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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 ≤ 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 ≤ 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[1].There are more than five million patients with RA in China, of whom 80.46% are women[2]. The direct cost of RA in China is $1917.21 ± $2559.06 per patient per year, which is a great economic burden[3]. The target of treatment for RA is to achieve low disease activity or remission. Methotrexate (MTX) is the first-line of therapy, and 40–50% of patients achieve remission or at least low disease activity with a dose of 25 mg weekly in combination with glucocorticoids[1]. 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[4].

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[5]. 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[6]. Filgotinib (Jyseleca®) is an oral ATP-competitive, reversible JAK1 preferential inhibitor

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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[7]. 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[8]. 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[9]. 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 ≥ 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) ≤ 3.2 at weeks 12 and 24, higher values indicate higher disease activity; (4) change from baseline in Short Form-36 (SF-36) Physical Component Summary (PCS) score at weeks 12 and 24, positive change in value indicates improvement and better quality of life; (5) change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at weeks 12 and 24, positive change in value indicates improvement; (6) change from baseline in Simplified Disease Activity Index (SDAI)/Clinical Disease Activity Index (CDAI) at weeks 12 and 24, a negative change from baseline indicates improvement; (7) change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at weeks 12 and 24,a negative change from baseline indicates improvement. For safety outcomes, we analyzed treatment-emergent adverse events (TEAEs) and serious TEAEs.

Information sources and search strategy

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

Selection process

Two researchers (YL W and L Y) independently reviewed titles and abstracts. The researchers then independently screened the titles and abstracts of all retrieved articles in pairs. In cases of disagreement, consensus on which articles to screen for full-text was reached by discussion. If necessary, a third researcher (DM M) was consulted to make a final decision. After this, two researchers (LJ L and B L) independently screened the full-text articles for inclusion. Again, in cases of disagreement, a consensus was reached on inclusion or exclusion by discussion, and if necessary, a third researcher (LM P) was consulted.

Data extraction

Two investigators (ZG L and JY R) independently extracted data from the studies. The following details were derived from each study: (1) study characteristics: first author, year of publication, region, number of patients, study design, drug doses and frequency, follow-up duration, and inclusion/exclusion criteria; (2) patient characteristics: age, disease duration, and disease severity at baseline; (3) the primary outcome: ACR20 response at week 12; (4) the secondary outcomes: ACR20 response at week 24; ACR50/ACR70 responses and DAS28-CRP ≤ 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[10]. We performed this meta-analysis in compliance with the guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11].

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 ofthe 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; $P<0.001$; $I^2=24\%$], ACR50 [*OR* 3.95; 95% *CI* 3.13 – 4.98; $P<0.001$; $I^2=0\%$], ACR70 responses [*OR* 4.35; 95% *CI* 3.20 – 5.93; $P<0.001$; $I^2=0\%$], and DAS28-CRP ≤ 3.2 [*OR* 3.34; 95% *CI* 2.60 – 4.28; $P<0.001$; $I^2=0\%$]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; $P<0.001$; $I^2=38\%$] and FACIT-Fatigue [*MD* 4.76; 95% CI 2.42 – 7.10; $P<0.001$; $I^2=71\%$] and lower SDAI [*MD* -9.90; 95% CI -13.32 to

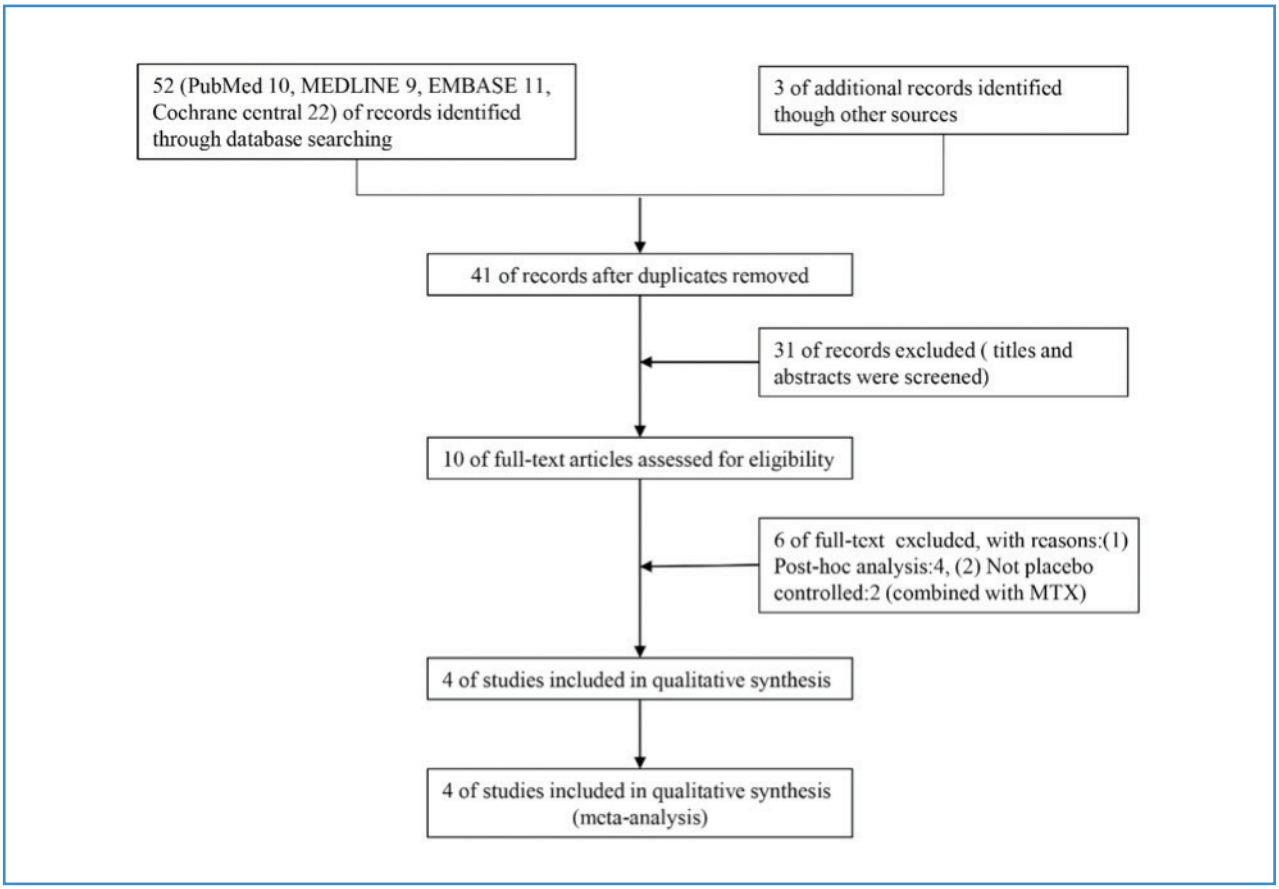

Figure 1. Flow diagram of study selection

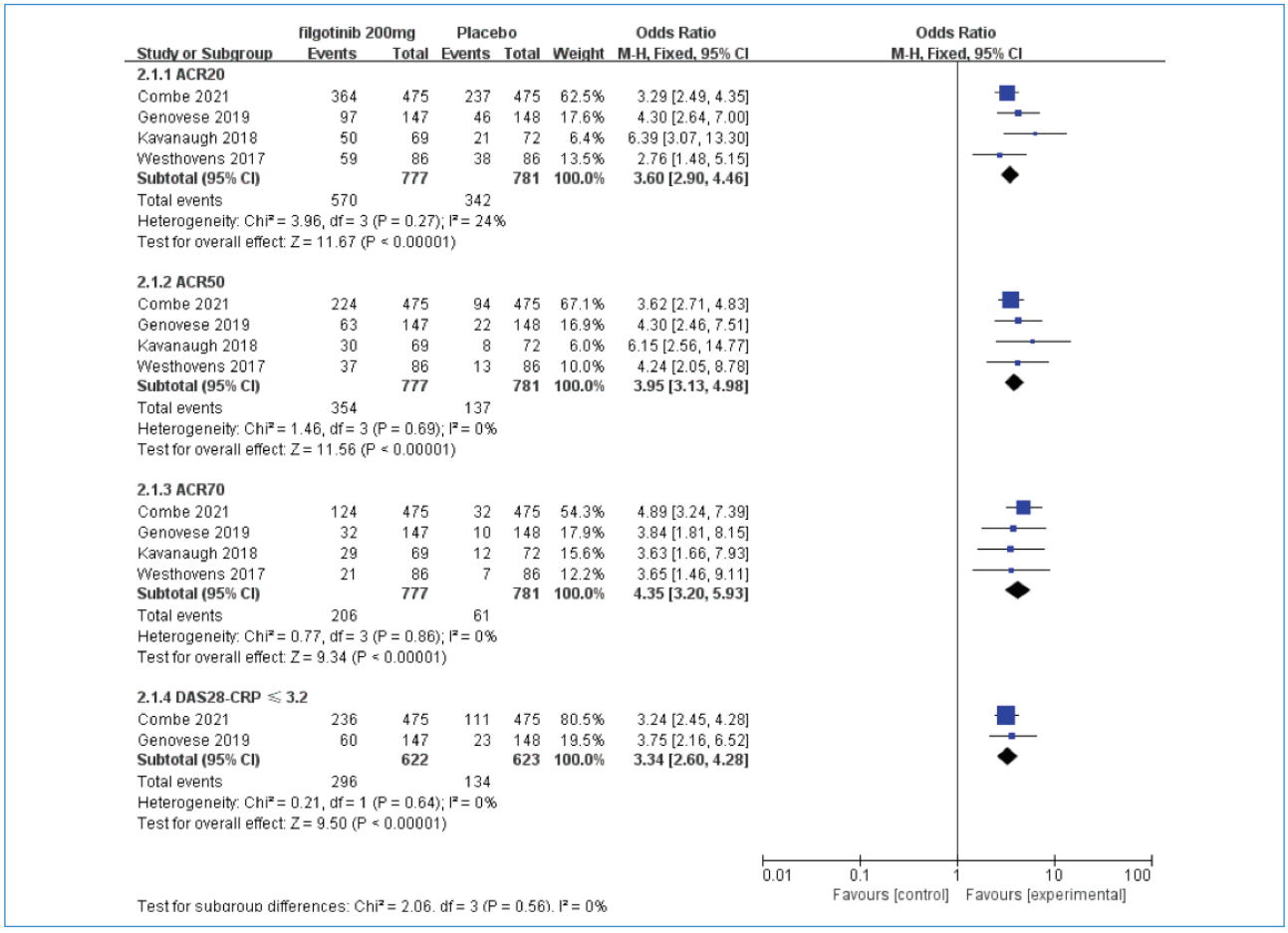

Figure 2A. Meta-analysis of filgotinib 200 mg versus placebo at week 12 (categorical outcomes)

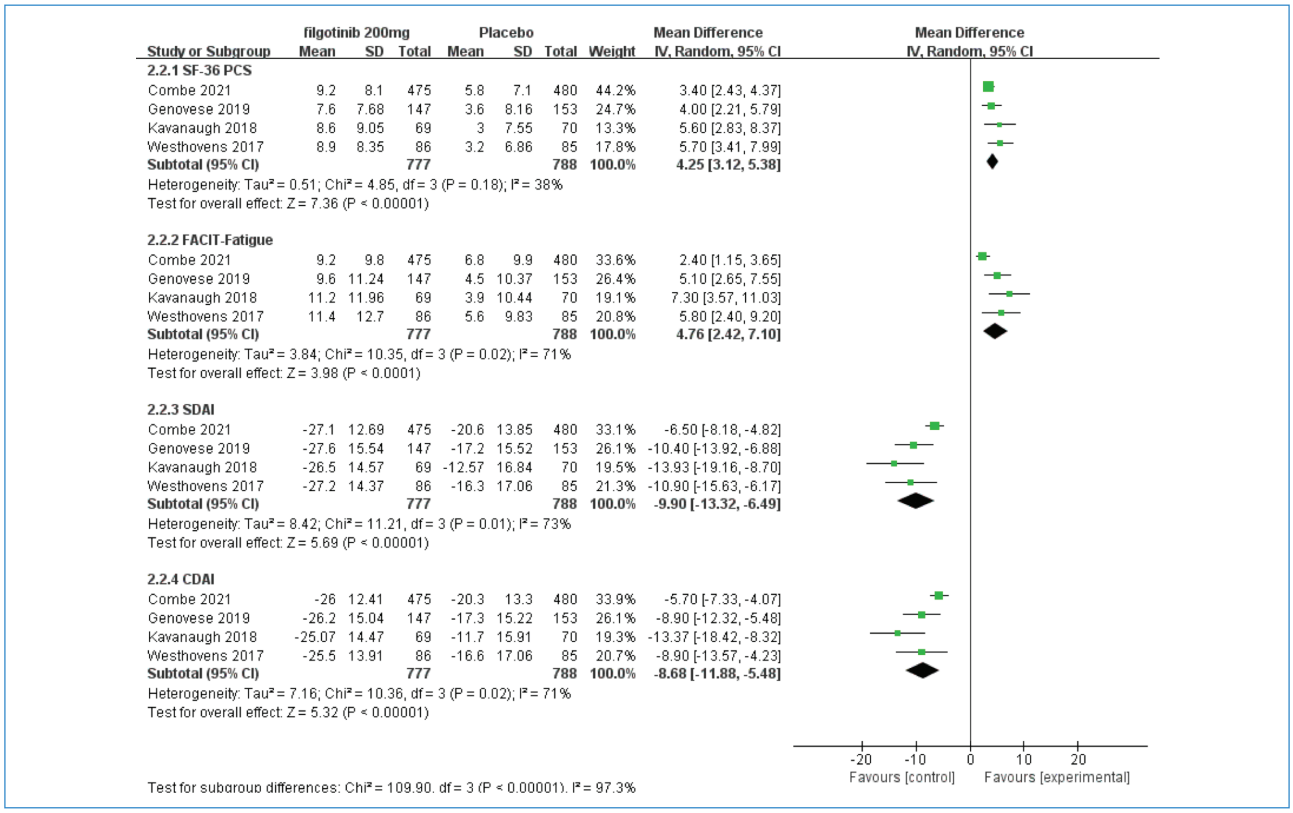

Figure 2B. Meta-analysis of filgotinib 200 mg versus placebo at week 12 (continuous outcomes)

-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 ≤ 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^2 = 61%], ACR50 [*OR* 3.28; 95% *CI* 2.38 – 4.53; $P<0.001$; I^2 = 33%], ACR70 responses [*OR* 3.57; 95% *CI* 2.72 – 4.68; $P<0.001$; I^2 = 0%], and DAS28-CRP ≤ 3.2 [*OR* 3.16; 95% *CI* 2.49 – 3.99; $P<0.001$; I^2 = 0%] at week 24 as shown in Figure 3A. There was no significant difference in safety outcomes between the two groups ($P>0.05$). The filgotinib 200 mg group had higher SF-36 PCS [*MD* 4.94; 95% *CI*

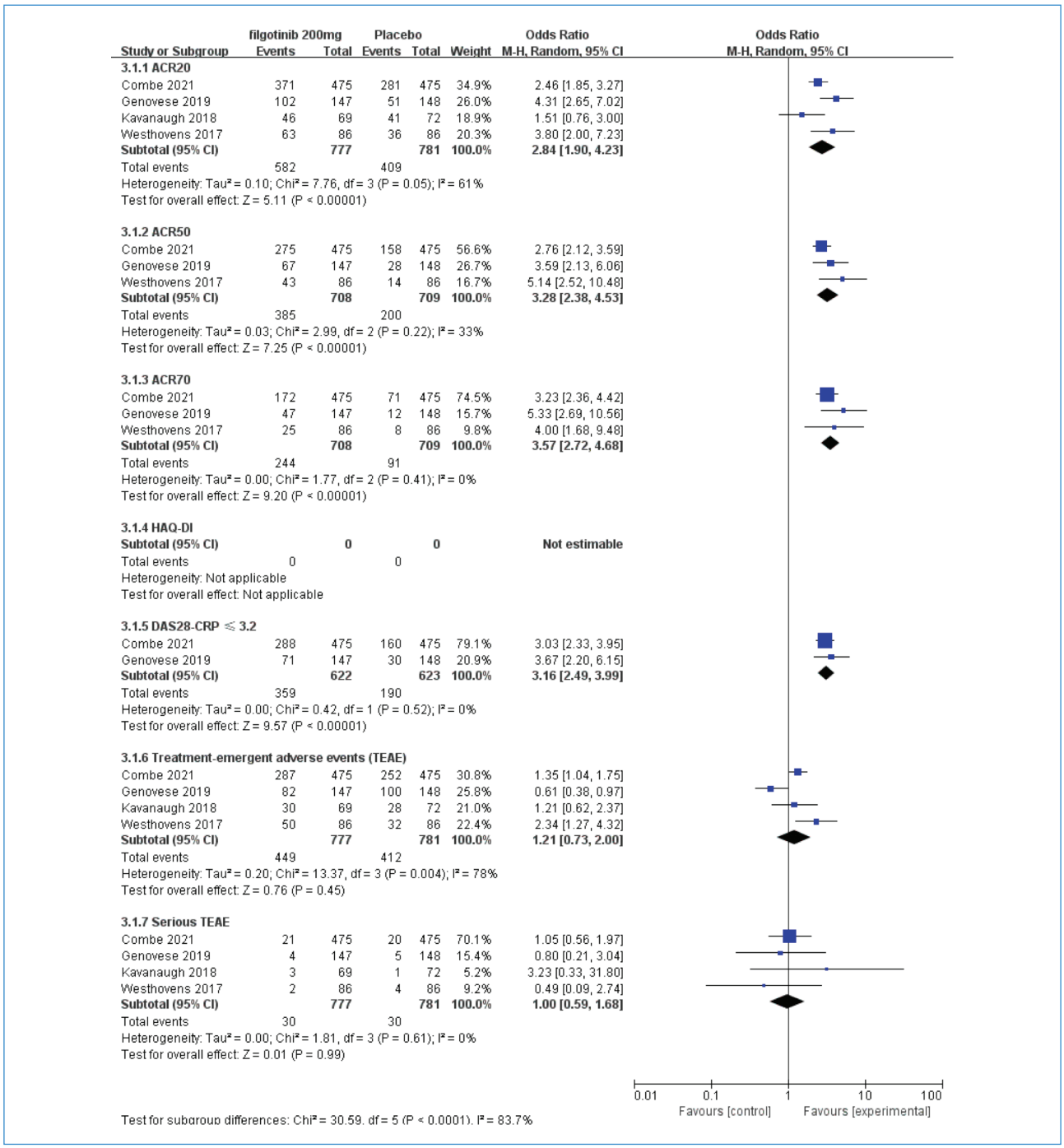

Figure 3A. Meta-analysis of filgotinib 200 mg versus placebo at week 24 (categorical outcomes)

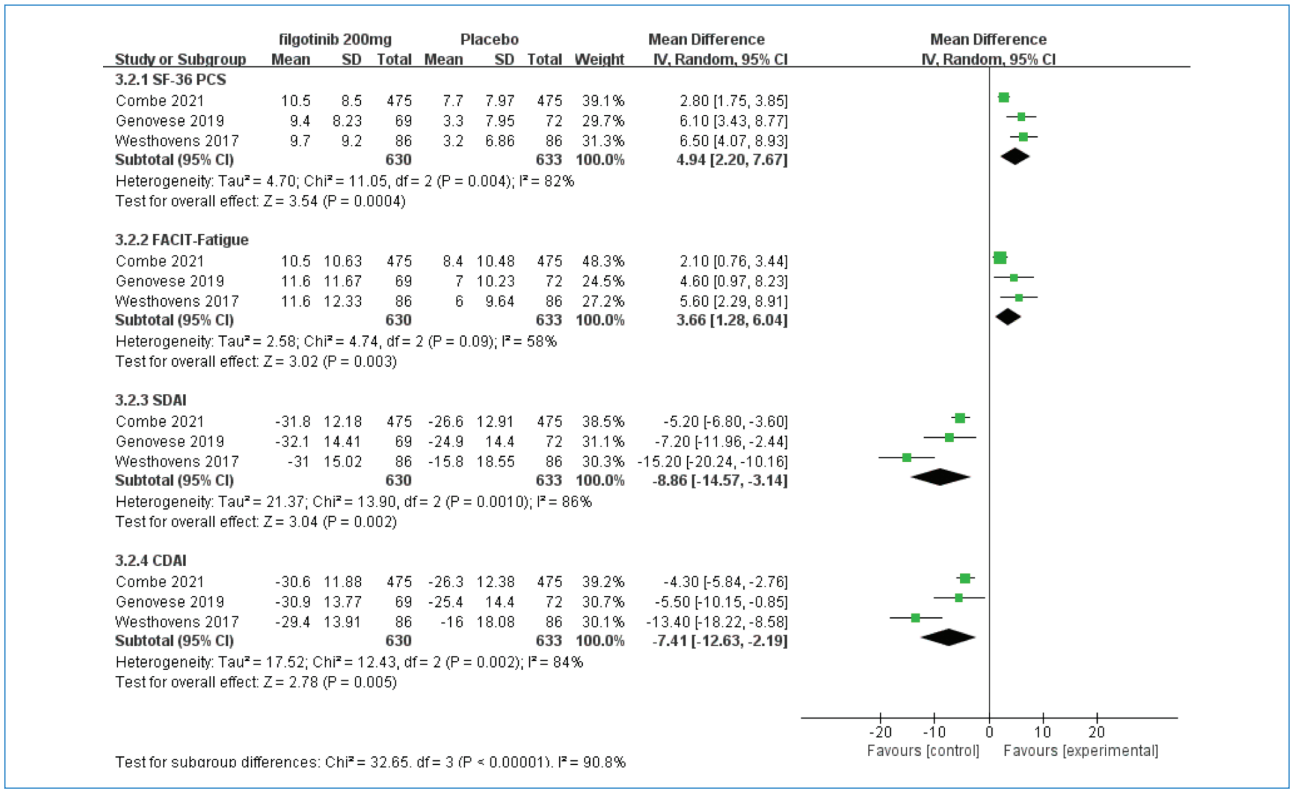

Figure 3B. Meta-analysis of filgotinib 200 mg versus placebo at week 24 (continuous outcomes)

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 ≤ 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; $P = 0.003$; $I^2 = 0\%$], ACR50 [*OR* 1.50; 95% *CI* 1.23 – 1.84; $P <0.001$; $I^2 = 0\%$], ACR70 responses [*OR* 1.47; 95% *CI* 1.16 – 1.87; $P = 0.002$; $I^2 = 0\%$], and DAS28-CRP ≤ 3.2 [*OR* 1.46; 95% *CI* 1.16 – 1.82; $P=0.001$; $I^2= 16\%$] 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; $P<0.001$; $I^2 = 0\%$] and CDAI [*MD* -2.46; 95% *CI* -3.76 to -1.15; $P <0.001$; $I^2 = 0\%$] 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; $P<0.001$; $I^2 = 61\%$], ACR50 [*OR* 1.26; 95% *CI* 1.03 – 1.54; $P = 0.03$; $I^2 = 0\%$], and DAS28-CRP ≤ 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; $P< 0.001$; $I^2 = 0\%$] and CDAI [*MD* -1.86; 95% CI -3.10 – -0.62; $P= 0.003$; $I^2 = 0\%$] 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-

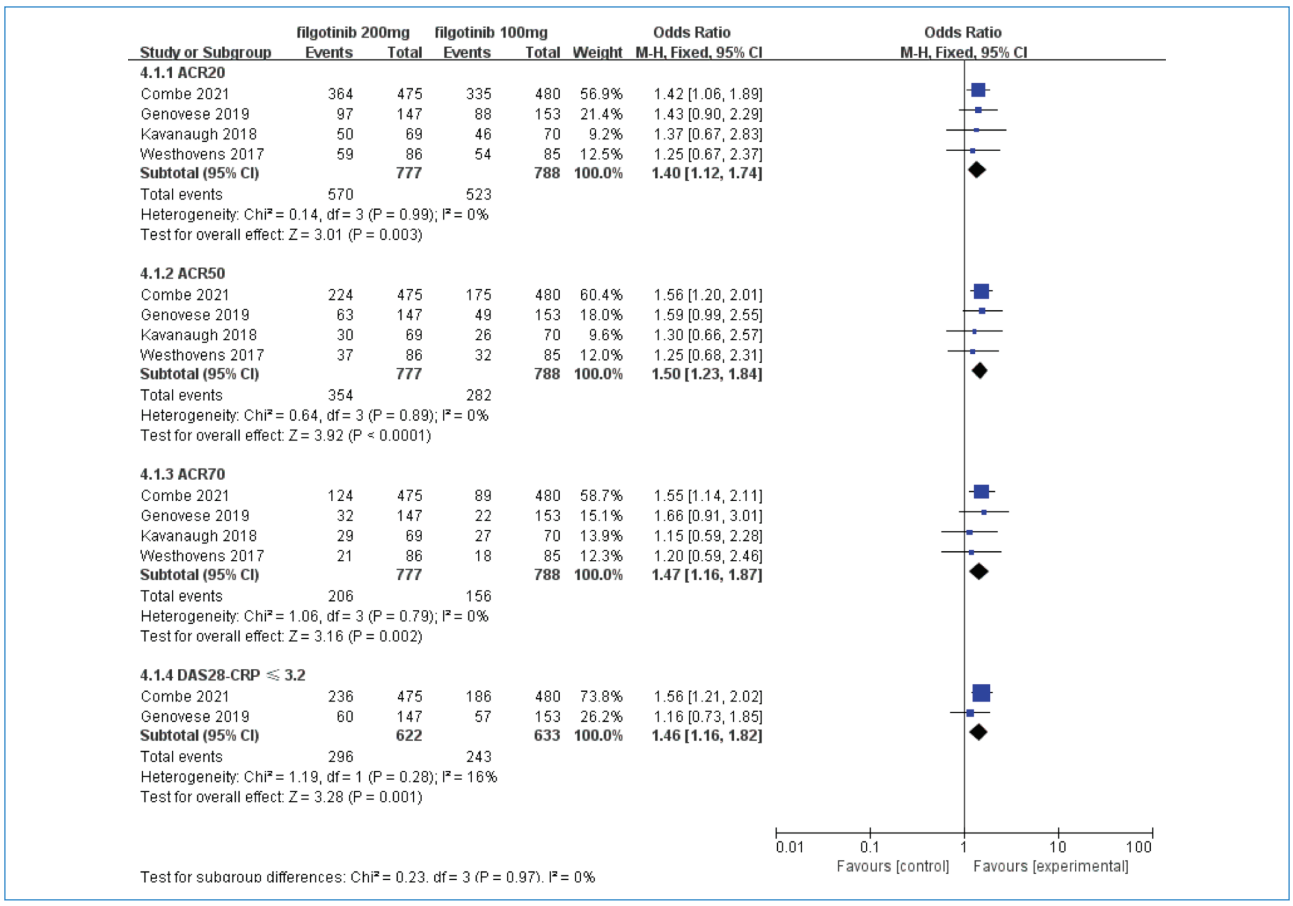

Figure 4A. Meta-analysis of filgotinib 200 mg versus 100 mg at week 12 (categorical outcomes)

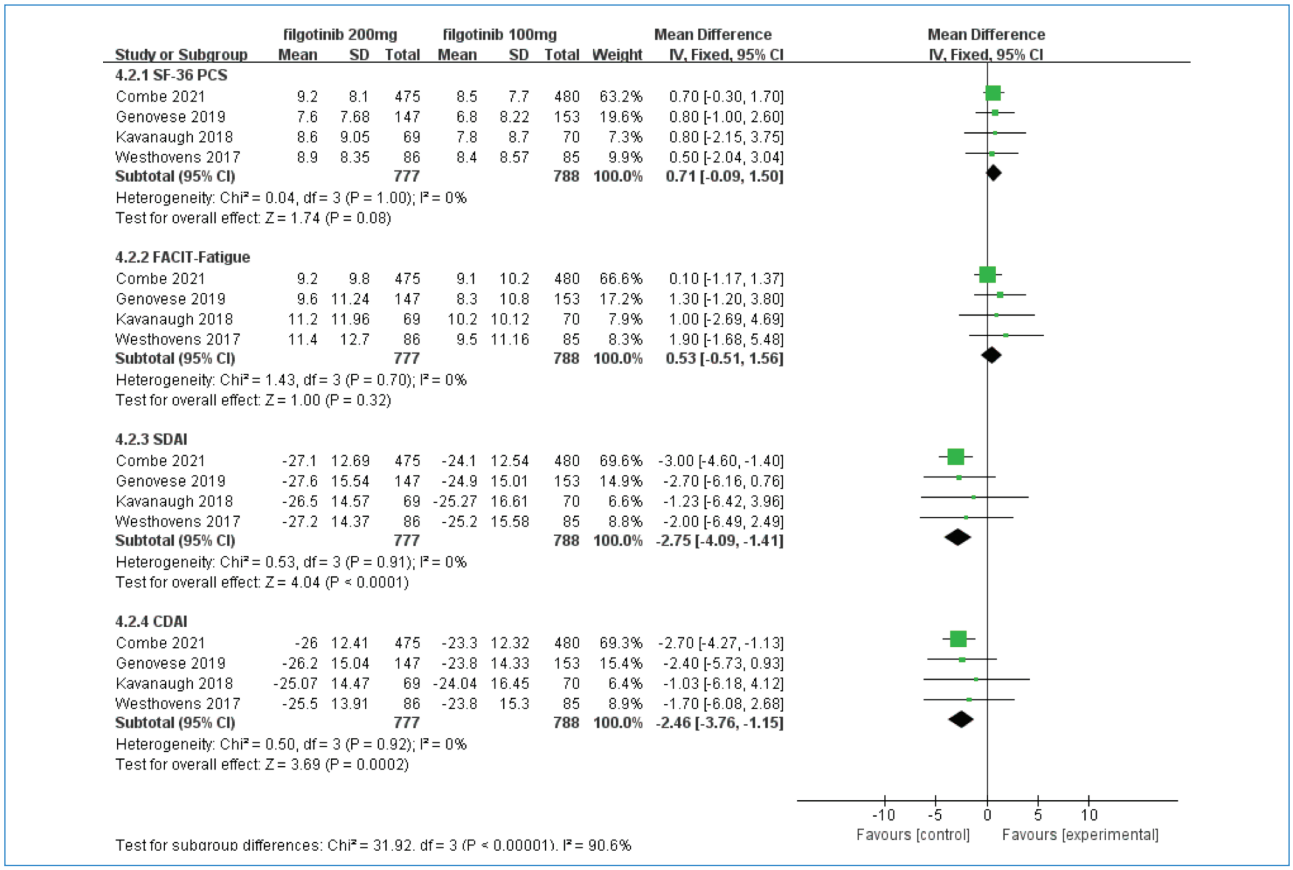

Figure 4B. Meta-analysis of filgotinib 200 mg versus 100 mg at week 12 (continuous outcomes)

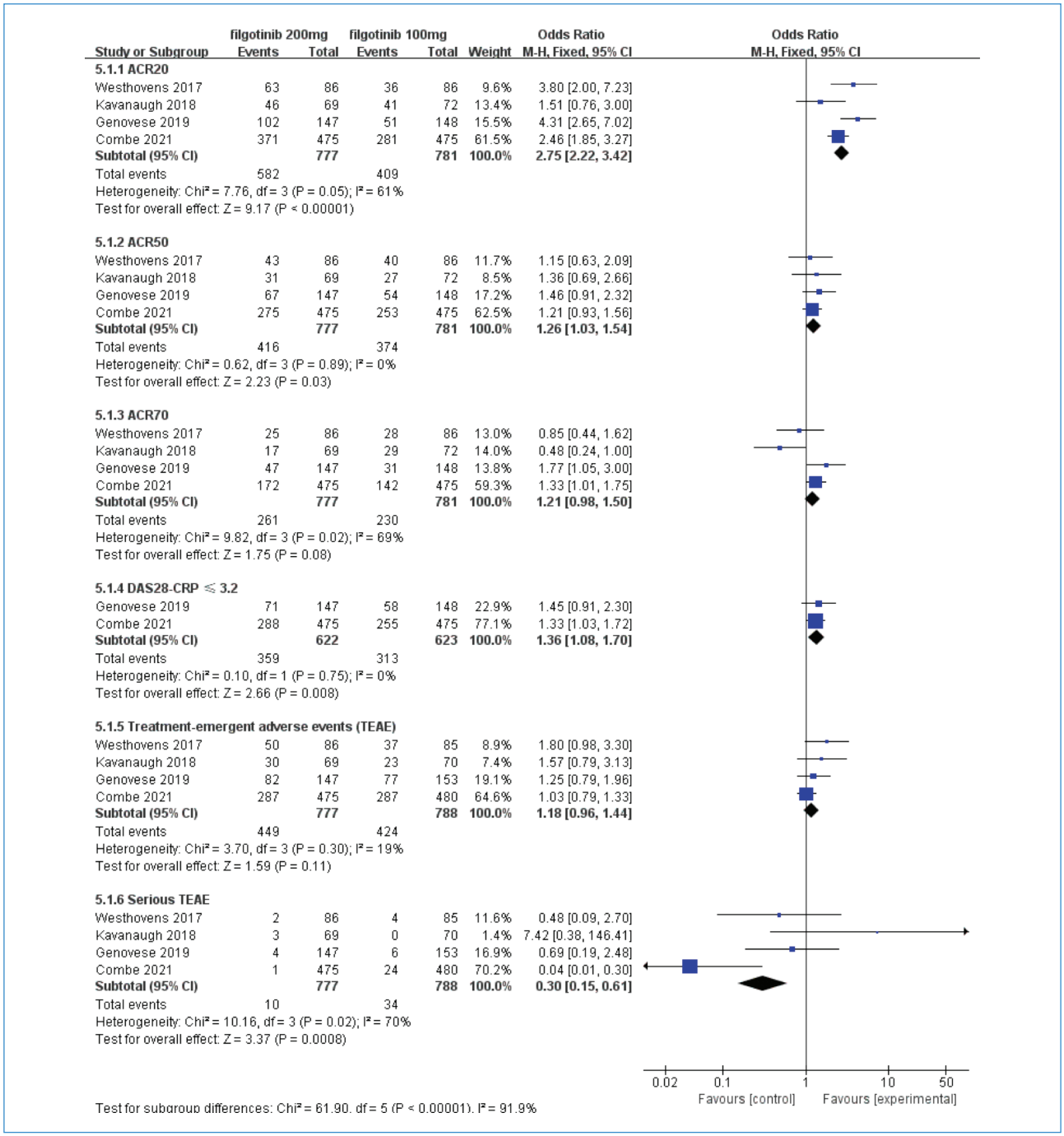

Figure 5A. Meta-analysis of filgotinib 200 mg versus 100 mg at week 24 (categorical outcomes)

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-

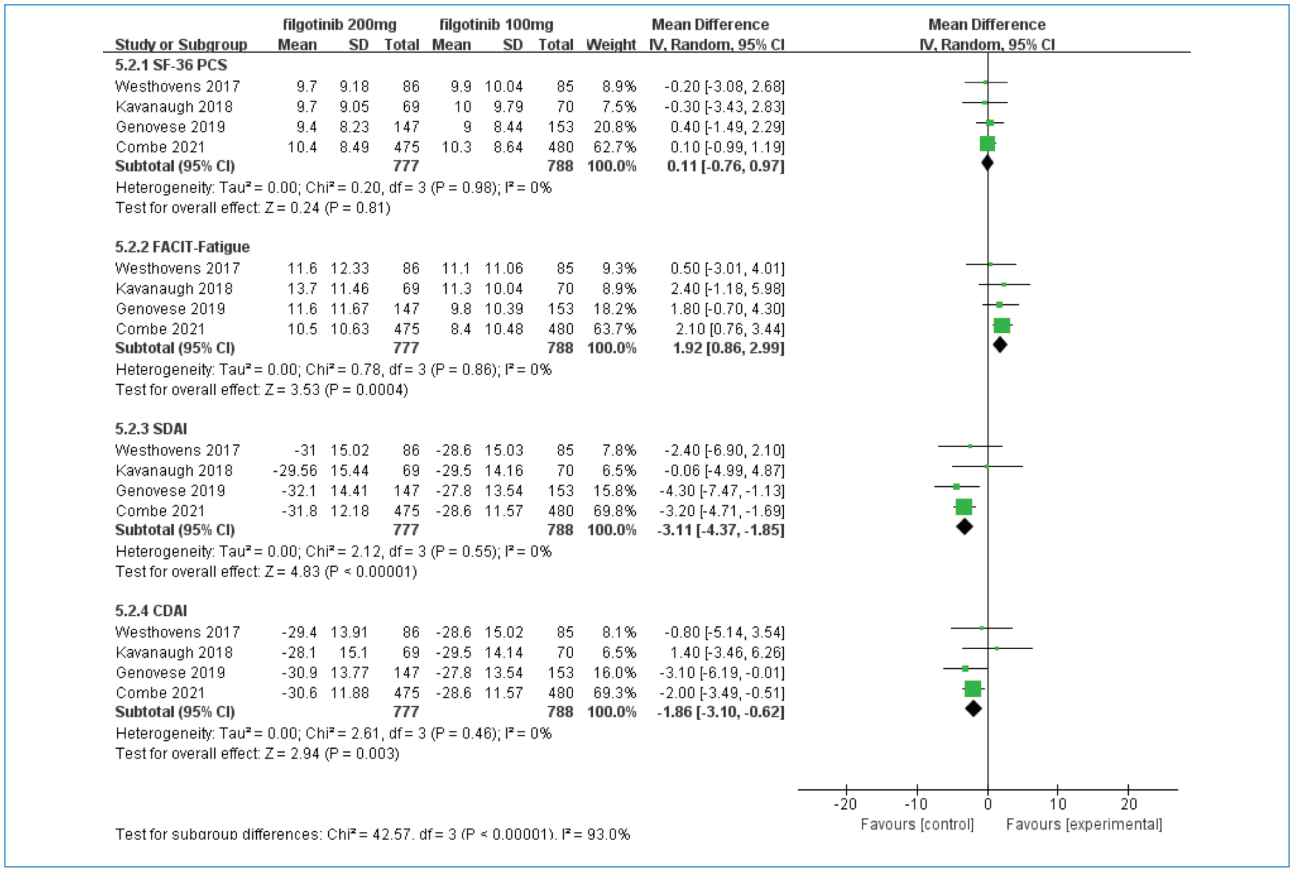

Figure 5B. Meta-analysis of filgotinib 200 mg versus 100 mg at week 24 (continuous outcomes)

stay of therapy for patients with early RA. MTX combined with glucocorticoid bridging is the mainstay of T2T therapy[16]. In 2019, EULAR suggested adopting MTX as the first choice of csDMARDs, regardless of disease activity[17]. The 2021 ACR Guideline for the treatment of RA recommends MTX as the first choice of DMARDs for patients with medium and high disease activity. Despite treatment with csDMARDs and bDMARDs, 30–40% of patients undergoing MTX treatment do not achieve ideal therapeutic effects and are prone to tolerance (18). JAK inhibitors (JAKs: JAK1, JAK2, and JAK3 inhibitors) are an important class of tsDMARDs. They selectively interfere with the ATP-binding site of JAKs, resulting in the suppression of downstream signaling pathways, which can have immunomodulatory effects on a wide range of pathological processes[19]. Small-molecule JAK inhibitors have been clinically developed for the treatment of RA. Assessment of drug–drug interaction potential suggests that to facitinib, baricitinib, and upadacitinib were generally beneficial with no perpetrator activity[20]. New JAK inhibitors may alter treatment paradigms through rapid dose-dependent action[21]. Filgotinib, a new JAK inhibitor, has been engineered to confer greater selectivity for JAK1 than for JAK2, JAK3, or Tyk2[22]. 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[23]. 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[24]. Another study showed that filgotinib has no clinically meaningful effect on exposure to atorvastatin, pravastatin, or rosuvastatin[25].

Song et al.[26] 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 ≤ 3.2 at week 12, with better improvement in SDAI and CDAI. At week 24, the efficacy of the 200 mg dose was also better in achieving ACR20/50, DAS28-CRP ≤ 3.2, FACIT-Fatigue, SDAI, and CDAI. There was no significant difference in TEAEs between 100 and 200 mg filgotinib ($P > 0.05$); however, the 200 mg dose had fewer serious TEAEs (3.86%, 30/777) than the 100 mg dose. This is consistent with the results of the latest pharmacokinetic study, which confirmed that filgotinib produced more robust therapeutic effects when administered at 200

mg once daily dosing than when administered at lower doses[27]. 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[28]. 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[29-31]. 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[5].

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 ≤ 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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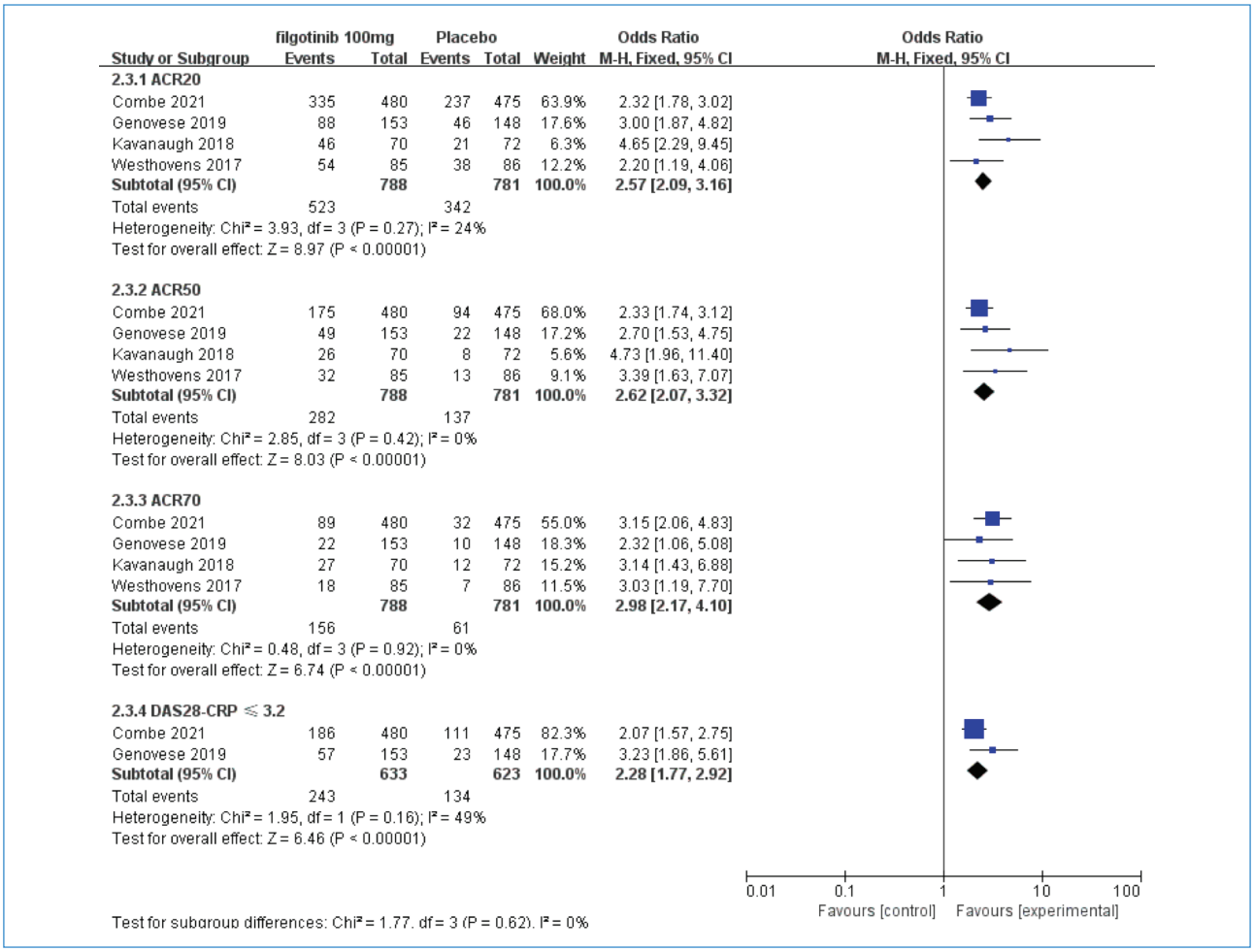
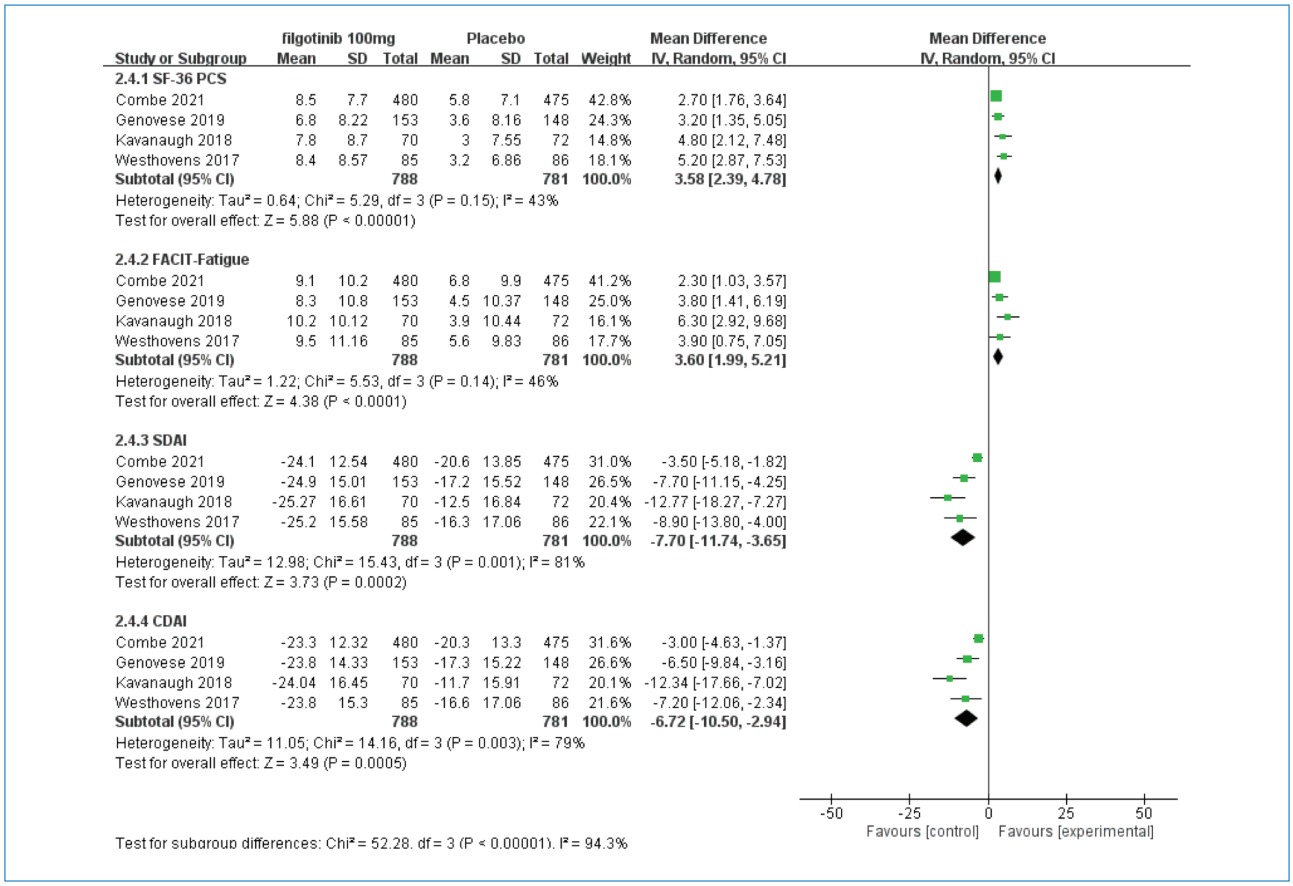
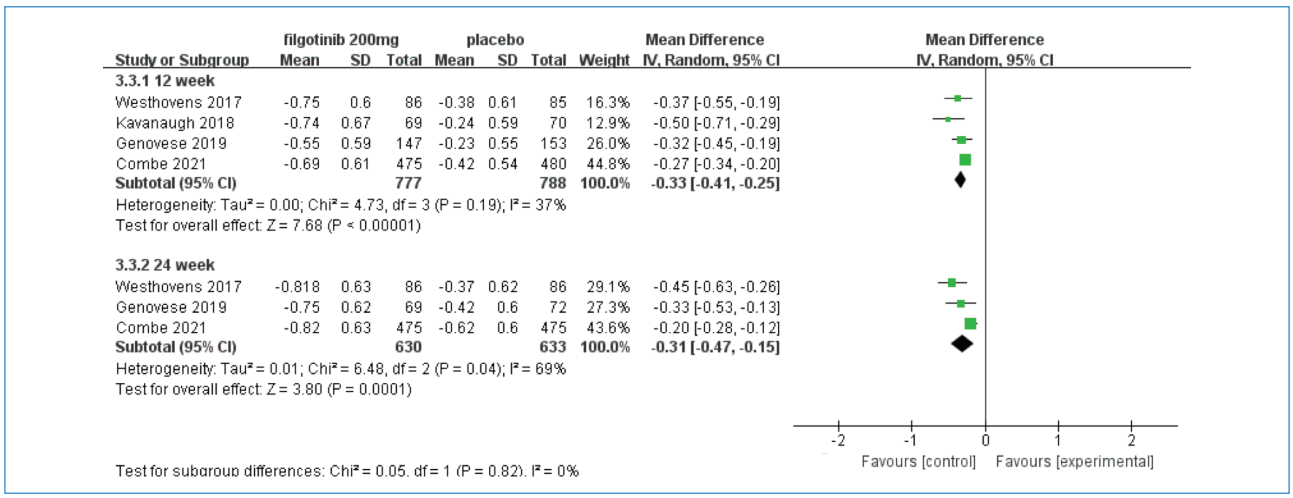
SUPPLEMENTARY MATERIAL



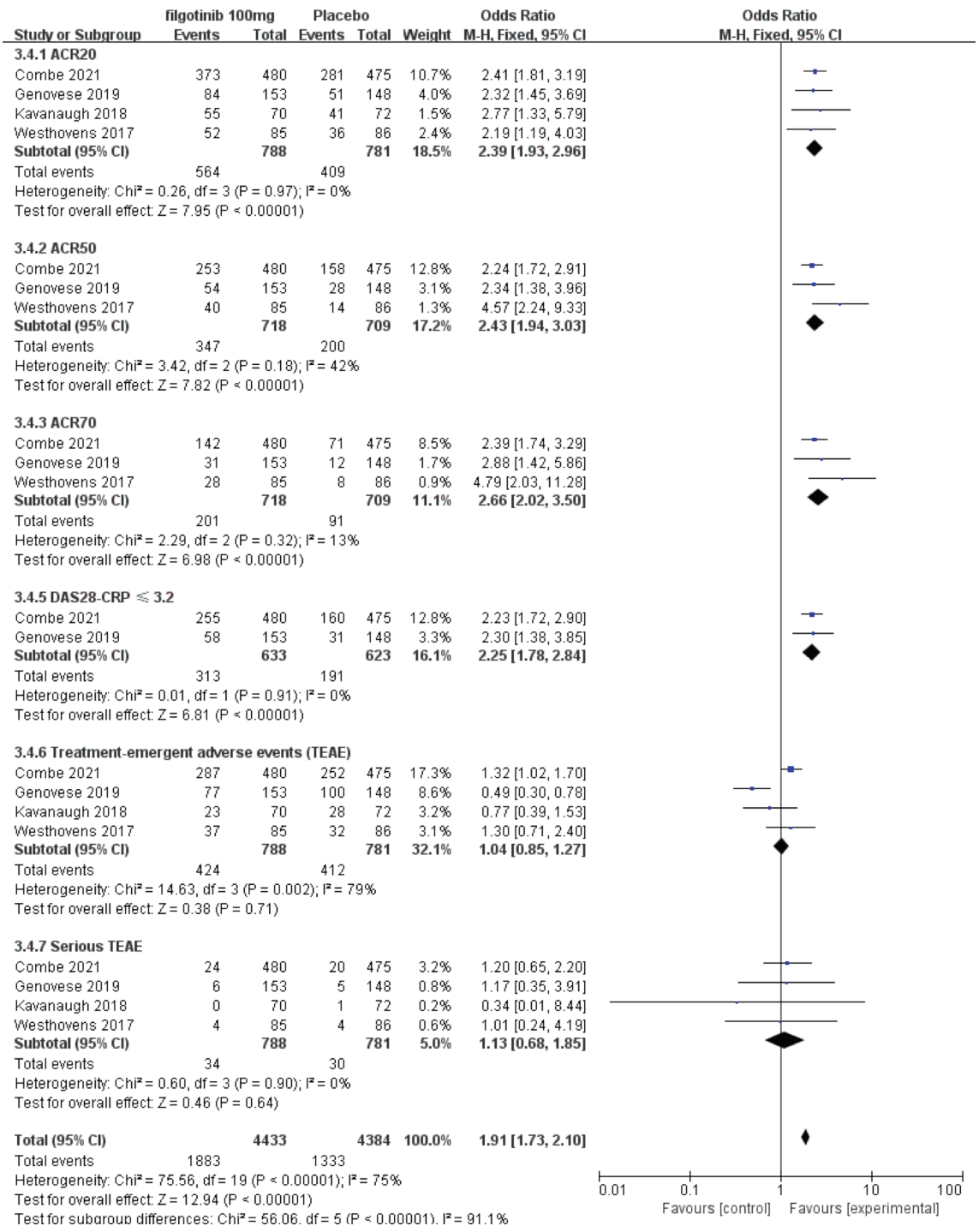
Supplementary figure 1. Meta-analysis of filgotinib 100 mg versus placebo at week 12 (categorical outcomes)



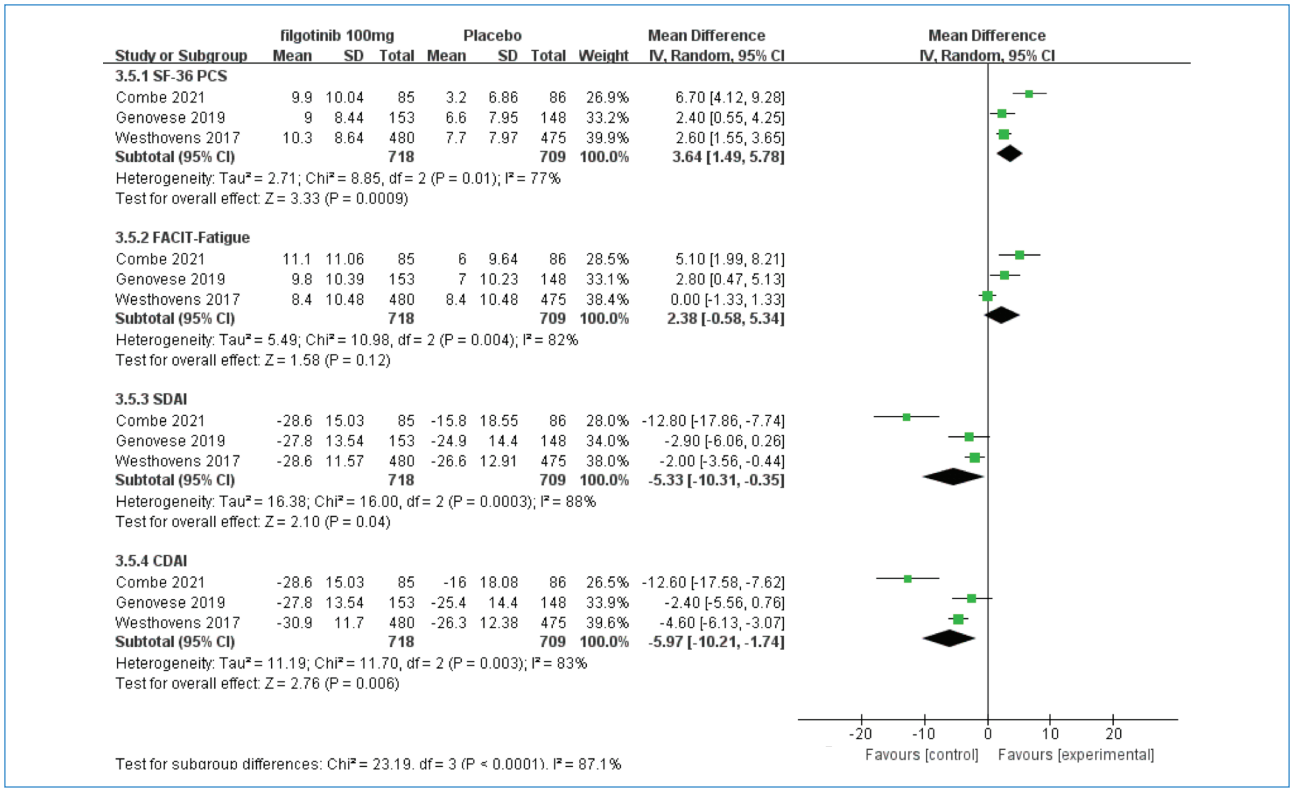
Supplementary figure 2. Meta-analysis of filgotinib 100 mg versus placebo at week 12 (continuous outcomes)



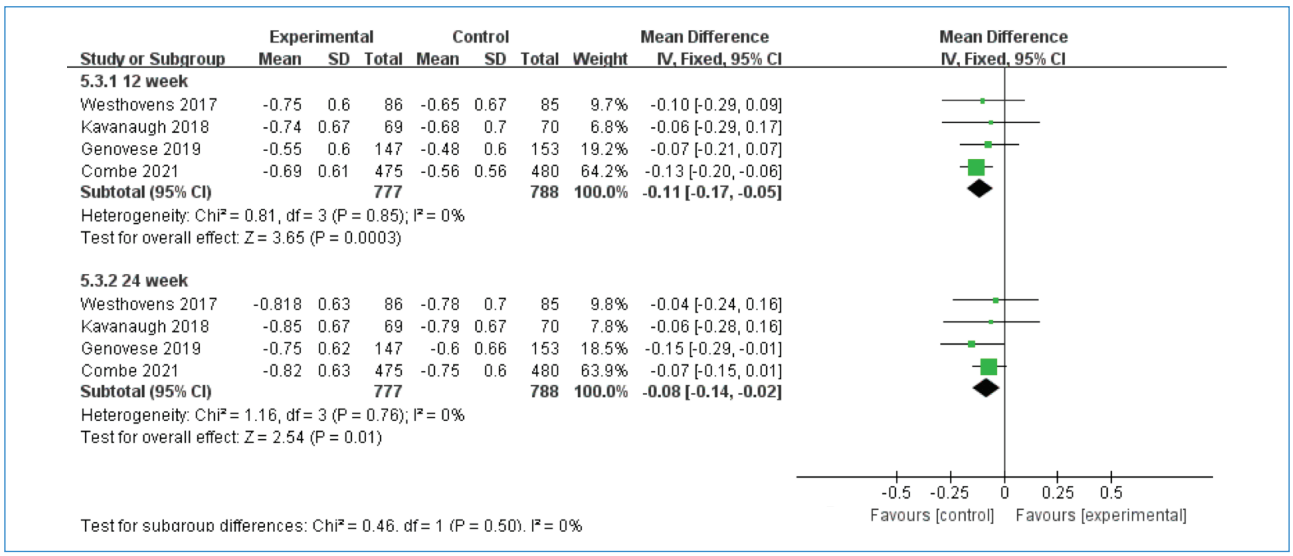
Supplementary figure 3. Meta-analysis of filgotinib 200 mg versus placebo (HAQ-DI)



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



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)