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REVIEW

# Are Janus kinase inhibitors safe and effective in treating the key clinical domains of psoriatic arthritis? A systematic review and meta-analysis

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## Abstract

**Objectives:** Psoriatic arthritis (PsA), is a complex inflammatory arthropathy with a heterogenous spectrum of disease presentation. Despite the vast therapeutic armamentarium, disease control in a considerable proportion of patients is suboptimal. The aim of this study was to assess the safety and efficacy of Janus kinase inhibitors (JAKi), in the management of key clinical domains of PsA including peripheral arthritis, psoriasis, enthesitis and dactylitis.

**Method:** Randomized placebo-controlled trials (RCTs) of JAKi in PsA were identified by a systematic literature search using EMBASE, PubMed and CENTRAL. All included studies underwent meta-analysis.

**Results:** A total of 5 RCTs were included. Patients were randomized to tofacitinib (n = 474), filgotinib (n = 65), upadacitinib (n = 1281) or placebo (n = 937). JAKi treatment was associated with superior efficacy across all primary outcome measures vs placebo: American College of Rheumatology (ACR) 20 (risk ratio [RR] 2.10, [95% CI 1.86–2.37], $P < .00001$, I2 = 19%); ACR 50 (RR 3.43, [95% CI 2.37–4.96], $P < .00001$, I2 = 66%); ACR 70 (RR 4.57, [95% CI 1.83–11.44], $P = .001$, I2 = 82%); Psoriasis Area and Severity Index 75 (RR 2.96, [95% CI 2.44–3.58], $P < .00001$, I2 = 0%); enthesitis resolution (RR 1.82, [95% CI 1.56–2.12], $P < .00001$, I2 = 0%); and dactylitis resolution (RR 1.85, [95% CI 1.57–2.16], $P < .00001$, I2 = 0%). JAKi were associated with an overall increased risk of adverse events (RR 1.14, [95% CI 1.07–1.21], $P = .0001$, I2 = 0%) with increased risk of infection (RR1.23, [95% CI 1.08–1.39], $P = .001$, I2 = 0%) vs placebo.

**Conclusion:** This pooled analysis demonstrates the efficacy of JAKi in treating key clinical domains of PsA. However, they are associated with an increased risk of adverse events, including infection. Further studies are required to corroborate these findings and further elucidate the safety profile.

KEYWORDS
dactylitis, enthesitis, filgotinib, Janus kinase inhibitors, psoriasis, psoriatic arthritis, tofacitinib, upadacitinib

## 1 | INTRODUCTION

Psoriatic arthritis (PsA) is a progressive, immune-mediated inflammatory arthropathy affecting up to 1% of the general population, and up to 42% of those with psoriasis.[1] It presents as a heterogenous spectrum of clinical manifestations including the key domains of peripheral and axial arthropathy, enthesitis, dactylitis, nail dystrophy and psoriasis,[2] as well as the extra-articular manifestations of uveitis and inflammatory bowel disease.[3]

In addition to the increased risk of medical comorbidities such as cardiometabolic disease, and osteoporosis,[4,5] the psychological burden and functional impairment associated with PsA is significant, with an overall marked reduction in health-related quality of life.[6-8]

Over the past 2 decades, the therapeutic armamentarium of PsA, similar to other autoimmune inflammatory conditions, has undergone a paradigm shift with the advent of biologic disease-modifying antirheumatic drugs (bDMARDs).[9-11] Tumor necrosis factor (TNF) inhibitors were the first licensed monoclonal antibodies in PsA treatment.[9] Despite the relative abundance of available approved therapeutic agents, and the relatively successful application of TNF inhibitors, there remains a number of unmet needs in the management of PsA. Potentially owing to the multifaceted clinical spectrum of PsA, up to 40% of patients fail to respond to, or experience only a partial response using current therapies.[12] Furthermore, bDMARDs must be administered either via intravenous or subcutaneous injection, given their large molecular size, posing potential issues with compliance and convenience. Therefore, there is a need for an alternative, effective, and conveniently administered agent to address all key domains of PsA, while maintaining tolerability and safety.

The Janus kinase (JAK) family of intracellular tyrosine kinases, comprising JAK1-3, and tyrosine kinase (TYK) 2, in association with signal transducers and activators of transcription (STAT), play a pivotal role in mediating downstream signaling of a large number of essential proinflammatory cytokines implicated in PsA pathogenesis.[13,14] Thus the role of the JAK/STAT pathway, and more precisely its intracellular inhibition through the orally administered small molecule JAK inhibitors (JAKi), have garnered much interest in the management of PsA. Inhibiting all JAK isoforms (pan-JAKi), or specific JAK isoforms (specific JAKi), results in the simultaneous inhibition of multiple cytokines, and thus the contemporaneous modulation of several inflammatory pathways which are responsible for the multiple clinical manifestations of PsA.[15,16] However, given the pleiotropic nature of JAK–STAT signaling, and its importance in normal cell survival and growth,[17] there is concern that its inhibition may come at the expense of devasting adverse events.[18]

To date, tofacitinib, a pan-JAKi, and upadacitinib, a selective JAK1 inhibitor, are the only JAKi approved for use in moderate to severe PsA, by both the US Food and Drug Administration and the European Medicines Agency in those refractory or intolerant to bDMARDs.[19]

The primary outcome of this study is to assess the pooled efficacy of JAKi relative to placebo in the management of PsA. Given the heterogenous nature of PsA presentation, this study will assess this outcome via multiple clinical endpoints, reflecting the key domains of the condition, including peripheral arthritis, psoriasis, enthesitis and dactylitis. The secondary outcome of this study will assess the safety profile of JAKi relative to placebo in the management of PsA.

Additionally, for the first time, this study aims to conduct a subgroup analysis evaluating the pooled safety and efficacy of individual JAKi in treating the key clinical domains of PsA.

## 2 | METHODOLOGY

This systematic literature review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[20]

### 2.1 | Data sources and searches

A systematic search of the literature was conducted by 2 independent reviewers (PH, EB) using PubMed, Ovid EMBASE and the Cochrane Central Register of controlled trials (CENTRAL), from the inception of each database until April 30, 2021. On January 10, 2022, the same search strategy was repeated to ensure any relevant studies published since April 30, 2021 were captured. Databases were searched using a combination of controlled vocabulary and free text terms relating to PsA and JAK inhibition. The PICO (Population, Intervention, Comparator, Outcome) model[21] (Figure S1) was utilized to define the literature search criteria. The complete search strategy employed for each database is available within supplementary material. Furthermore, included studies reference lists were evaluated to identify additional relevant literature.

### 2.2 | Study selection

Citations retrieved from all databases were imported into Covidence, a web-based review management software. Duplicates were removed, and title and abstract screening was performed by 2 review authors (PH, EB) independently to identify studies suitable for inclusion (Table S1). The full text of positively identified studies were then screened by 2 review authors (PH, EB) to ensure eligibility criteria were satisfied (Table S1).

### 2.3 | Data extraction and outcome measures

Data extraction was undertaken by 2 review authors (PH, EB) using an electronic data collection form. Baseline study characteristics extracted included: lead author, year of publication, trial identifier, design, duration, population studied, number of patients, gender, mean age, mean disease duration, experimental drug(s) and dosage, active comparator(s) and dosage, concomitant methotrexate and glucocorticoid use.

The primary outcome, evaluating the clinical efficacy of JAKi in PsA in the core clinical domains of peripheral arthritis, enthesitis, dactylitis and psoriasis, was evaluated using standardized assessment measures. These include: American College of Rheumatology (ACR) 20/50/70 response, Psoriasis Area and Severity Index (PASI) 75 response, Leeds Enthesitis Index (LEI) and Leeds Dactylitis Index (LDI) (Table S2).

The secondary outcome, assessing the safety of JAKi in the management of PsA, was evaluated using the outcome measures outlined in Figure S1.

A subgroup analysis was performed evaluating the efficacy of individual JAKi, using the standardized assessment measures. Safety was assessed using total adverse events.

### 2.4 | Data synthesis

Qualitative data synthesis was undertaken for the results of each outcome measure. Data were pooled from all trials that reported results for the predefined outcome measures. Where data were sufficiently similar, they were utilized to conduct a meta-analysis. Pooled risk ratios (RR) with corresponding 95% confidence intervals (CI) were determined for dichotomous data using the Cochrane Mantel–Haenszel statistical method and random effects analysis model due to the anticipated heterogeneity. Analysis of continuous outcomes was not performed in this study. Quantitative data analysis was performed using Review Manager (RevMan) 5.4. *P* values <.05 were deemed statistically significant. Heterogeneity was assessed using the $I^2$ metric.

### 2.5 | Risk of bias

An assessment of risk of bias in the included trials was performed by 2 review authors (PH, EB) independently using the Cochrane Risk of Bias Tool for randomized clinical trials.[22]

## 3 | REVIEW

### 3.1 | Search results and study characteristics

A total of 307 publications were identified through the database search, of which 98 were duplicates. A PRISMA flow diagram (Figure 1) illustrates study attrition from initial search to final studies chosen for data synthesis. Ultimately, a total of 5 placebo-controlled RCTs were eligible for inclusion,[23-27] including a total of 3292 unique patients, of whom 1820 received a JAKi. These trials, and their baseline patient characteristics are summarized in Table 1. Two of the included trials[26,27] evaluated the pan-JAKi tofacitinib (n = 474), 1 trial[23] evaluated the JAK1 selective filgotinib (n = 65), and 2 trials[24,25] evaluated the JAK1 selective upadacitinib (n = 1281). One trial was a phase 2 RCT,[23] while the other 4 were phase 3 RCTs.

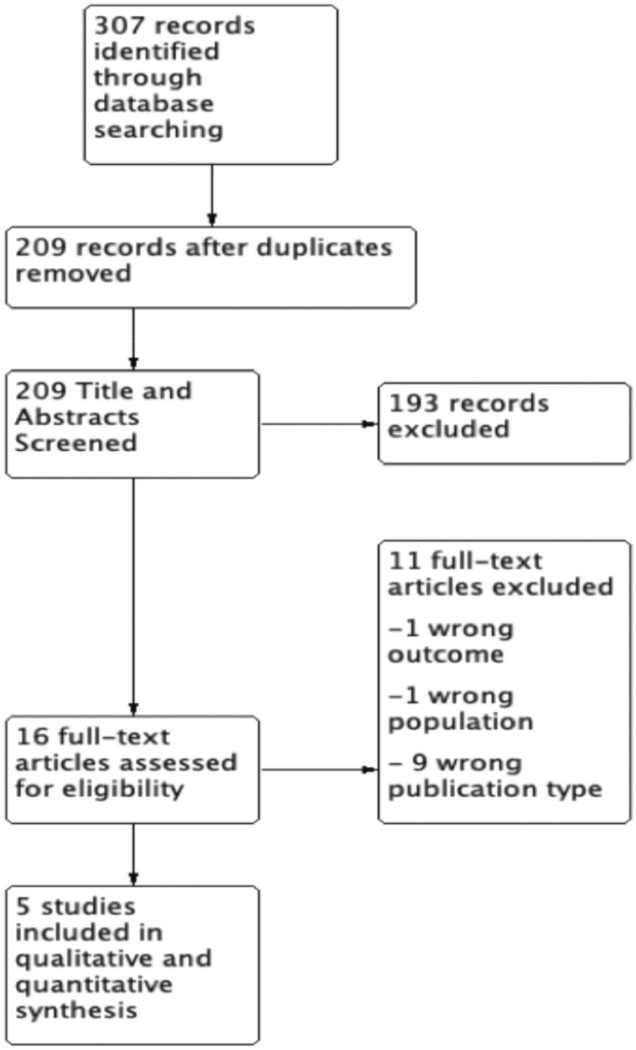


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating study selection

### 3.2 | Risk of bias

The risk of bias for each of the included studies is illustrated in Figure S2. All measures of bias for the included trials were considered to be of low risk, with the exception of the unclear risk of potential reporting bias in 1 study.[24]

### 3.3 | Efficacy outcomes

#### 3.3.1 | ACR response

All 5 RCTs[23-27] evaluated the clinical efficacy of JAKi according to ACR 20/50/70 response (Table 2). Four of the 5 trials[24-27] evaluated response after 12 weeks, and 1 trial[23] after 16 weeks.

The overall result of the pooled analysis demonstrates a statistically significant superiority of JAKi vs placebo in achieving an ACR20 response with up to 16 weeks of treatment (RR 2.10, 95%

**TABLE 1** Summary of included studies and baseline patient characteristics

| Reference | Trial identifier and study type | Trial duration | Population | Comparator(s); experimental drug(s) | Number of patients, n |
|---|---|---|---|---|---|
| Mease 2018[23] | NCT03101670<br>EQUATOR<br>Phase 2 RCT | 16 weeks | cs-DMARD-IR | Placebo<br>Filgotinib 200 mg | 66<br>65 |
| Gladman 2017[27] | NCT01882439<br>OPAL Beyond<br>Phase 3 RCT | 6 months | TNFi-IR | Placebo<br>Tofacitinib 5 mg BD<br>Tofacitinib 10 mg BD | 131<br>131<br>132 |
| Mease 2017[26] | NCT01877668<br>OPAL Broaden<br>Phase 3 RCT | 12 months | cs-DMARD-IR<br>bDMARD naïve | Placebo<br>Adalimumab 40 mg alt. wks<br>Tofacitinib 5 mg BD<br>Tofacitinib 10 mg BD | 105<br>106<br>107<br>104 |
| Mease 2021[25] | NCT03104374<br>SELECT-PsA 2<br>Phase 3 RCT | 24 weeks | bDMARD-IR | Placebo<br>Upadacitinib 15 mg OD<br>Upadacitinib 30 mg OD | 212<br>211<br>218 |
| McInnes 2021[24] | NCT03104400<br>SELECT-PSA1<br>Phase 3 RCT | 24 weeks | cs-DMARD-IR<br>bDMARD naïve | Placebo<br>Adalimumab 40 mg<br>Upadacitinib 15 mg OD<br>Upadacitinib 30 mg OD | 423<br>429<br>429<br>423 |

| Reference | Females n (%) | Mean age y (*SD*) | Mean disease duration y (*SD*) | Concomitant MTX n (%) | Concomitant glucocorticoid n (%) |
|---|---|---|---|---|---|
| Mease 2018[23] | 30 (45)<br>36 (55) | 50 (10.9)<br>49 (12.2) | 7 (6.2)<br>7 (6.7) | 43 (65)<br>41 (63) | 16 (24)<br>17 (26) |
| Gladman 2017[27] | 80 (61)<br>64 (49)<br>74 (56) | 49.0 (12.6)<br>49.5 (12.3)<br>51.3 (10.9) | 9.4 (8.1)<br>9.6 (7.6)<br>9.1 (6.8) | 101 (77)<br>98 (75)<br>91 (69) | 31 (24)<br>37 (28)<br>25 (19) |
| Mease 2017[26] | 56 (53)<br>50 (47)<br>57 (53)<br>62 (60) | 47.7 (12.3)<br>47.4 (11.3)<br>49.4 (12.6)<br>46.9 (12.4) | 6.4 (6.4)<br>5.3 (5.3)<br>7.3 (8.2)<br>5.4 (5.8) | 92 (88)<br>79 (75)<br>91 (85)<br>92 (88) | 18 (17)<br>23 (22)<br>29 (27)<br>11 (11) |
| Mease 2021[25] | 120 (56.6)<br>113 (53.6)<br>115 (52.8) | 54.1 (11.5)<br>53.0 (12.0)<br>53.0 (11.9) | 11.0 (10.3)<br>9.6 (8.4)<br>9.7 (8.7) | 75 (35.4)<br>74 (35.1)<br>73 (33.5) | 24 (11.3)<br>22 (10.4)<br>13 (6.0) |
| McInnes 2021[24] | 211 (49.9)<br>222 (51.7)<br>238 (55.5)<br>236 (55.8) | 50.4 (12.2)<br>51.4 (12)<br>51.6 (12.2)<br>49.9 (12.4) | 6.2 (7)<br>5.9 (7.1)<br>6.2 (7.4)<br>5.9 (6.4) | 267 (63.1)<br>270 (62.9)<br>279 (65)<br>268 (63.4) | 70 (16.5)<br>72 (16.8)<br>73 (17)<br>71 (16.8) |

Abbreviations: BD, twice daily; bDMARD, biologic disease-modifying antirheumatic agent; csDMARD, conventional synthetic disease-modifying antirheumatic agent; IR, intolerance +/− resistance; MTX, methotrexate; n, number of patients; OD, once daily; *SD*, standard deviation; TNFi, tumor necrosis factor inhibitor.

CI [1.86–2.37], $P < .00001$, $I^2 = 19\%$) (Figure 2A). Similarly, JAKi demonstrated a superiority in achieving ACR50 (RR 3.43, 95% CI [2.37–4.96], $P < .00001$, $I^2 = 66\%$) (Figure 2B) and ACR70 (RR 4.57, 95%CI [1.83–11.44], $P = .001$, $I^2 = 82\%$) (Figure 2C) response with up to 16 weeks of treatment, vs placebo. Heterogeneity in the pooled analysis of ACR50 and ACR70, was substantial with $I^2$ values of 66% and 82% respectively.

### 3.3.2 | PASI 75 response

All 5 trials[23-27] evaluated PASI 75 response in those patients suitable for analysis (ie those entering the trial with at least 3% of their body surface area covered by psoriasis). Four trials[23-26] evaluated this response after 16 weeks, and 1 trial[27] after 12 weeks. JAKi were superior to placebo in achieving a PASI 75 response up to 16 weeks (RR 2.96, 95%CI [2.44–3.58], $P < .00001$, $I^2 = 0\%$), with 52.3% of those treated with a JAKi, and 17.45% of those treated with placebo achieving PASI 75, indicating an absolute treatment benefit of 34.85% (Table 2, Figure 3A).

### 3.3.3 | Resolution of enthesitis

Four[24-27] trials evaluated the attainment of a LEI of 0. A total of 1686 patients (JAKi, n = 1143; placebo, n = 543), were included in this analysis. Three trials[25-27] evaluated this clinical endpoint at 12 weeks, and 1 trial[24] at 24 weeks. Those treated with JAKi demonstrated

**TABLE 2** Summary of efficacy outcomes

| Study Reference | Treatment arms (n) | ACR20 response n/N (%) | ACR50 response n/N (%) | ACR 70 response n/N (%) | Leeds Enthesitis Index = 0 | Leeds Dactylitis Index = 0 | PASI 75 |
|---|---|---|---|---|---|---|---|
| Mease 2018[23] | Placebo (66) | 22/66 (33.3) | 10/66 (15.2) | 4/66 (6.1) | NR | NR | 6/40 (15) |
| | Filgotinib 200 mg (65) | 52/65 (80) | 31/65 (47.7) | 15/65 (23.1) | NR | NR | 9/42 (45.2) |
| Gladman 2017[27] | Placebo (131) | 31/131 (24) | 19/131 (15) | 13/131 | 20/93 (21.5) | 18/63 (28.6) | 12/86 (14) |
| | Tofacitinib 5 mg BD (131) | 65/131 (50) | 39/131 (30) | 22/131 (17) | 33/83 (39.8) | 34/66 (51.5) | 17/80 (21) |
| | Tofacitinib 10 mg BD (132) | 62/132 (47) | 37/132 (28) | 19/132 (14) | 32/99 (32.3) | 33/65 (50.8) | 35/81 (43) |
| Mease 2017[26] | Placebo (105) | 35/105 (33.3) | 10/105 (10) | 5/105 (5) | 14/65 (21.5) | 19/58 (32.8) | 12/82 (15) |
| | Adalimumab (106) | 55/106 (52) | 35/106 (33) | 20/106 (19) | 36/76 (47.4) | 27/58 (46.6) | 30/77 (39) |
| | Tofacitinib 5 mg BD (107) | 54/107 (50) | 30/107 (28) | 18/107 (17) | 25/75 (33.3) | 21/61 (36.4) | 35/82 (43) |
| | Tofacitinib 10 mg BD (104) | 63/104 (61) | 42/104 (40) | 15/104 (14) | 26/64 (40.6) | 36/60 (60) | 31/70 (44) |
| Mease 2021[25] | Placebo (212) | 51/212 (24) | 10/212 (4.7) | 1/212 (0.5) | 29/144 (20.1) | 23/64 (35.9) | 21/131 (16) |
| | Upadacitinib 15 mg OD (211) | 120/211 (56.9) | 67/211 (31.8) | 18/211 (8.5) | 52/133 (39.1) | 35/55 (63.6) | 68/130 (52.3) |
| | Upadacitinib 30 mg OD (218) | 139/218 (63.8) | 82/218 (37.6) | 36/218 (16.5) | 73/152 (48) | 38/50 (76) | 74/131 (56.5) |
| McInnes 2021[24] | Placebo (423) | 153/423 (36.2) | 56/423 (13.2) | 10/423 (2.4) | 78/241 (32.4) | 50/126 (39.7) | 45/211 (21.3) |
| | Upadacitinib 15 mg OD (429) | 303/429 (70.6) | 161/429 (37.5) | 67/429 (15.6) | 145/270 (53.7) | 104/136 (76.5) | 134/214 (62.6) |
| | Upadacitinib 30 mg OD (423) | 332/423 (78.5) | 219/423 (51.8) | 107/423 (25.3) | 154/267 (57.7) | 101/127 (79.5) | 131/210 (62.4) |
| | Adalimumab (429) | 279/429 (65) | 161/429 (37.5) | 59/429 (13.8) | 125/265 (47.2) | 94/127 (74) | 112/211 (53.1) |

Abbreviations: ACR, American College of Rheumatology; BD, twice daily; n, number of patients; N, total number of patients; OD, once daily; PASI 75, Psoriasis Area and Severity Index 75.

a statistically significantly higher attainment of enthesitis resolution, vs those treated with placebo (RR 1.79, 95%CI [1.54–2.08], $P < .00001$, $I^2 = 0\%$) (Table 2, Figure 3B).

### 3.3.4 | Resolution of dactylitis

Four[24-27] trials evaluated the attainment of a LDI of 0. A total of 931 patients (JAKi, n = 620; placebo, n = 311) were included in this analysis. Three trials[25-27] evaluated this clinical endpoint at 12 weeks, and 1 trial[24] at 24 weeks. Those treated with JAKi demonstrated a statistically significant higher attainment of dactylitis resolution, vs those treated with placebo (RR 1.85, 95%CI [1.57–2.16], $P < .00001$, $I^2 = 0\%$) (Table 2, Figure 3C).

## 3.4 | Safety outcomes

The evaluated safety outcomes of JAKi compared to placebo are summarized in Table 3.

Safety outcome analyses were performed at 12 weeks in 2 trials,[26,27] 16 weeks in 1 trial[23] and 24 weeks in 2 trials.[24,25]

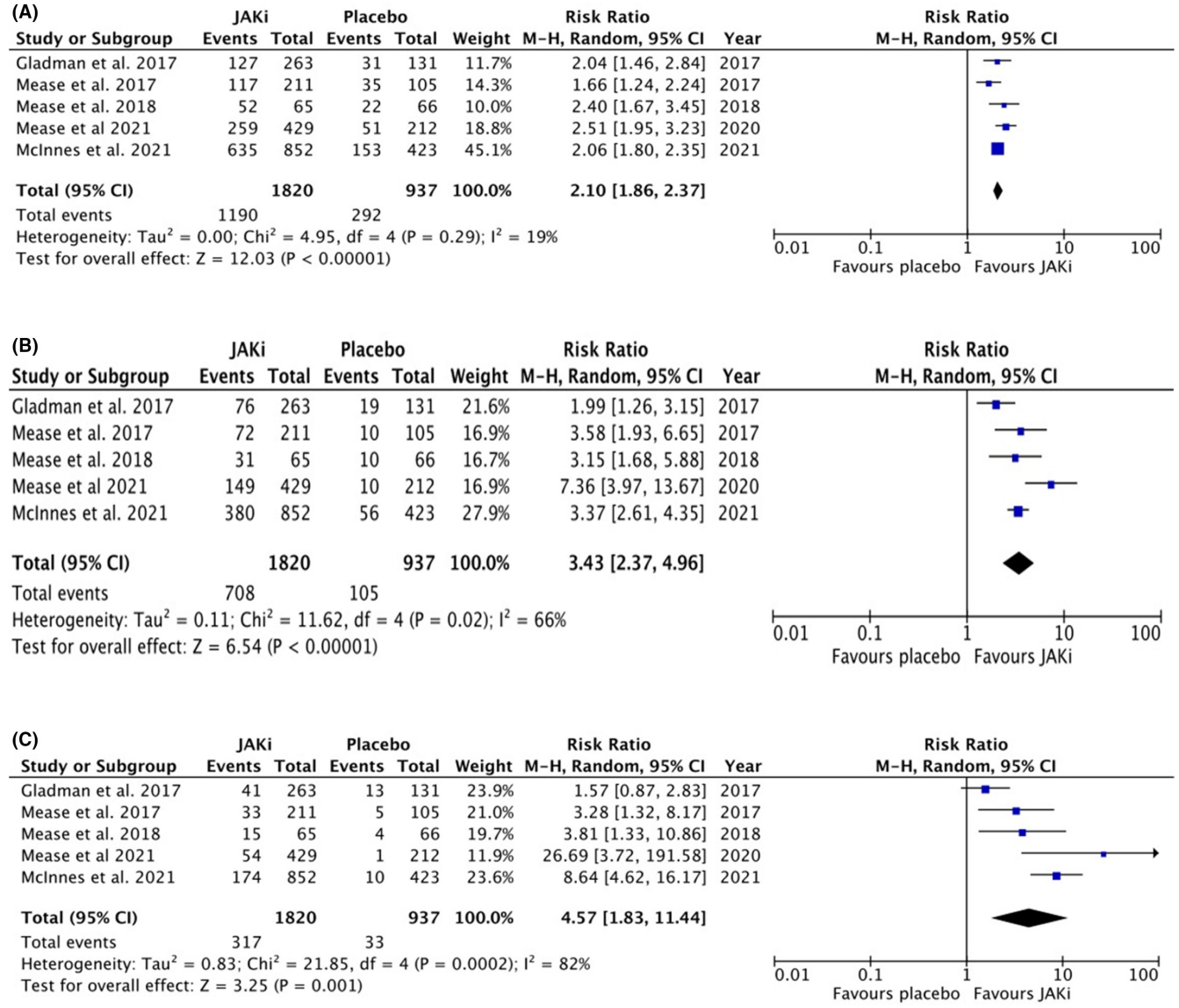


FIGURE 2 (A) Forest plot demonstrating pooled efficacy of Janus kinase inhibitors (JAKi) in achieving American College of Rheumatology (ACR)20 response at up to 16 weeks, vs placebo. (B) Forest plot demonstrating pooled efficacy of JAKi in achieving ACR50 response at up to 16 weeks, vs placebo. (C) Forest plot demonstrating pooled efficacy of JAKi in achieving ACR70 response at up to 16 weeks, vs placebo. M-H, Mantel–Haenszel statistical method

Pooled analysis of all reported adverse events demonstrated that JAKi were associated with a statistically significant higher overall relative risk of adverse events (RR 1.14, 95%CI [1.07–1.21], $P = .0001$, $I^2 = 0\%$) (Figure S3), and serious adverse events (RR 1.67, 95%CI [1.02–2.74], $P = .04$, $I^2 = 2\%$) (Figure S4) vs placebo.

The pooled relative risk of treatment withdrawal secondary to an adverse event with a JAKi vs placebo was not statistically significant (RR 1.40, 95%CI [0.94–2.10], $P = .10$, $I^2 = 0\%$) (Figure S5).

Three trials[23-25] provided adequate data on total infections. The pooled analysis of these 3 trials showed a statistically significant increased relative risk of infection (RR 1.23, 95%CI [1.08–1.39], $P = .001$, $I^2 = 0\%$) associated with JAKi treatment vs placebo (Figure S6).

Pooled analysis did not demonstrate a statistically significant increased relative risk of opportunistic infections (RR 2.15, 95%CI [0.46–10.07], $P = .33$, $I^2 = 0\%$) (Figure S7), or venous thromboembolic events (VTE) (RR 0.79, 95%CI [0.10–6.44], $P = .83$, $I^2 = 0\%$) (Figure S8) in the intervention arm. Only 2 trials[24,25] contributed to the pooled analysis evaluating VTE.

Furthermore, pooled analysis of all 5 trials did not reveal any statistically significant increased relative risk of herpes zoster (HZ) in those treated with a JAKi vs placebo (RR 2.00, 95%CI [0.84–4.74], $P = .12$, $I^2 = 0\%$) (Figure S9).

There were 11 malignancies (excluding non-melanoma skin cancers) reported across all trials: 8 occurred in those treated with a JAKi, and a further 3 occurred in those treated with adalimumab (Table S3).

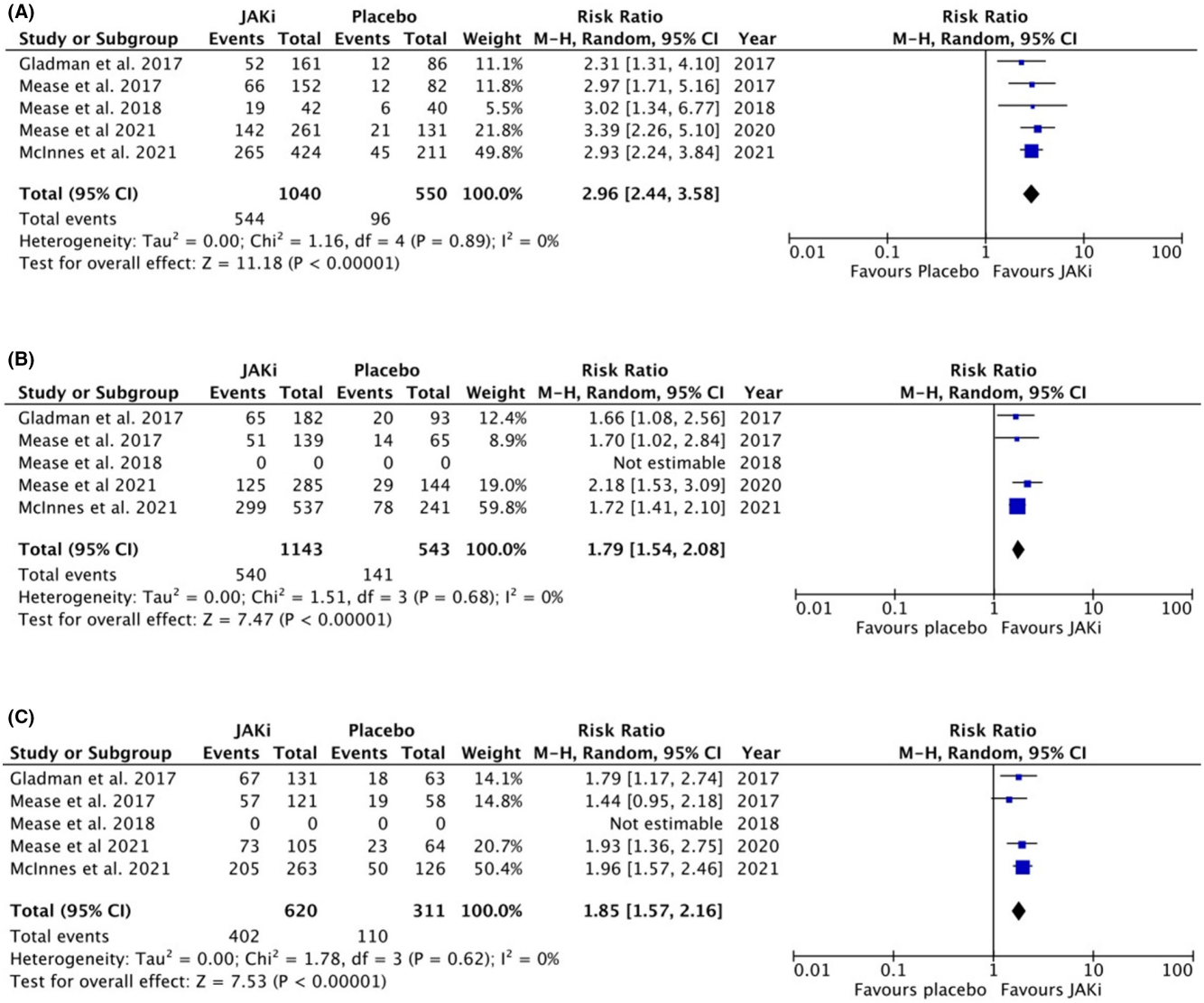


**FIGURE 3** (A) Forest plot demonstrating pooled efficacy of Janus kinase inhibitors (JAKi) in achieving Psoriasis Area and Severity Index 75 (PASI 75) response at up to 16 weeks, vs placebo. (B) Forest plot demonstrating the pooled efficacy of JAKi in enthesitis resolution (Leeds Enthesitis Index = 0) up to 24 weeks. (C) Forest plot demonstrating the pooled efficacy of JAKi in dactylitis resolution (Leeds Dactylitis Index = 0) up to 24 weeks. M-H, Mantel–Haenszel statistical method

Five cardiovascular events were reported across the 5 trials: 2 in those treated with a JAKi, 2 in those treated with adalimumab and 1 in those treated with placebo (Table 3).

A total of 3 deaths were recorded across all trials: 1 in a JAKi treated patient, and the other 2 in patients treated with placebo (Table 3).

### 3.4.1 | Subgroup analysis of individual JAKi

Four trials[24-27] were eligible for this pooled subgroup analysis. Two trials[26,27] evaluated tofacitinib, at doses of 5 mg twice daily (BD) and 10 mg BD, and 2 trials[24,25] assessed upadacitinib, at doses of 15 mg once daily (OD) and 30 mg OD. Pooled efficacy analysis was performed for the following outcome measures: ACR20/50/70, PASI 75, enthesitis resolution and dactylitis resolution. Across all of the aforementioned efficacy outcome measures, upadacitinib (15 mg OD and 30 mg OD) demonstrated statistically significant superiority to tofacitinib (Table S4; Figure S10-S15). Furthermore, upadacitinib 30 mg OD, showed a statistically significant superiority to upadacitinib 15 mg across all efficacy outcome measures (Table S4; Figure S10-S15). Regarding safety, pooled subgroup analysis of the relative risk of an adverse event in those treated with individual JAKi is displayed in Figure 4.

## 4 | DISCUSSION

Overall, pooled JAKi demonstrated a statistically significant superior efficacy vs placebo, across all predefined efficacy endpoints: ACR20/50/70, PASI 75, LEI and LDI. Both ACR20/50/70 and PASI

TABLE 3 Summary of safety outcomes

| Study reference | Analysis timepoint | Treatment arms (n) | Any adverse event n/N (%) | Serious A/E n/N (%) | A/E related withdrawal n/N (%) | Opportunistic infection n/N (%) |
|---|---|---|---|---|---|---|
| Mease 2018[23] | 16 weeks | Placebo (66) | 39/66 (59) | 1/66 (2) | 0/66 (0) | 0/66 (0) |
| | | Filgotinib 200 mg (65) | 37/65 (57) | 1/65 (2) | 1/65 (2) | 0/65 (0) |
| Gladman 2017[27] | 12 weeks | Placebo (131) | 58/131 (44) | 3/131 (2) | 5/131 (4) | 0/131 (0) |
| | | Tofacitinib 5 mg BD (131) | 72/131 (55) | 1/131 (1) | 2/131 (2) | 1/131 (1) |
| | | Tofacitinib 10 mg BD (132) | 70/132 (53) | 3/132 (2) | 10/132 (8) | 0/132 (0) |
| Mease 2017[26] | 12 weeks | Placebo (105) | 37/105 (35) | 1/105 (1) | 1/105 (1) | 0/105 (0) |
| | | Adalimumab (106) | 49/106 (46) | 2/106 (2) | 2/106 (2) | 0/106 (0) |
| | | Tofacitinib 5 mg BD (107) | 42/107 (39) | 3/107 (3) | 3/107 (3) | 1/107 (1) |
| | | Tofacitinib 10 mg BD (104) | 47/104 (45) | 0/104 (0) | 0/104 (0) | 0/104 (0) |
| Mease 2021[25] | 24 weeks | Placebo (212) | 139/212 (65.6) | 4/212 (1.9) | 11/212 (5.2) | 0/212 (0) |
| | | Upadacitinib 15 mg OD (211) | 135/211 (64) | 12/211 (5.7) | 15/211 (7.1) | 0/211 (0) |
| | | Upadacitinib 30 mg OD (218) | 170/218 (78) | 18/218 (8.3) | 20/218 (9.2) | 2/218 (0.9) |
| McInnes 2021[24] | 24 weeks | Placebo (423) | 252/423 (59.6) | 13/423 (3.1) | 13/423 (3.1) | 0/423 (0)) |
| | | Upadacitinib 15 mg OD (429) | 287/429 (66.9) | 14/429 (3.3) | 13/429 (3) | 1/429 (0.2) |
| | | Upadacitinib 30 mg OD (423) | 306/423 (72.3) | 26/423 (6.1) | 21/423 (5) | 2/423 (0.5) |
| | | Adalimumab (429) | 278/429 (64.8) | 16/429 (3.7) | 22/429 (5.1) | 0/429 (0) |

| Study reference | Treatment arms (n) | Total infection(s) n/N (%) | Herpes zoster infection n/N (%) | VTE n/N (%) | Cardiovascular event n/N (%) | Malignancy (excluding NMSC) n/N (%) | Death n/N (%) |
|---|---|---|---|---|---|---|---|
| Mease 2018[23] | Placebo (66) | 14/66 (21) | 0/66 (0) | 0/66 (0) | 0/66 (0) | 0/66 (0) | 0/66 (0) |
| | Filgotinib 200 mg (65) | 14/65 (22) | 1/65 (2) | 0/65(0) | 1/65 (2) | 0/65 (0) | 1/65 (2) |
| Gladman 2017[27] | Placebo (131) | NR | 0/131(0) | NR | 0/131 (0) | 0/131 (0) | 0/131 (0) |
| | Tofacitinib 5 mg BD (131) | NR | 1/131 (1) | NR | 0/131 (0) | 0/131 (0) | 0/131 (0) |
| | Tofacitinib 10 mg BD (132) | NR | 1/132 (1) | NR | 0/132 (0) | 0/132 (0) | 0/132 (0) |

TABLE 3 (Continued)

| Study reference | Treatment arms (n) | Total infection(s) n/N (%) | Herpes zoster infection n/N (%) | VTE n/N (%) | Cardiovascular event n/N (%) | Malignancy (excluding NMSC) n/N (%) | Death n/N (%) |
|---|---|---|---|---|---|---|---|
| Mease 2017[26] | Placebo (105) | NR | 0/105 (0) | NR | 0/105 (0) | 0/105 (0) | NR |
| | Adalimumab (106) | NR | 0/106 (0) | NR | 0/106 (0) | 0/106 (0) | NR |
| | Tofacitinib 5 mg BD (107) | NR | 1/107 (1) | NR | 0/107 (0) | 2/107 (2) | NR |
| | Tofacitinib 10 mg BD (104) | NR | 0/104 (0) | NR | 0/104 (0) | 0/104 (0) | NR |
| Mease 2021[25] | Placebo (212) | 73/212 (34.4) | 2/212 (0.9) | 0/212 (0) | 0/212 (0) | 0/212 (0) | 1/212 (0.5) |
| | Upadacitinib 15 mg OD (211) | 71/211 (33.6) | 3/211 (1.4) | 1/211(0.5) | 1/211 (0.5) | 2/211 (0.9) | 0/211 (0) |
| | Upadacitinib 30 mg OD (218) | 108/218 (49.5) | 8/218 (3.7) | 0/218 (0) | 0/218 (0) | 2/218 (0.9) | 0/218 (0) |
| McInnes 2021[24] | Placebo (423) | 140/423 (33.1) | 3/423 (0.7) | 1/423 (0.2) | 1/423 (0.2) | 0/423 (0) | 1/423 (0.2) |
| | Upadacitinib 15 mg OD (429) | 169/429 (39.4) | 4/429 (0.9) | 0/429 (0) | 0/429 (0) | 1/429 (0.2) | 0/429 (0) |
| | Upadacitinib 30 mg OD (423) | 183/423 (43.3) | 5/423 (1.2) | 1/423 (0.2) | 0/423 (0) | 1/423 (0.2) | 0/423 (0) |
| | Adalimumab (429) | 146/429 (34.0) | 0/429 (0) | 2/ 429 (0.5) | 2/ 429 (0.5) | 3/429 (0.7) | 0/429 (0) |

Abbreviations: A/E, adverse events; BD, twice daily; N, total number of patients; n, number of patients; NMSC, non-melanoma skin cancer; NR, not reported; OD, once daily; VTE, venous thromboembolic events.

75 responses were assessed at up to 16 weeks treatment duration, and irrespective of this short treatment duration, pooled JAKi demonstrated statistically significant superiority vs placebo in these domains.

Despite enthesitis and dactylitis contributing considerably to the overall burden of disease and disability in those with PsA,[28] there is a dearth of evidence pertaining to their distinct management. Suitable data for the assessment of enthesitis and dactylitis resolution were only available in 4[24-27] trials, which on pooled analysis demonstrated a statistically significant treatment benefit in the management of enthesitis (RR 1.79, 95%CI [1.54–2.08], $P < .00001$, $I^2 = 0\%$) (Figure 3B) and dactylitis (RR 1.85, 95%CI [1.57–2.16], $P < .00001$, $I^2 = 0\%$) (Figure 3C) in those treated with JAKi vs placebo. However, this must be interpreted with caution as the trial[24] which represented the greatest weighting in the pooled analysis had a treatment follow-up duration of 24 weeks, compared to 12 weeks in the other 3.[25-27] While this demonstrates therapeutic benefit of JAKi in both enthesitis and dactylitis resolution, the rapidity of efficacy observed in the other therapeutic domains analyzed up to 16 weeks, cannot be inferred for either dactylitis or enthesitis.

All included patients had a long disease duration, with similar concomitant glucocorticoid use (Table 1). However, there was considerable variability between trials relating to concomitant conventional synthetic DMARD (csDMARD) use, notably concomitant methotrexate use, with less than 40% of patients in 1 study[25] receiving concomitant methotrexate, vs greater than 60% of patients in all other included studies.[23,24,26,27] Moreover, 2 studies used the anti-TNF inhibitor adalimumab as an active comparator (Table 1),[24,26] with JAKi demonstrated to be non-inferior at currently licensed dosages (tofacitinib 5 mg BD and upadacitinib 30 mg OD) in achieving primary outcomes. This yields exciting promise for the role of JAKi as effective therapeutic agents in those deemed to be insufficient responders to csDMARDs.

The pooled analysis of safety outcomes for JAKi demonstrated an overall statistically significantly higher relative risk of adverse events (RR 1.14, 95%CI [1.07–1.21], $P = .0001$, $I^2 = 0\%$) (Figure S3), and serious adverse events (RR 1.67, 95%CI [1.02–2.74], $P = .04$, $I^2 = 0\%$) (Figure S4) in those treated with a JAKi vs placebo. Regarding specific safety signals, there was a statistically significant increased risk of infection (RR 1.23, 95%CI [1.08–1.39], $P = .001$, $I^2 = 0\%$) associated with JAKi vs placebo (Figure S6).

A class effect safety signal associated with JAKi is that of a dose-dependent increase in HZ infection,[29] in addition to VTE.[30] Furthermore, there is increasing concern over their cardiovascular safety profile.[31]

Unfortunately, this study did not demonstrate pooled statistically significant results in these safety domains owing to the small

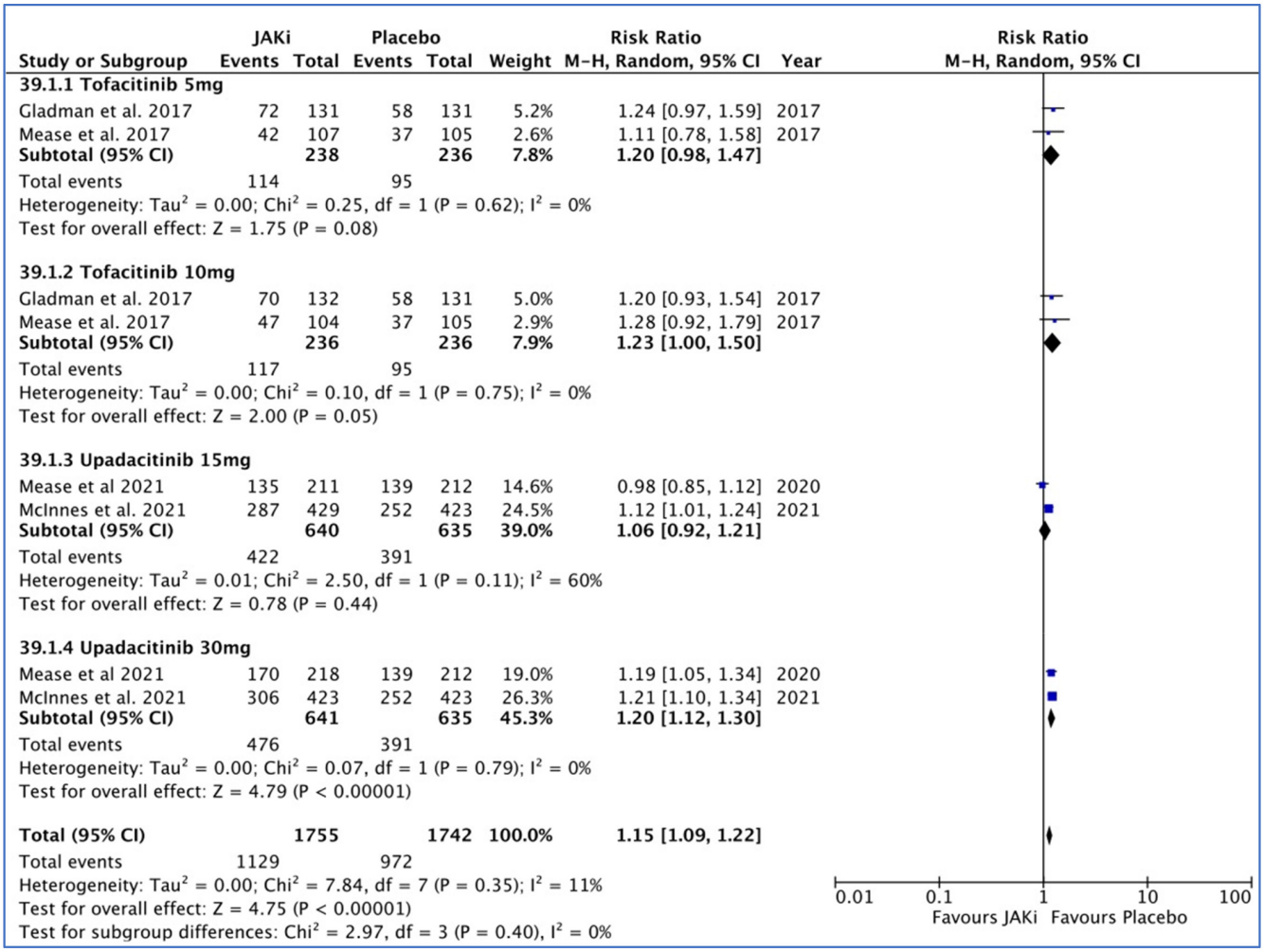


FIGURE 4 Forest plot demonstrating the pooled subgroup analysis of the relative risk of an adverse event in those treated with a Janus kinase inhibitor (JAKi) vs placebo. M-H, Mantel–Haenszel statistical method

number of inadequately powered trials assessing these outcomes, and the short treatment follow-up.

A subgroup analysis of the efficacy of individual JAKi was performed assessing tofacitinib (5 mg BD and 10 mg BD) and upadacitinib (15 mg OD and 30 mg OD) using the predefined clinical outcome measures. Across all efficacy domains, pooled analysis of upadacitinib at either 15 mg OD, or 30 mg OD, demonstrated statistically significant superiority to both doses of tofacitinib. Furthermore, upadacitinib 30 mg showed statistically significant superiority to upadacitinib 15 mg across all efficacy domains. To date tofacitinib, at a dosage of 5 mg BD, and upadacitinib at a dose of 15 mg OD, are the only licensed JAKi in the management of PsA.[19] The evidence found in this study suggests superior efficacy of upadacitinib. Unfortunately, owing to an insufficient number of trials, a dose–response analysis for each JAKi was not possible.

Furthermore, pooled subgroup analysis of the individual JAKi did not demonstrate a statistically significant difference in total adverse events (Figure 4), likely secondary to the small number of inadequately powered trials included in the analysis, combined with short treatment follow-up.

## 4.1 | Strengths and limitations

As evident throughout this discussion, the results of this study should be interpreted with caution owing to some of its associated limitations. Despite including all eligible RCTs, the number of fully reported placebo-controlled RCTs remains small, thus restricting the potential for subgroup and sensitivity analysis.

Furthermore, there was considerable heterogeneity evident in treatment follow-up duration between trials which undoubtedly may influence outcome measures and analysis. In addition to this, all trials had a short follow-up duration ranging from 12 to 24 weeks, which is an insufficient time frame within which to sufficiently assess all outcome measures, particularly safety outcomes. Some trials incorporated an "early escape" into their methodology, whereby a subgroup or all placebo-treated patients switched to treatment groups after a defined time period, further limiting analysis to short-term data. A previously published systematic literature review and meta-analysis[32] also explores the safety and efficacy of JAKi in PsA; however, our study is novel in a number of ways. First, we performed the first

subgroup analysis of the individual JAKi in PsA, in addition to including all trialed doses of JAKi, enabling the novel demonstration of the statistically significant superiority of upadacitinib 30 mg OD in terms of efficacy across all PsA domains compared to other JAKi trialed. However, long-term data, most notably safety data, are necessary before this can be incorporated into every day clinical practice. Finally, the aforementioned study[32] utilized odds ratio in their meta-analysis; however, given the superiority in clinician interpretation and application of RR, we opted to use this in our analysis.[33]

## 5 | CONCLUSION

PsA is a complex heterogenous condition, with multiple clinical manifestations of disease presentation. This systematic review and meta-analysis demonstrated the pooled statistically significant superiority of JAKi in the management of multiple clinical domains of PsA disease presentation. However, the overall pooled risk of adverse events was higher in those treated with JAKi vs placebo, with an increased total infection rate.

Before these agents can be fully assimilated within the PsA treatment algorithm, additional high-powered trials, providing head to head comparison of therapeutic agents, with long-term safety outcome follow-up are necessary.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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