3.5.3 SDAI									
3.5.3 SDAI Combe 2021	-28.6	15.03	85	-15.8	18.55	86	28.0%	-12.80 [-17.86, -7.74]	
<b>3.5.3 SDAI</b> Combe 2021 Genovese 2019	-28.6 -27.8	15.03 13.54	85 153	-15.8 -24.9	18.55 14.4	86 148	28.0% 34.0%	-12.80 [-17.86, -7.74] -2.90 [-6.06, 0.26]	
<b>3.5.3 SDAI</b> Combe 2021 Genovese 2019 Westhovens 2017	-28.6 -27.8 -28.6	15.03 13.54 11.57	85 153 480	-15.8 -24.9 -26.6	18.55 14.4 12.91	86 148 475	28.0% 34.0% 38.0%	-12.80 [-17.86, -7.74] -2.90 [-6.06, 0.26] -2.00 [-3.56, -0.44]	<u>-</u>
3.5.3 SDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI)	-28.6 -27.8 -28.6	15.03 13.54 11.57	85 153 480 <b>718</b>	-15.8 -24.9 -26.6	18.55 14.4 12.91	86 148 475 <b>709</b>	28.0% 34.0% 38.0% <b>100.0</b> %	-12.80 [-17.86, -7.74] -2.90 [-6.06, 0.26] -2.00 [-3.56, -0.44] - <b>5.33 [-10.31, -0.35]</b>	
3.5.3 SDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> =	-28.6 -27.8 -28.6 = 16.38; (	15.03 13.54 11.57 Chi <sup>2</sup> = 11	85 153 480 <b>718</b> 6.00, df	-15.8 -24.9 -26.6 = 2 (P =	18.55 14.4 12.91	86 148 475 <b>709</b> (); I <sup>2</sup> = 8	28.0% 34.0% 38.0% <b>100.0</b> %	-12.80 [-17.86, -7.74] -2.90 [-6.06, 0.26] -2.00 [-3.56, -0.44] - <b>5.33 [-10.31, -0.35]</b>	
3.5.3 SDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	-28.6 -27.8 -28.6 = 16.38; ( : Z = 2.10	15.03 13.54 11.57 Chi <sup>2</sup> = 11 I (P = 0.1	85 153 480 <b>718</b> 6.00, df 04)	-15.8 -24.9 -26.6 = 2 (P =	18.55 14.4 12.91	86 148 475 <b>709</b> I); I <sup>2</sup> = 8	28.0% 34.0% 38.0% <b>100.0%</b> 8%	-12.80 [-17.86, -7.74] -2.90 [-6.06, 0.26] -2.00 [-3.56, -0.44] - <b>5.33 [-10.31, -0.35]</b>	
3.5.3 SDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.5.4 CDAI	-28.6 -27.8 -28.6 = 16.38; ( : Z = 2.10	15.03 13.54 11.57 Chi <sup>2</sup> = 11 I (P = 0.1	85 153 480 <b>718</b> 5.00, df 04)	-15.8 -24.9 -26.6 = 2 (P =	18.55 14.4 12.91	86 148 475 <b>709</b> I); I <sup>2</sup> = 8	28.0% 34.0% 38.0% <b>100.0%</b>	-12.80 [-17.86, -7.74] -2.90 [-6.06, 0.26] -2.00 [-3.56, -0.44] - <b>5.33 [-10.31, -0.35]</b>	
3.5.3 SDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.5.4 CDAI Combe 2021	-28.6 -27.8 -28.6 = 16.38; ( : Z = 2.10 -28.6	15.03 13.54 11.57 Chi <sup>2</sup> = 11 (P = 0.1 15.03	85 153 480 <b>718</b> 5.00, df 04) 85	-15.8 -24.9 -26.6 = 2 (P = -16	18.55 14.4 12.91 0.0003	86 148 475 <b>709</b> (); I <sup>2</sup> = 8 86	28.0% 34.0% 38.0% <b>100.0%</b> 8% 26.5%	-12.80 [-17.86, -7.74] -2.90 [-6.06, 0.26] -2.00 [-3.56, -0.44] -5.33 [-10.31, -0.35]	
3.5.3 SDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.5.4 CDAI Combe 2021 Genovese 2019	-28.6 -27.8 -28.6 = 16.38; ( : Z = 2.10 -28.6 -27.8	15.03 13.54 11.57 Chi <sup>2</sup> = 11 (P = 0.1 15.03 13.54	85 153 480 <b>718</b> 5.00, df 04) 85 153	-15.8 -24.9 -26.6 = 2 (P = -16 -25.4	18.55 14.4 12.91 0.0003 18.08 14.4	86 148 475 <b>709</b> (); I <sup>2</sup> = 8 86 148	28.0% 34.0% 38.0% <b>100.0%</b> 8% 26.5% 33.9%	-12.80 [-17.86, -7.74] -2.90 [-6.06, 0.26] -2.00 [-3.56, -0.44] -5.33 [-10.31, -0.35] -12.60 [-17.58, -7.62] -2.40 [-5.56, 0.76]	
3.5.3 SDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> Test for overall effect: 3.5.4 CDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (05% CI)	-28.6 -27.8 -28.6 = 16.38; ( : Z = 2.10 -28.6 -27.8 -30.9	15.03 13.54 11.57 Chi <sup>2</sup> = 11 (P = 0.1 15.03 13.54 11.7	85 153 480 <b>718</b> 3.00, df 04) 85 153 480 <b>719</b>	-15.8 -24.9 -26.6 = 2 (P = -16 -25.4 -26.3	18.55 14.4 12.91 0.0003 18.08 14.4 12.38	86 148 475 <b>709</b> 0); I <sup>2</sup> = 8 86 148 475 <b>700</b>	28.0% 34.0% 38.0% <b>100.0%</b> 8% 26.5% 33.9% 39.6%	-12.80 [-17.86, -7.74] -2.90 [-6.06, 0.26] -2.00 [-3.56, -0.44] -5.33 [-10.31, -0.35] -12.60 [-17.58, -7.62] -2.40 [-5.56, 0.76] -4.60 [-6.13, -3.07] -2.40 [-2.1, -1.74]	
3.5.3 SDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>3.5.4 CDAI</b> Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI)	-28.6 -27.8 -28.6 = 16.38; ( : Z = 2.10 -28.6 -27.8 -30.9	15.03 13.54 11.57 Chi <sup>2</sup> = 11 (P = 0.1 15.03 13.54 11.7	85 153 480 <b>718</b> 5.00, df 04) 85 153 485 153 480 <b>718</b>	-15.8 -24.9 -26.6 = 2 (P = -16 -25.4 -26.3	18.55 14.4 12.91 0.0003 18.08 14.4 12.38	86 148 475 <b>709</b> 0); I <sup>2</sup> = 8 86 148 475 <b>709</b>	28.0% 34.0% 38.0% 100.0% 8% 26.5% 33.9% 39.6% 100.0%	-12.80 [-17.86, -7.74] -2.90 [-6.06, 0.26] -2.00 [-3.56, -0.44] -5.33 [-10.31, -0.35] -12.60 [-17.58, -7.62] -2.40 [-5.56, 0.76] -4.60 [-6.13, -3.07] -5.97 [-10.21, -1.74]	
3.5.3 SDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3.5.4 CDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	-28.6 -27.8 -28.6 = 16.38; ( : Z = 2.10 -28.6 -27.8 -30.9 = 11.19; ( : Z = 2.76	$15.03 \\ 13.54 \\ 11.57 \\ Chi2 = 10 \\ (P = 0.0 \\ 15.03 \\ 13.54 \\ 11.7 \\ Chi2 = 11 \\ (P = 0.0 \\ Chi2 = 0.0 \\ (P = 0.0 \\ Chi2 = 0.0 \\ (P = 0.0 \\ Chi2	85 153 480 <b>718</b> 5.00, df 04) 85 153 480 <b>718</b> 1.70, df 006)	-15.8 -24.9 -26.6 = 2 (P = -16 -25.4 -26.3 = 2 (P =	18.55 14.4 12.91 0.0003 18.08 14.4 12.38	86 148 475 <b>709</b> ();  ² = 8 86 148 475 <b>709</b> ;  ² = 83	28.0% 34.0% 38.0% <b>100.0</b> % 8% 26.5% 33.9% 39.6% <b>100.0</b> %	-12.80 [-17.86, -7.74] -2.90 [-6.06, 0.26] -2.00 [-3.56, -0.44] -5.33 [-10.31, -0.35] -12.60 [-17.58, -7.62] -2.40 [-5.56, 0.76] -4.60 [-6.13, -3.07] -5.97 [-10.21, -1.74]	
3.5.3 SDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>=</sup> = Test for overall effect: 3.5.4 CDAI Combe 2021 Genovese 2019 Westhovens 2017 Subtotal (95% CI) Heterogeneity: Tau <sup>=</sup> = Test for overall effect:	-28.6 -27.8 -28.6 : Z = 2.10 -28.6 -27.8 -30.9 = 11.19; ( : Z = 2.76	15.03 13.54 11.57 Chi <sup>z</sup> = 11 (P = 0.1 15.03 13.54 11.7 Chi <sup>z</sup> = 11 (P = 0.1	85 153 480 <b>718</b> 5.00, df 04) 85 153 480 <b>718</b> 1.70, df 006)	-15.8 -24.9 -26.6 = 2 (P = -16 -25.4 -26.3 = 2 (P =	18.55 14.4 12.91 0.0003 18.08 14.4 12.38 0.003)	86 148 475 <b>709</b> 1);  ² = 8 86 148 475 <b>709</b> ;  ² = 83	28.0% 34.0% 38.0% <b>100.0</b> % 8% 26.5% 33.9% 39.6% <b>100.0</b> %	-12.80 [-17.86, -7.74] -2.90 [-8.06, 0.26] -2.00 [-3.56, -0.44] -5.33 [-10.31, -0.35] -12.60 [-17.58, -7.62] -2.40 [-5.56, 0.76] -4.60 [-6.13, -3.07] -5.97 [-10.21, -1.74]	

Supplementary figure 5. Meta-analysis of filgotinib 100 mg versus placebo at week 24 (continuous outcomes)



Supplementary figure 6. Meta-analysis of filgotinib 200 mg versus 100 mg (HAQ-DI)