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## **Safety of Janus Kinase Inhibitors in Patients with Inflammatory Bowel Diseases or Other Immune-mediated Diseases: a Systematic Review and Meta-Analysis**

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PO: bibliographic search; inclusion and exclusion of studies for systematic review and meta-analysis; quality assessment of included studies; draft elaboration. JL: bibliographic search; inclusion and exclusion of studies for systematic review and meta-analysis; meta-analysis and statistical analysis; draft elaboration. SB: bibliographic search; inclusion and exclusion of studies for systematic review and meta-analysis; meta-analysis and statistical analysis. SD: quality assessment of included studies; critical review of draft; LPB: study design and conception; draft elaboration and critical review of draft.

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**ABSTRACT:**

**Background & Aims:** Inhibitors of Janus kinases (JAKs) are being developed for treatment of inflammatory bowel diseases and other immune-mediated diseases. Tofacitinib is effective in treatment of ulcerative colitis, but there are safety concerns. We performed a systematic review and meta-analysis to investigate the safety profile of tofacitinib, upadacitinib, filgotinib, and baricitinib in patients with rheumatoid arthritis, inflammatory bowel diseases, psoriasis, or ankylosing spondylitis.

**Methods:** We searched the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials from January 1, 1990 through July 1, 2019. We performed a manual review of conference databases from 2012 through 2018. The primary outcome was incidence rates of adverse events (AEs) and serious AEs. We also estimated incidence rates of serious infections, herpes zoster infection, non-melanoma skin cancer, other malignancies, major cardiovascular events, venous thromboembolism, and mortality. We performed a meta-analysis, which included controlled studies, to assess the relative risk of these events.

**Results:** We identified 973 studies; of these 82 were included in the final analysis, comprising 66159 patients with immune-mediated diseases who were exposed to a JAK inhibitor. Two-thirds of the included studies were randomized controlled trials. The incidence rate of AEs was 42.65 per 100 person-years and of serious AEs was 9.88 per 100 person-years. Incidence rates of serious infections, herpes zoster infection, malignancy, and major cardiovascular events were 2.81 per 100 person-years, 2.67 per 100 person-years, 0.89 per 100 person-years, and 0.48 per 100 person-years, respectively. Mortality was not increased in patients treated with JAK inhibitors compared to patients given placebo or active comparator (relative risk 0.72; 95% CI, 0.40–1.28). The meta-analysis showed a significant increase in risk of herpes zoster infection among patients who received JAK inhibitors (relative risk 1.57; 95% CI, 1.04–2.37).

**Conclusions:** In a systematic review and meta-analysis, we found an increased risk of herpes zoster infection among patients with immune-mediated diseases treated with JAK inhibitors. All other AEs were not increased among patients treated with JAK inhibitors.

**KEY WORDS:** NMSC, IBD, immunosuppression, small molecule

## INTRODUCTION

Inflammatory bowel disease (IBD) comprise two potentially disabling diseases: Crohn's disease (CD) and ulcerative colitis (UC).<sup>1,2</sup> Currently available therapeutic options include aminosalicylates, immunomodulators, and biologic drugs (i.e. anti-tumor necrosis factor [TNF] agents, vedolizumab, and ustekinumab).<sup>3</sup> The introduction of biologics two decades ago has changed dramatically treatment paradigm in IBD. However, available treatment options have several limitations, in terms of primary non-response, secondary loss of response, potentially serious adverse events (SAEs), and treatment-related costs.<sup>4</sup> In this context, novel biologic and small-molecule drugs engaging different targets are being tested in IBD.<sup>5</sup>

Janus kinase (JAK) inhibitors are a family of small molecules that block one or more of the intracellular tyrosine kinases: JAK1, JAK2, JAK3 and TYK2. Many cytokines exert their biological functions by activating the JAK-STAT pathway, which has a critical role in intracellular cytokine signaling.<sup>6</sup> These compounds can block several cytokines and inflammatory pathways simultaneously, and thus inducing immunosuppression.<sup>7</sup> Tofacitinib has been the first JAK inhibitor to receive regulatory approval for the treatment of UC,<sup>8</sup> but there are currently other JAK inhibitory compounds in late stage of development in IBD, namely upadacitinib and filgotininib. Some of these compounds and others have been approved or are currently being tested in other immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriasis (PSO).<sup>9</sup> Tofacitinib has been approved by de US Food and Drug Administration (FDA) for the treatment of moderately to severely active RA since late 2012,<sup>10</sup> and since 2017 for the treatment of active psoriatic arthritis.<sup>11</sup> Baricitinib has received regulatory approval from FDA and European Medicines Agency (EMA) for the treatment of moderately to severely active RA.<sup>12,13</sup> JAK inhibitors have been associated with potential adverse events (AEs), including infections, serious infections, herpes zoster, major adverse cardiovascular events (MACE), and thromboembolic events.

Many concepts currently applied in the management of IBD, have been extrapolated from other IMIDs, particularly from RA, such as treat to target, tight control, early intervention, and disease-modifying interventions.<sup>14</sup> Additionally, most of the currently available biosimilar compounds have been tested in other IMIDs, and they have been approved in IBD due to extrapolation of indications.<sup>15</sup> Finally, previous systematic reviews and meta-analyses have evaluated the safety of interventions in the myriad of IMIDs.<sup>16,17</sup>

With an increasing therapeutic armamentarium, treatment algorithms in IBD will become more complex, with several drug classes and many compounds within each class will become difficult to determine adequate drug positioning. Knowing the exact safety profile of JAK inhibitors will help to adequately weigh the risk/benefit ratio of this drug class.

The aim of this systematic review and meta-analysis was to evaluate the risk of AEs, SAEs, and AEs of special interest in IBD and other IMIDs.

## **MATERIALS AND METHODS**

Our study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO - <http://www.crd.york.ac.uk/prospere>).<sup>18</sup> We followed the methodology for conducting and reporting a systematic review described in the Cochrane Handbook, the MOOSE proposal, and the PRISMA statement.

### *Inclusion Criteria*

We searched for clinical trials (randomized or non-randomized) and cohort studies (prospective or retrospective) involving adult patients with UC, CD, RA, AS or PSO. All articles irrespective of publication type were considered for inclusion. In the case of multiple studies involving the same population, data from the most recent or most comprehensive one would be included. We focused on JAK inhibitors that are approved or are under development in the aforementioned conditions (tofacitinib, filgotinib, baricitinib and upadacitinib), whether they were used as monotherapy or associated with immunomodulators (i.e., methotrexate) or steroids. We did not apply language restrictions.

### *Outcomes*

Our primary outcome was to assess the incidence rate of AEs and SAEs. Additionally, we estimated incidence rates of the following AEs: mortality, serious infections, herpes zoster infection, non-melanoma skin cancer (NMSC), other type of malignancy and MACE, including venous thromboembolism. Incidence rates were estimated taking into consideration time of follow up, and also proportion of patients exposed to any JAK inhibitor, regardless of the time of exposure. Additionally, we compared the incidence of the aforementioned outcomes between patients exposed to JAK inhibitors versus placebo and/or an active comparator in controlled clinical trials.

### *Information Sources and Search Strategy*

Published studies were identified using MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from January 1 1990 until July 1 2019. Major congresses databases (Gastroenterology: European Crohn's and Colitis Organization, Digestive Disease Week, and United European Gastroenterology Week; Rheumatology: American College of Rheumatology Annual Meeting;

Dermatology: American Academy of Dermatology Annual Meeting) in the period 2015-2019 were also reviewed manually.

Search algorithms included the following MESH terms: ["JAK inhibitor" OR ("tofacitinib" OR "CP-690550") OR ("filgotinib" OR "GLPG0634") OR ("upadacitinib" OR "ABT-494") OR ("baricitinib" OR "LY3009104") AND ["Crohn's disease" OR "ulcerative colitis" OR "inflammatory bowel disease" OR "rheumatoid arthritis" OR "ankylosing spondylitis" OR "psoriasis"] AND ["safety" OR "adverse events" OR "side effects" OR "infection" OR "herpes zoster" OR "malignancy" OR "cardiovascular events"]].

### *Selection Process and Data Extraction*

Three authors (PO, JL, SB) independently reviewed titles/abstracts of studies identified in the search, and excluded those that are clearly irrelevant. The full text of the selected articles was analyzed to determine whether it contained information on the topic of interest. Their reference lists (and those of relevant systematic reviews and meta-analyses) were hand-searched to identify further relevant publications.

The following information from each study was abstracted into a specially designed data extraction form: citation data, first author's last name, study design, underlying condition, number of patients, study duration, population characteristics, exposure definition (drug, dose, duration), concomitant treatments, and reported outcomes. Differences in data extraction were settled by consensus, referring back to the original article.

### *Meta-analysis*

Controlled studies were selected for meta-analysis. AEs, SAEs as well as AEs of interest were compared. RevMan software was used for this purpose (Version 5.3. Copenhagen. The Nordic Cochrane Center, the Cochrane Collaboration, 2014). Heterogeneity among studies was evaluated by means of Chi Square and I<sup>2</sup> tests. A random-effects model was used to give a more conservative estimate of the effect of individual therapies, allowing for any heterogeneity among studies. Outcome measures were described as Relative Risks (RR), with their corresponding 95% confidence intervals. Possible publication bias was assessed by means of the Egger test.

## **RESULTS**

### *Literature search results*

Bibliographic search yielded 973 citations from which 82 were finally included (Supplementary Figure 1). These studies comprised 53 studies conducted on RA patients,<sup>19-70</sup> 11 studies on patients with PSO,<sup>71-81</sup>

16 studies on IBD patients<sup>82-93</sup> and 2 studies on AS patients.<sup>94,95</sup> Forty three studies were finally included for meta-analysis: 29 studies on patients with RA, 5 studies on patients with PSO, 7 studies on patients with IBD and 2 on patients with AS.

Table 1 shows the main characteristics of included studies. Most of included studies (74.39%) were phase 2 or phase 3 RCTs, followed by observational cohort studies. Overall, 101925 subjects were evaluated and 66159 patients were exposed to a JAK inhibitor; 87.16% received tofacitinib. The studies included 86308 RA patients, 9311 PSO patients, 5987 IBD patients and 319 AS patients. Median time of JAK inhibitor exposure was 26 weeks (25-75%IQR: 12-52), with a wide variability in terms of treatment duration among studies. Considerable differences in terms of baseline characteristics of participants were seen among studies: RA studies included a higher proportion of female subjects who were also older when compared to IBD or PSO studies (Supplementary Table 1).

#### *AEs and SAEs*

Supplementary Table 2 shows the proportion of patients who experienced AEs and SAE. In the case of RCTs, these proportions are also described for comparator arms. Mean incidence rates of AEs and SAEs were 42.69 per 100 person-years and 9.98 per 100 person-years, respectively. Mean incidence rates of AEs and SAEs on patients exposed to a comparator were 124.41 per 100 person-years and 9.08 per 100 person-years, respectively.

AEs of special interest such as serious infections, herpes zoster infections, malignancy, NMSC and MACE were registered (Supplementary Table 3). Supplementary Table 4 also shows the incidence rates of the aforementioned AEs, both globally as well as classified according the type of JAK inhibitor. Supplementary Figures 2 and 3 show the forest plots describing the pooled analysis on AEs and SAEs respectively of controlled studies: 16318 patients were exposed to JAK inhibitors and 5797 to a comparator (4680 were exposed to placebo). The overall RR of AEs was 1.01 (0.97-1.06) whereas the RR of SAEs was 0.98 (0.83-1.15). We conducted a sensitivity analysis excluding those studies where the comparator was not placebo: the pooled RR for AEs and SAEs were 1.02 (0.97-1.07) and 0.92 (0.78-1.09), respectively. Pooled analysis of the risk of AEs and SAEs stratified by JAK inhibitors dosage and JAK inhibitor type were performed (Supplementary Table 5 and Supplementary Table 6).

#### *Mortality*

Sixty-eight studies reported mortality; 347 deaths were described, 331 (95.39%) of them occurred on patients exposed to JAK inhibitors. Overall mortality rate among patients exposed to JAK inhibitors was 0.37 per 100 person-years. Pooled analysis of 40 controlled studies assessing mortality showed a RR of 0.72 (0.40-1.28).



### *Serious Infections*

Serious infection was assessed in 51 studies (27 tofacitinib studies, 11 baricitinib studies, 7 filgotinib studies and 6 upadacitinib studies). These studies included 42646 patients exposed to JAK inhibitors. Global incidence rate was 3.36 per 100 patient-years, whereas its incidence rate among patients exposed to the comparator was 2.01. Pooled analysis of 35 controlled studies, which included 15207 patients, exposed to JAK inhibitors (Figure 1); RR was 1.03 (0.76-1.40); when considering only placebo-controlled studies, the RR was 1 (0.71-1.41).

### *Herpes Zoster Infection*

Herpes zoster infection was assessed in 44 studies (26 tofacitinib studies, 6 baricitinib studies, 5 filgotinib studies and 7 upadacitinib studies) and included 48093 patients exposed to JAK inhibitors. Its incidence rate was 2.11 per 100 patient-years (incidence rate among patients exposed to comparator: 1.23 per 100 patient-years). Figure 2 shows the pooled analysis of controlled studies – it comprised 23 studies that included 9572 patients exposed to JAK inhibitors. The RR of Herpes Zoster infection was significantly higher among patients who received JAK inhibitors [1.57 (1.04-2.37)]. The RR remained significant when analyzing placebo-controlled studies [1.72 (1.07-2.76)].

### *Malignancy and non-melanoma skin cancer (NMSC)*

NMSC was assessed in 23 studies (13 tofacitinib studies, 4 baricitinib studies, 1 filgotinib study and 5 upadacitinib studies), which included 26334 patients exposed to JAK inhibitors. Incidence rate of NMSC was 0.51 per 100 patient-years (incidence rate among patients exposed to comparator: 0.27 per 100 patient-years). Figure 3 shows the Forest plot of pooled analysis of 17 controlled studies (8524 patients exposed to JAK inhibitors); the RR of NMSC was 1.05 (0.47-2.35) [RR when excluding studies with an active comparator was 1.22 (0.50-2.95)].

Other malignancy was assessed in 33 studies (20 on tofacitinib studies; 5 on baricitinib studies 1 on filgotinib studies and 7 on upadacitinib studies), which included 32131 patients exposed to JAK inhibitors. Its incidence rate was 0.75 per 100 patient-years (incidence rate among patients exposed to comparator: 0.18 per 100 patient-years). Pooled analysis of 21 controlled studies (9916 patients exposed to JAK inhibitors) is shown in Figure 4: the RR of malignancy was 1.39 (0.68-2.85) [RR when considering only placebo-controlled studies was 1.50 (0.68-3.32)].

### *Major cardiovascular events (MACE)*

Thirty studies assessed MACE on 32765 patients exposed to JAK inhibitors (17 tofacitinib patients; 4 baricitinib patients; 3 filgotinib patients and 6 upadacitinib patients). Its incidence rate was 0.67 per 100 patient-years (incidence rate among patients exposed to comparator: 0.45 per 100 patient-years). Pooled analysis of 22 controlled studies (10701 patients exposed to JAK inhibitors) is shown in Figure 5: the RR of MACE was 1.07 (0.56-2.03) [RR when including only placebo-controlled studies was 1.09 (0.54-2.21)].

### *Venous thrombotic events*

Deep-vein thrombosis and pulmonary embolism was assessed by 17 studies (7 tofacitinib studies; 3 upadacitinib studies; 3 filgotinib studies and 4 baricitinib studies), which included 24128 patients exposed to JAK inhibitors. Its incidence rate was 0.31 per 100 patient-years. Figure 6 shows the pooled analysis of the 10 controlled studies involving 5143 patients exposed to JAK inhibitors: the RR was 0.90 (0.32-2.54).

## **DISCUSSION**

In this systematic review we reviewed for the first time available safety data from both interventional and observational studies of the JAK inhibitors tofacitinib, filgotinib, upadacitinib and baricitinib in four IMIDs: IBD, RA, PSO, and AS. Evidence regarding occurrence of AEs, SAEs, and AEs of special interest (i.e. infections, serious infections, herpes zoster, malignancy and MACE) from 67 studies were synthesized. To the best of our knowledge, this is the first systematic review evaluating the risk profile of JAK inhibitors in a wide spectrum of IMIDs.

Drug pipeline in IBD is rapidly increasing; with new compounds with different targets expected to become available in a foreseeable future, thus treatment algorithms will soon need to be updated.<sup>5</sup> The recent approval of tofacitinib in UC has opened the therapeutic avenue of JAK inhibition in IBD.<sup>8</sup> Tofacitinib has shown considerable efficacy in both biologic-naïve and –experienced UC patients,<sup>87</sup> and is increasingly used in the clinic worldwide. However, defining the safety profile is paramount, since the risk/benefit ratio of JAK inhibition in IBD and other immune-mediated conditions will influence patterns of use.

Overall, AE in RCTs ranged from 10.36 to 81.94%, both in placebo and intervention arms. Most of them were mild, and included worsening of the underlying condition, probably showing lack of efficacy. The occurrence of SAEs showed significant heterogeneity, ranging from 0 to 28.6%.

Given the wide spectrum immunosuppressive effects of JAK inhibition, concerns about infections, serious infections, as well as risk of malignancy have arisen. Theoretically, selectivity of JAK isoform inhibition

could limit AEs and infections, although this selectivity is dose and tissue dependent and it could be lost with increasing doses.<sup>96</sup>

The JAK-STAT pathway has several key functions in inflammatory cytokines and immune response,<sup>4</sup> hence the risk of infections with the use of JAK inhibitors in IMiDs appears to be considerable.<sup>97</sup> Most of the serious infections were of bacterial origin, including community-acquired pneumonia, urinary tract infections and skin infections. On the other hand, JAK inhibition appears to be associated with a particular high risk of viral infections, especially of herpes zoster. Patients with some IMiDs intrinsically have an increased risk of herpes zoster infection.<sup>98,99</sup> Additionally disease-modifying agents, immunosuppressants, and steroids increase the risk further,<sup>100–102</sup> and among biologics, non-anti-TNF agents appear to have a higher risk than anti-TNF agents. According to Marra et al, the pooled risk of herpes zoster among patients with IMiDs exposed to non anti-TNF $\alpha$  agents such as abatacept, tocilizumab, ustekinumab or natalizumab was significantly higher versus placebo [RR 2.19 (1.20-4.02)], whereas this risk did not achieve a significant difference versus placebo when considering anti-TNF $\alpha$  biologics [RR1.28 (0.69-2.40)].<sup>102</sup> Regarding the risk of herpes zoster with JAK inhibitors, the largest evidence comes from the use of tofacitinib, but it appears to be a class effect, with a clear dose dependent effect.<sup>102</sup> Additional factors that influence the risk, include increasing age, combination with steroids and methotrexate, and Asian population.<sup>103</sup> Although the exact pathogenic mechanism of the increased risk of herpes zoster in this context is unknown,<sup>104</sup> it is correlated to impairment in cell-mediated immunity.<sup>97</sup> Notably most of the cases of herpes zoster associated with the use of JAK inhibitors are non-complicated and with single dermatome involvement.<sup>103</sup> Among the AEs of special interest that were assessed in our meta-analysis, herpes zoster infection was significantly increased in patients receiving JAK inhibitors when compared to other therapies and/or placebo. Additionally, in subgroup analysis we found a higher RR of herpes zoster among patients exposed to tofacitinib or baricitinib versus filgotinib or upadacitinib. Although this is merely a qualitative comparison, this difference could be related to the fact that both filgotinib and upadacitinib are selective JAK1 inhibitors, whereas tofacitinib is a JAK1/JAK3 inhibitor and baricitinib a JAK 1/JAK2 inhibitor. Further studies are needed to determine if JAK isoform selectivity affects the risk of herpes zoster.

JAK inhibition has been associated with alterations of serum lipids profile and the possible occurrence of MACE. However, changes seen in cholesterol levels are small and transient, with the total/HDL cholesterol ratio usually stable, and with an overall low incidence of MACE in RCTs and observational studies.<sup>105,106</sup> On the other hand, the risk of thromboembolic events with the use of JAK inhibitors has been recently highlighted.<sup>107,108</sup> In an ongoing phase 3b/4 study (A3921133, NCT02092467) the safety of tofacitinib 5 mg bid and 10 mg bid versus adalimumab and etanercept in RA patients older than 50 years old and with  $\geq 1$  cardiovascular risk factor is being evaluated. Preliminary results showed a 5-fold increase in the risk of pulmonary thromboembolism with tofacitinib 10 mg bid compared with the anti-TNF arms, as well as an increase in the mortality risk. These findings prompted a mandatory dose reduction to

tofacitinib 5 mg bid, and a recommendation of EMA to practitioners to adhere to the 5 mg bid dose approved for RA.<sup>107</sup> Additionally, results of RCTs of baricitinib in RA pointed out a safety signal of increased risk of thromboembolic events, especially with at 4 mg qd.<sup>109</sup> Based on this finding the FDA only approved baricitinib at 2mg qd for RA in the United States.<sup>12</sup> Although appears to be dose dependent, currently is unknown whether this risk is modulated by JAK selectivity or by disease-specific factors related exclusively to RA. A recently published post hoc analysis of the OCTAVE programme showed that venous thromboembolism events occurred in five UC patients exposed to tofacitinib 10 mg bid (one patient had deep vein thrombosis and four had pulmonary embolism; all in the open label extension phase).<sup>110</sup> Of note, patients who developed these events had at least one risk factor for venous thromboembolism.<sup>110</sup> However, we did not find an increased risk of thromboembolic events among patients exposed to JAK inhibitors on our meta-analysis. This finding could be explained by the fact that our meta-analysis included all patients exposed to JAK inhibitors, and not only patients with risk factors for thromboembolic events. Additionally, active inflammation may cause a hypercoagulation state; hence the risk in patients who received placebo in controlled trials might have been balanced due to active disease. As observed by Sandborn et al, four patients developed thromboembolic events in the induction and maintenance phase of the program, all of which received placebo and none tofacitinib.<sup>110</sup> Furthermore, the type of studies published so far – and thus included in our systematic review and meta-analysis – include a majority of controlled trials with a relatively short time of follow up. Uncontrolled observational cohort studies assess the risk of long-term adverse events, but they lack of a comparator and as a consequence they are ineligible for meta-analysis. Although further evidence is needed, caution should be taken if a JAK inhibitor is considered as a therapeutic alternative among patients with known risk factors for thromboembolic events and/or MACE.

The present study has several limitations. First, there are other JAK inhibitors than the four selected for this systematic review. These four compounds were selected because tofacitinib and baricitinib are already FDA approved (tofacitinib for RA, psoriatic arthritis and UC; baricitinib for RA) and are relatively non-selective (tofacitinib inhibits JAK3 and JAK 1, and baricitinib JAK 1 and JAK 2), compared with upadacitinib – which has been recently approved by the FDA for RA - and filgotinib which show JAK1 selectivity. Other JAK inhibitors that are currently in development for IMIDs include peficitinib (pan-JAK inhibitor, approved in Japan for moderate-to-severe RA, evaluated for RA, psoriasis, and UC), decernotinib (JAK3 and JAK1 inhibitor, evaluated for RA), and TD-1473 (intestinally restricted pan-JAK inhibitor, evaluated for UC and CD). Second, the majority of studies were conducted in RA, followed by psoriasis, IBD and AS. Certainly there are disease-specific considerations that prevent from making generalizations of the safety profile of these compounds. Third, a significant heterogeneity was seen between studies, regarding design, time of drug exposure, follow-up, and characteristic of patients. Additionally, definitions of AEs and SAEs might have differed in observational studies, compared to RCTs where a standardized definition is used. This has probably influenced in the marked difference in reported

rates of some AE, such as SAEs. Fourth, most of the included studies were RCTs, and selection bias due to strict inclusion criteria in these studies may lead to differences in AEs in the real world setting. What is more, the time frame of RCTs usually does not permit correct evaluation of AEs that usually require time to develop, such as malignancy.

In conclusion, the present systematic review shows a varied incidence of AEs among patients exposed to JAK inhibitors. Herpes zoster and serious infections seem to be rather common among these patients, whereas the incidence of malignancy and MACE seem to be low, and relation to therapy remains to be confirmed. More studies with long follow-up and in the real world setting, in the different conditions will be needed to fully elucidate the safety profile of the different JAK inhibitors.

#### FIGURE LEGENDS

Figure 1: Pooled analysis of serious infections in controlled studies.

Figure 2: Pooled analysis of herpes zoster in controlled studies.

Figure 3: Pooled analysis of non-melanoma skin cancer in controlled studies.

Figure 4: Pooled analysis of other malignancies in controlled studies.

Figure 5: Pooled analysis of major cardiovascular events in controlled studies.

Figure 6: Pooled analysis of thromboembolic in controlled studies.

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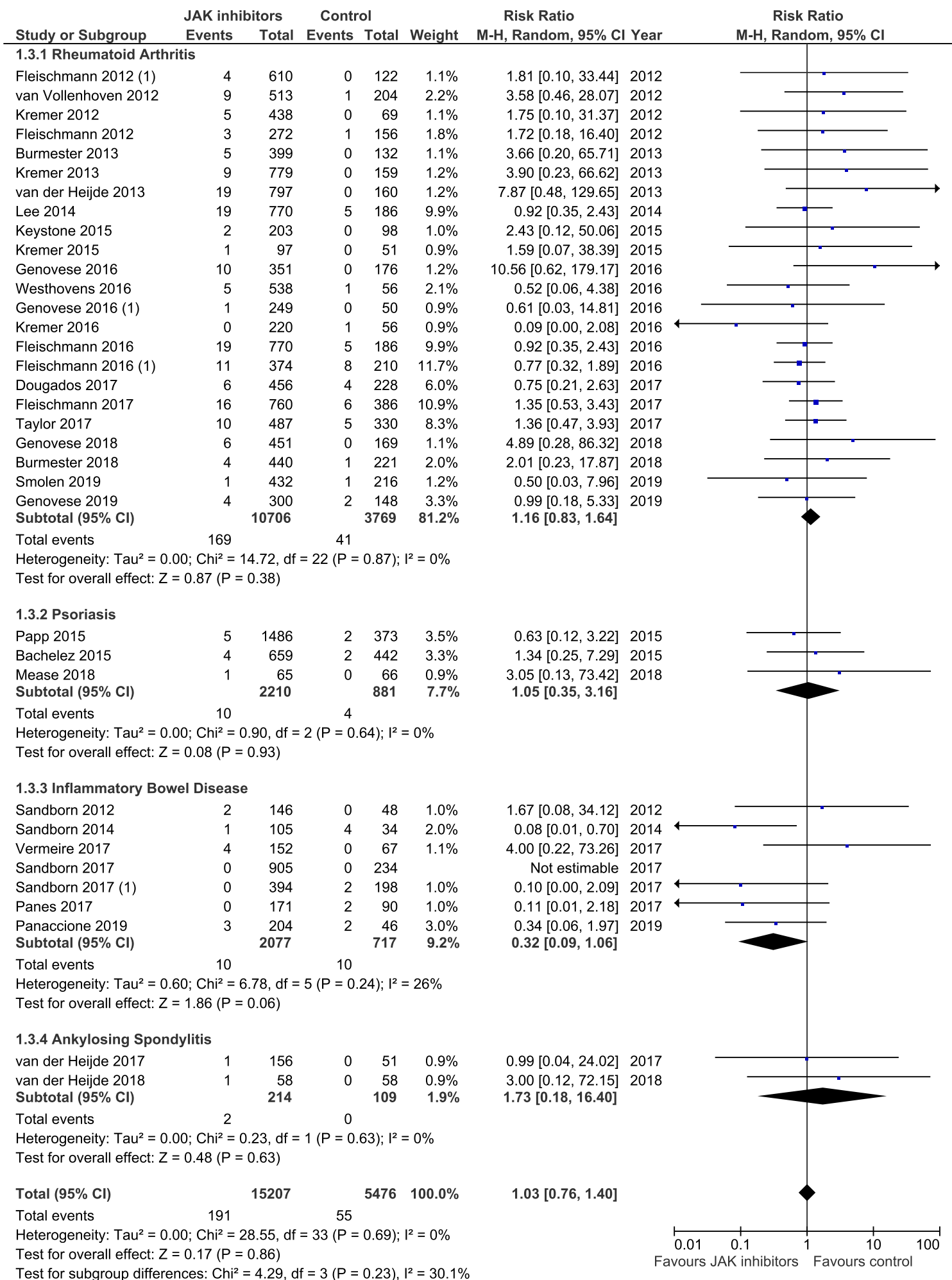
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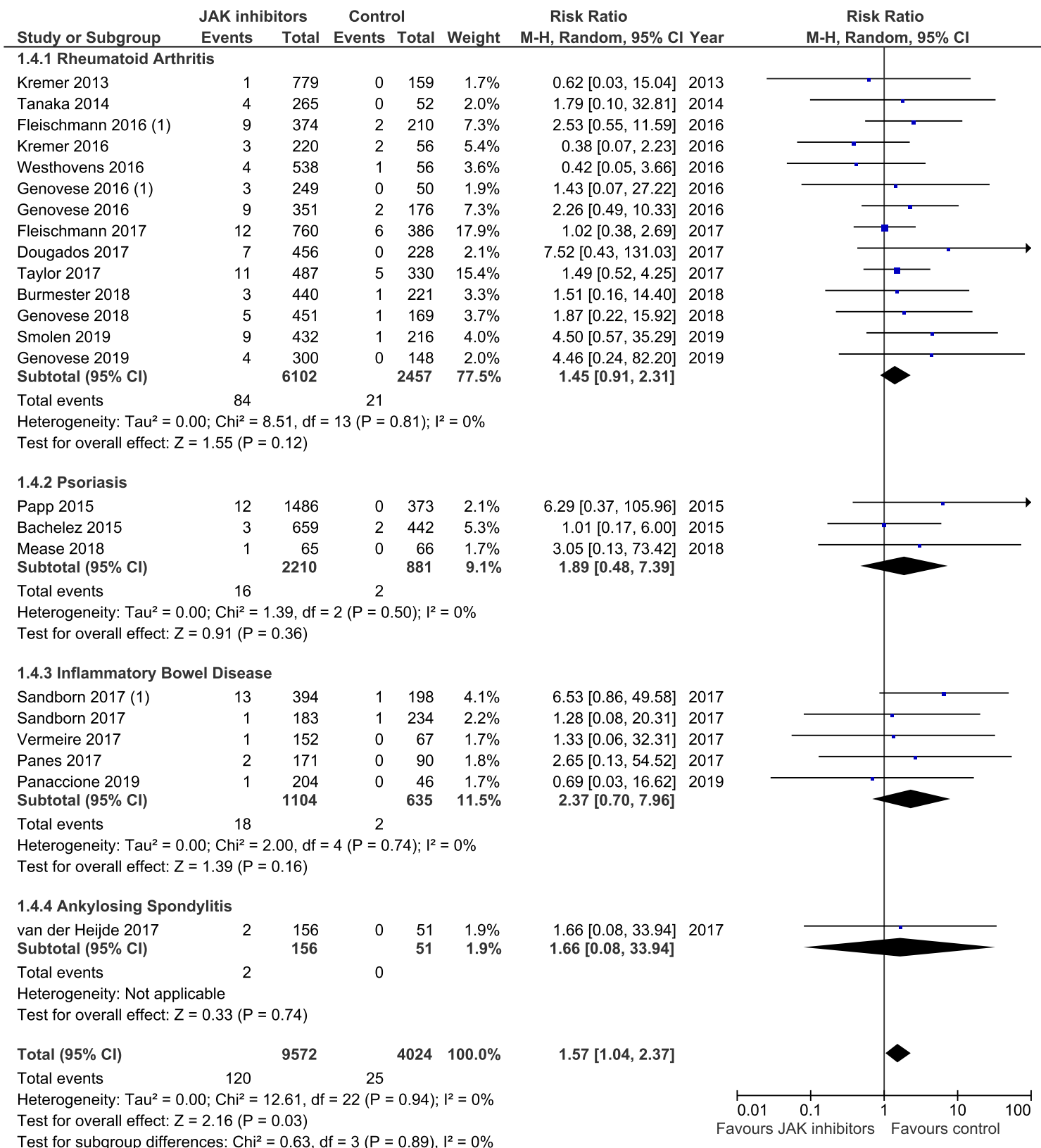
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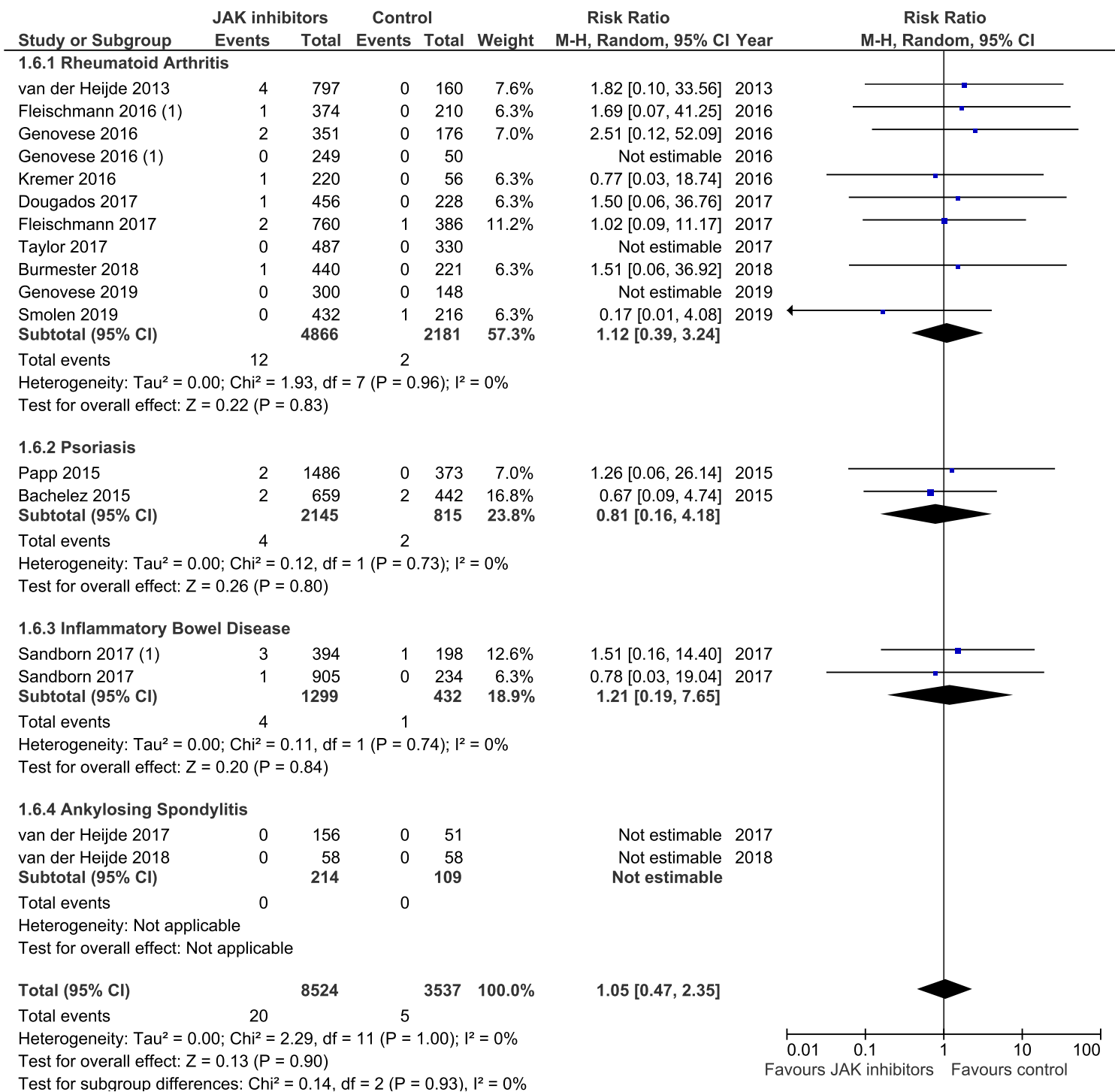
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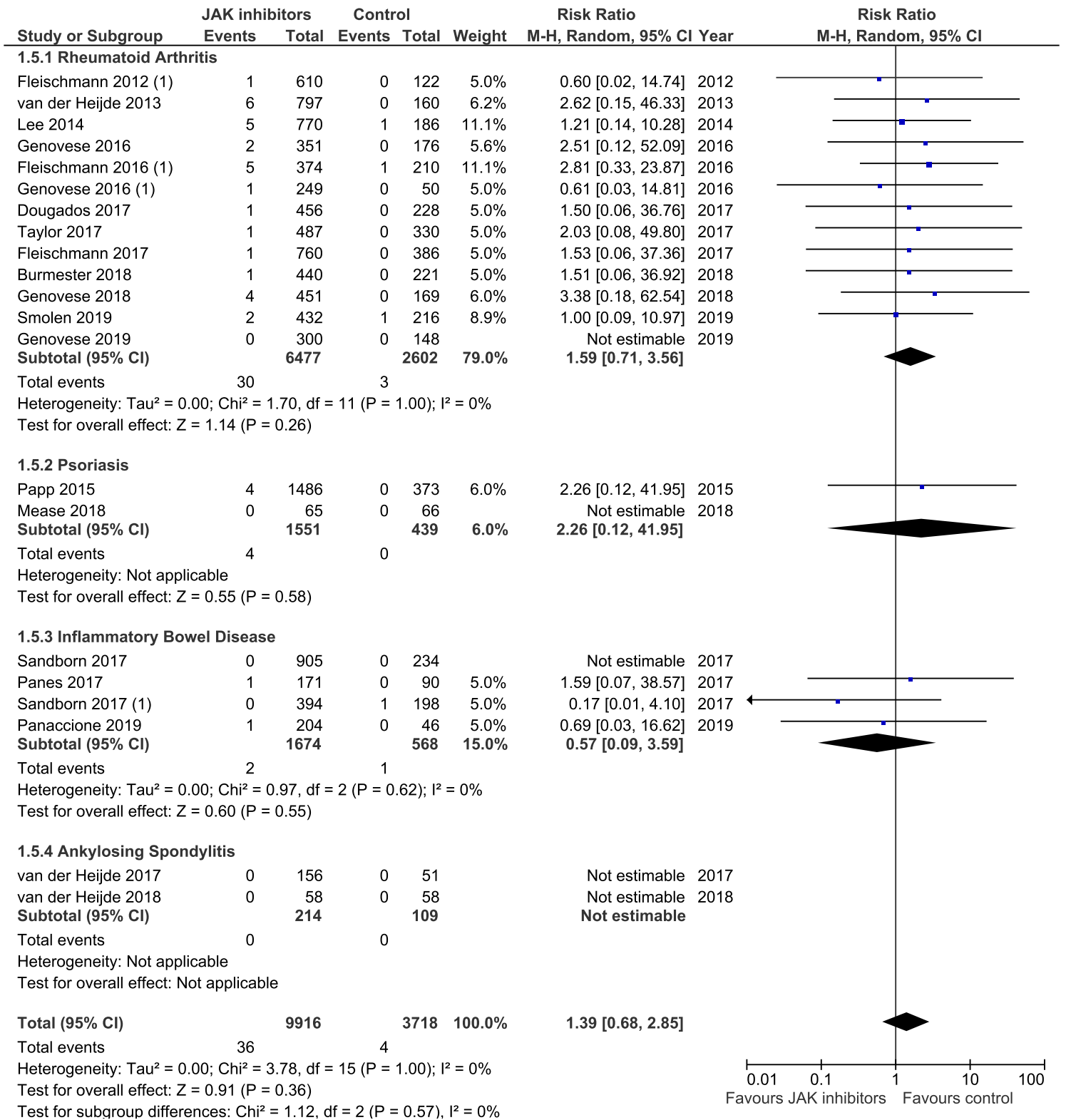
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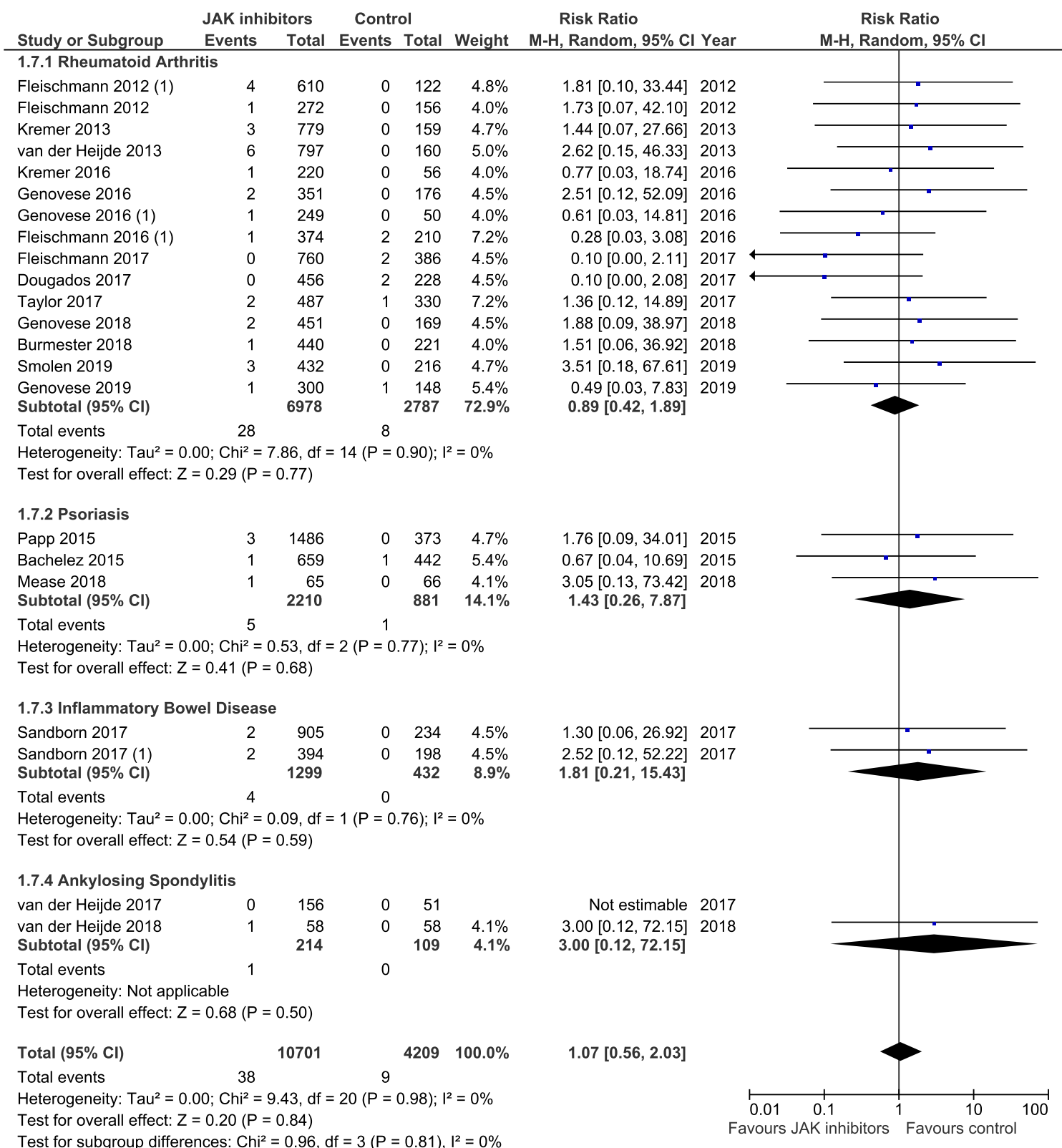












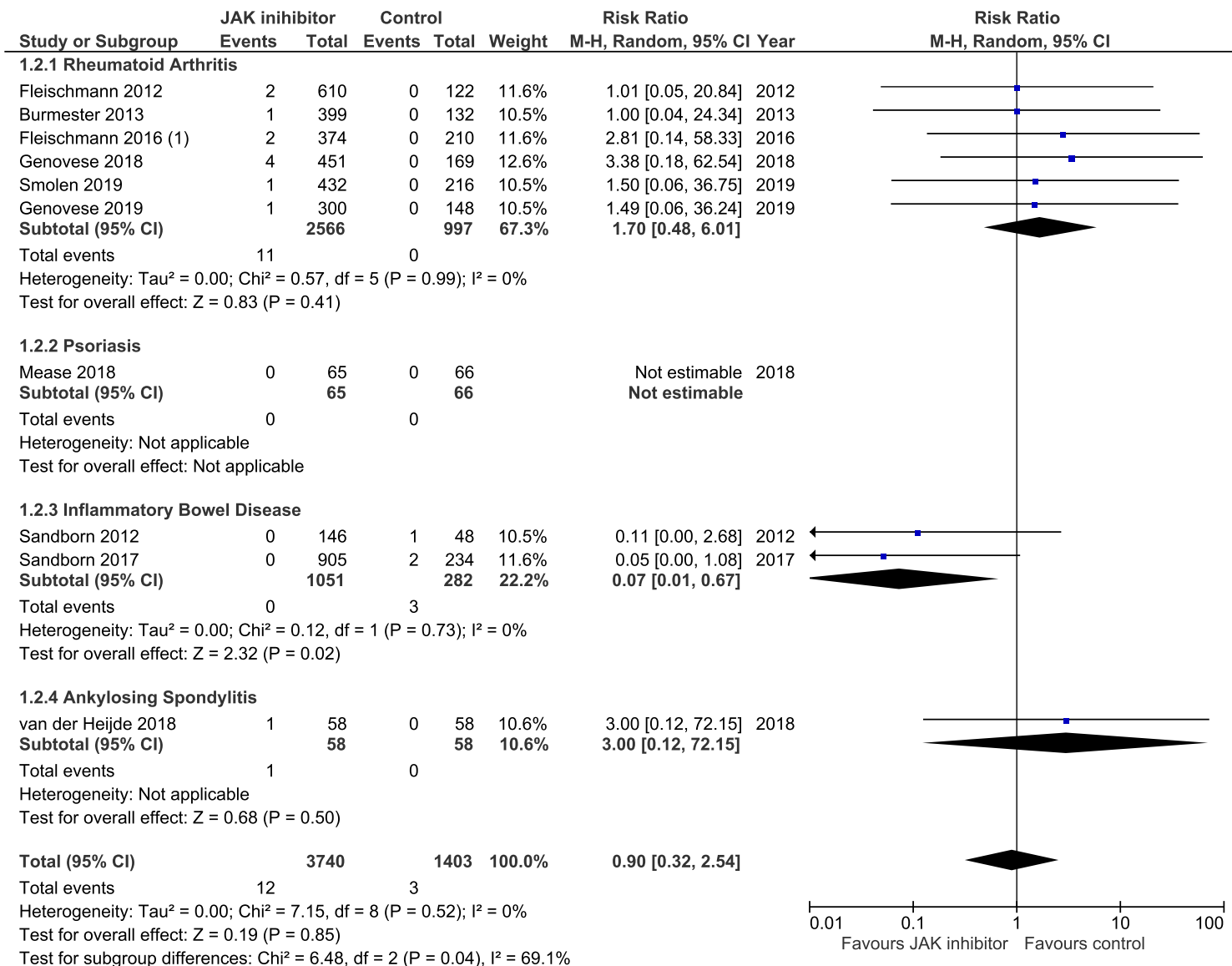


Table 1. Main characteristics of included studies

Author	Study Design	N of patients	Study Duration	Exposure
<b>Rheumatoid Arthritis</b>				
<b>Kremer 2009</b>	Phase 2a, randomized, double-blind, placebo-controlled, parallel-group study	264	8 weeks	Tofacitinib 5 mg BID; Tofacitinib 15 mg BID; Tofacitinib 30 mg BID; placebo
<b>Cohen 2010</b>	Phase 1, open-label study	12	9 days	Tofacitinib 30 mg
<b>Tanaka 2011</b>	Phase 2, randomized, double-blind, placebo-controlled, parallel-group study	136	12 weeks	Tofacitinib 1 mg BID; Tofacitinib 3 mg BID; Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo
<b>Fleischmann 2012</b>	Phase 2b, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study	384	24 weeks	Tofacitinib 1 mg BID; Tofacitinib 3 mg BID; Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; Tofacitinib 15 mg BID; Adalimumab 40 mg EOW; Placebo
<b>Fleischmann 2012</b>	Phase 3, randomized, double-blind, placebo-controlled, parallel group study	611	26 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID
<b>Kremer 2012</b>	Phase 2b, randomized, double-blind, placebo-controlled study	507	24 weeks	Tofacitinib 1 mg BID; Tofacitinib 3 mg BID; Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; Tofacitinib 15 mg BID; Tofacitinib 20 mg BID; Placebo
<b>van Vollenhoven 2012</b>	Phase 3, randomized, double-blind, placebo-controlled study	717	52 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; Adalimumab 40 mg EOW; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID
<b>Burmester 2013</b>	Phase 3, randomized, double-blind, placebo-controlled, parallel-group study	399	26 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID
<b>Kremer 2013</b>	Phase 3, randomized, double-blind, placebo-controlled study	792	52 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID
<b>Mc Inness 2013</b>	Phase 2, open-label for Tofacitinib and blinded for Atorvastatin	111	12 weeks	Tofacitinib 10 mg BID
<b>van der Heijde 2013</b>	Phase 3, randomized, double-blind, parallel-group, placebo-controlled study	797	26 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID
<b>Lee 2014</b>	Phase 3, randomized, double-blind, parallel group study	956	96 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; MTX
<b>Sonomoto 2014</b>	Phase 2/3 randomized, double-blind, placebo-controlled with further open-label extension study	44	52 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID
<b>Tanaka 2014</b>	Phase 2, randomized, double-blind, placebo-	318	12 weeks	Tofacitinib 1 mg BID; Tofacitinib 3 mg BID; Tofacitinib 5 mg BID; Tofacitinib 10

	controlled, parallel group study			mg BID; Tofacitinib 15 mg BID; placebo
<b>Wollenhaupt 2014</b>	Open-label, long-term extension study	4102	76 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID
<b>Keystone 2015</b>	Phase 2b, double-blind, placebo-controlled study	301	24 weeks	Baricitinib 1 mg QD; Baricitinib 2 mg QD; Baricitinib 4 mg QD; Baricitinib 8 mg QD; placebo
<b>Kremer 2015</b>	Phase 1, randomized, placebo-controlled, parallel group study	148	12 weeks	Tofacitinib 10 mg BID; placebo
<b>Curtis 2016</b>	Retrospective cohort study	2526	313 weeks	Tofacitinib at any dose
<b>Fleischmann 2016</b>	Phase 3, randomized, double-blind, parallel-group study	956	24 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo
<b>Fleischmann 2016</b>	Phase 3, randomized, double-blind, active-controlled studies	584	52 weeks	MTX; Baricitinib 4 mg QD; Baricitinib 4 mg QD + MTX
<b>Genovese 2016</b>	Phase 2b, randomized, placebo-controlled study	299	12 weeks	Upadacitinib 3 mg BID; Upadacitinib 6 mg BID; Upadacitinib 12 mg BID; Upadacitinib 18 mg BID; Upadacitinib 24 mg QD; Placebo
<b>Genovese 2016</b>	Phase 3, randomized, double-blind, placebo-controlled study	527	24 weeks	Baricitinib 2 mg QD; Baricitinib 4 mg QD; placebo
<b>Kavanaugh 2016</b>	Phase 2b, randomized, placebo-controlled study	283	24 weeks	Filgotinib 50 mg QD; Filgotinib 100 mg QD; Filgotinib 200 mg QD; placebo
<b>Kremer 2016</b>	Phase 2b, randomized, placebo-controlled study	276	12 weeks	Upadacitinib 3 mg BID; Upadacitinib 6 mg BID; Upadacitinib 12 mg BID; Upadacitinib 18 mg BID; Placebo
<b>Mohamed 2016</b>	Phase 1, randomized, placebo-controlled study	114	4 weeks	Upadacitinib 6 mg BID; Upadacitinib 12 mg BID; Upadacitinib 2 4mg BID; Placebo
<b>Tanaka 2016</b>	Phase 2b, randomized, double-blind, placebo-controlled study	145	12 weeks	Baricitinib 1 mg QD; Baricitinib 2 mg QD; Baricitinib 4 mg QD; Baricitinib 8 mg QD; placebo
<b>Westhovens 2016</b>	Phase 2b, randomized, placebo-controlled study	594	24 weeks	Filgotinib 50 mg QD; Filgotinib 100 mg QD; Filgotinib 200 mg QD; Filgotinib 50 mg BID; Filgotinib 100 mg BID; Filgotinib 200 mg BID; placebo
<b>Yamanaka 2016</b>	Open-label, long-term extension study	486	288 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID
<b>Dougados 2017</b>	Phase 3, randomized, placebo-controlled study	684	24 weeks	Baricitinib 2 mg QD; Baricitinib 4 mg QD; Placebo
<b>Fleischmann 2017</b>	Phase 3/4, head to head, non-inferiority, randomized, controlled study	1146	52 weeks	Tofacitinib 5 mg BID; tofacitinib 5 mg BID + MTX; adalimumab 40 mg EOW + MTX
<b>Iwamoto 2017</b>	Prospective cohort study	70	24 weeks	Tofacitinib at any dose
<b>Keystone 2017</b>	Open-label, long-term extension study	133	128 weeks	Previous exposure to Baricitinib or Placebo, then OLE with Baricitinib 4 mg QD
<b>Mimori 2017</b>	Post-marketing study on safety	2882	24 weeks	Tofacitinib at any dose
<b>Tanaka 2017</b>	Phase 2b, randomized, placebo-controlled study	142	64 weeks	Baricitinib 1 mg QD; baricitinib 2 mg QD; baricitinib 4 mg QD; baricitinib 8 mg QD or placebo. After 12 weeks, baricitinib 4 mg or baricitinib 8 mg QD
<b>Taylor 2017</b>	Phase 3, randomized, double-blind, placebo and active-controlled, parallel –	1305	52 weeks	Baricitinib 4 mg QD; Placebo then Baricitinib 4 mg QD; Adalimumab 40 mg EOW

<b>Vanhoutte 2017</b>	group study Phase 2a, randomized, placebo-controlled study	127	4 weeks	Filgotinib 30 mg QD; filgotinib 75 mg QD; filgotinib 150 mg QD; filgotinib 300 mg QD; filgotinib 100 mg QD; filgotinib 200 mg QD; placebo
<b>Avila Machado 2018</b>	Retrospective cohort study	21832 (164 treated w/Tofacit inib)	260 weeks	All patients treated with either MTX, DMARD, Tofacitinib
<b>Burmester 2018</b>	Phase 3, randomized, double-blind, placebo- controlled study	661	12 weeks	Upadacitinib 15 mg QD; Upadactinib 30 mg QD; placebo
<b>Cohen 2018</b>	Post-marketing surveillance study	34223	156 weeks	Tofacitinib 5 mg BID
<b>Desai 2018</b>	Retrospective cohort study	2905	192 weeks	Tofacitinib at any dose
<b>Genovese 2018</b>	Phase 3, randomized, double-blind, placebo- controlled study	499	24 weeks	Weeks 0-12: Upadacitinib 15 mg QD; Upadacitinib 30 mg QD; Placebo. Weeks 12-24: Upadacitinib 15 mg QD; Upadacitinib 30 mg QD
<b>Takeuchi 2018</b>	Phase 3, randomized, double-blind, placebo- controlled trial with open- label extension study	559	48 weeks	Baricitinib 4 mg QD; Baricitinib 2 mg QD. After having received Baricitinib 4 mg QD for >15 months
<b>Tanaka 2018</b>	Phase 3, randomized, double-blind, double- dummy, parallel group, non- inferiority study	209	12 weeks	Tofacitinib MR 11 mg QD; Tofacitinib 5 mg BID
<b>Yun 2018</b>	Retrospective cohort study	2155	24 weeks	Tofacitinib at any dose
<b>Curtis 2019</b>	Retrospective cohort study	8030	260 weeks	Tofacitinib at any dose
<b>Fleischmann 2019</b>	Long-term extension study	423	24 weeks	Baricitinib 4 mg QD
<b>Genovese 2019</b>	Phase 3, randomized, double-blind, placebo- controlled study	448	24 weeks	Filgotinib 200 mg QD; Filgotinib 100 mg QD; placebo
<b>Smolen 2019</b>	Phase 3, randomized, double-blind, double- dummy study	648	14 weeks	Upadacitinib 15 mg QD; Upadacitinib 30 mg QD; MTX
<b>Takeuchi 2019</b>	Long-term extension study	559	48 weeks	Baricitinib 2 mg QD; Baricitinib 4 mg QD
<b>Tanaka 2019</b>	Open-label study after phase 3 double-blind, placebo-controlled trial and follow up of baricitinib- rescued patients	694	24 weeks	Baricitinib 4 mg QD
<b>Tanaka 2019</b>	Phase 3, randomized, double-dummy, parallel- group study	209	12 weeks	Tofacitinib 5 mg BID; Tofacitinib modified-release 11 mg QD
<b>van der heijde 2019</b>	Phase 3, randomized, placebo-controlled study	797	104 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; Placebo then Tofacitinib 5 mg BID; Placebo then Tofacitinib 10 mg BID
<b>Wollenhaupt 2019</b>	Open-label, long-term extension study	4481	456 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID
<b>Psoriasis Papp 2012</b>	Phase 2b, randomized, double-blind, parallel- group, placebo-controlled study	197	16 weeks	Tofacitinib 2 mg BID; Tofacitinib 5 mg BID; Tofacitinib 15 mg BID; placebo
<b>Ports 2013</b>	Phase 2a, randomized,	71	4 weeks	Topical Tofacitinib 2%; placebo

	double-blind, vehicle-controlled, parallel-group study			
<b>Bissonnette 2014</b>	Phase 3, randomized, double-blind, parallel-group, treatment withdrawal and re-treatment study	674	56 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID
<b>Bachelez 2015</b>	Phase 3, randomized, double-dummy, placebo-controlled, parallel-group study	1106	16 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; Etanercept 50 mg twice/week; placebo
<b>Papp 2015</b>	Phase 3, double-blind, placebo-controlled study	1859	16 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo
<b>Asahina 2016</b>	Phase 3, randomized, double-blind study	99	52 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID
<b>Papp 2016</b>	Phase 3, randomized, double-blind, placebo-controlled studies and open-label extension study	1770	52 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID
<b>Papp 2016</b>	Phase 2b, randomized, double-blind, placebo-controlled study	271	24 weeks	Baricitinib 2 mg QD; Baricitinib 4 mg QD; Baricitinib 8 mg QD; Baricitinib 10 mg QD; placebo
<b>Zhang 2017</b>	Phase 3, randomized, placebo-controlled study	266	52 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID
<b>Mease 2018</b>	Phase 2, randomized, placebo-controlled study	131	16 weeks	Filgotinib 200 mg QD; placebo
<b>Valenzuela 2018</b>	Open-label, long-term extension study	2867	142 weeks	Tofacitinib 10 mg BID
<b>Inflammatory Bowel Disease</b>				
<b>Sandborn 2012</b>	Phase 2, randomized, double-blind, placebo-controlled study	194	12 weeks	Tofacitinib 0.5 mg BID; Tofacitinib 3 mg BID; Tofacitinib 10 mg BID; Tofacitinib 15 mg BID; placebo
<b>Sandborn 2014</b>	Phase 2, randomized, double-blind, placebo-controlled study	239	8 weeks	Tofacitinib 1 mg BID; Tofacitinib 5 mg BID; Tofacitinib 15 mg BID; placebo
<b>Panes 2017</b>	Phase 2b randomized placebo-controlled study	279	26 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo. Those on clinical response or remission after 8 weeks = Tofacitinib 5 mg BID; Tofacitinib 10 mg BID
<b>Sandborn 2017</b>	Phase 3, randomized, double-blind, placebo-controlled studies	1139	8 weeks	Tofacitinib 10 mg BID; placebo
<b>Sandborn 2017</b>	Phase 3, randomized, double-blind, placebo-controlled study	593	52 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo
<b>Sandborn 2017</b>	Phase 2, randomized, double-blind, placebo-controlled study	220	16 weeks	Upadacitinib 3 mg BID; Upadacitinib 6 mg BID; Upadacitinib 12 mg BID; Upadacitinib 24 mg BID; Upadacitinib 24 mg QD; Placebo
<b>Vermeire 2017</b>	Phase 2, randomized, placebo-controlled study	174	20 weeks	Filgotinib 200 mg QD; Placebo for 10 weeks. Then, Filgotinib 100 mg QD; Filgotinib 200 mg QD; placebo
<b>Lichtenstein 2018</b>	Phase 3, open-label, long-term extension	944	232 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID



	study			
<b>Rubin 2018</b>	Post hoc analysis of Phase 3 randomized, placebo-controlled, double-blind study	22	8 weeks	Tofacitinib 15 mg BID
<b>Sandborn 2018</b>	Phase 2b, double-blind, placebo-controlled, dose-ranging study	250	8 weeks	Upadacitinib 7.5 mg QD; Upadacitinib 15 mg QD; Upadacitinib 30 mg QD; Upadacitinib 45 mg QD; Placebo
<b>Panes 2018</b>	Phase 2, randomized, double-blind study	178	36 weeks	Upadacitinib 3 mg BID; Upadacitinib 12 mg BID; Upadacitinib 24 mg QD
<b>Deepak 2019</b>	Retrospective cohort study	140	11 weeks	Tofacitinib 10 mg BID
<b>Panaccione 2019</b>	Phase 2b, randomized, double-blind study	250	8 weeks	Upadacitinib 7.5 mg QD; Upadacitinib 15 mg QD; Upadacitinib 30 mg QD; Upadacitinib 45 mg QD; placebo
<b>Panes 2019</b>	Phase 2b, open-label extension study	150	52 weeks	Tofacitinib 5 mg BID; Tofacitinib 10 mg BID
<b>Weisshof 2019</b>	Retrospective cohort study	58	52 weeks	Tofacitinib 5 mg BID or 10 mg BID
<b>Ankylosing Spondylitis</b>				
<b>van der Heijde 2017</b>	Phase 2, randomized, placebo-controlled study	207	16 weeks	Tofacitinib 2 mg BID; Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo
<b>van der Heijde 2018</b>	Phase 2, randomized, double-blind, placebo-controlled study	112	12 weeks	Filgotinib 200 mg QD; placebo

BID: *bis in die*

DMARD: Disease-Modifying Antirheumatic Drug

EOW: Every Other Week

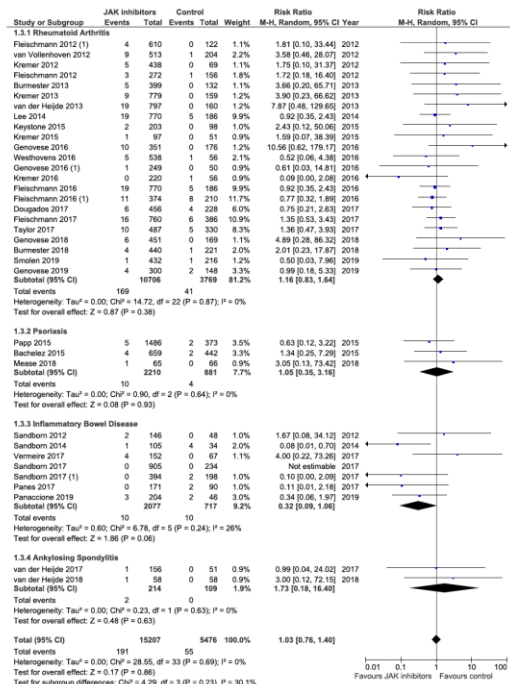
MTX: Methotrexate

QD: *quaque die*

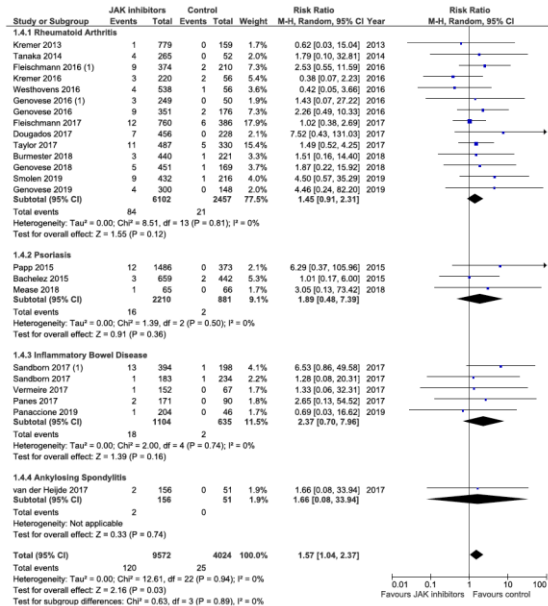
# **Safety of Janus Kinase Inhibitors in Patients with Inflammatory Bowel Diseases or Other Immune-mediated Diseases: a Systematic Review and Meta-Analysis**

Pablo Olivera MD; Juan Lasa MD, MSc; Stefanos Bonovas MD, PhD;  
Silvio Danese MD, PhD; Laurent Peyrin-Biroulet MD, PhD

# Pooled analysis of serious infections



# Pooled analysis of herpes zoster



Gastroenterology