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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

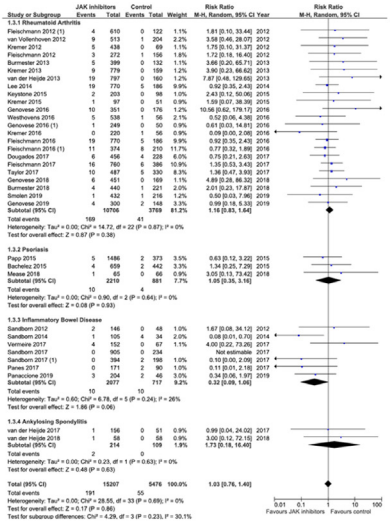
**Pablo A. Olivera**,[1,*] **Juan S. Lasa**,[1,2,*] Stefanos Bonovas,[3,4] Silvio Danese,[3,4] and Laurent Peyrin-Biroulet[5]

*[1]Gastroenterology Section, Department of Internal Medicine, Centro de Educación Médica e Investigaciones Clínicas (CEMIC), Buenos Aires, Argentina; [2]Gastroenterology Department, Hospital Británico de Buenos Aires, Argentina; [3]Department of Biomedical Sciences, Humanitas University, Milan, Italy; [4]IBD Center, Department of Gastroenterology, Humanitas Clinical and Research Center, Milan, Italy; and [5]INSERM NGERE and Department of Hepatogastroenterology, Nancy University Hospital, Lorraine University, Vandoeuvre-lés-Nancy, France*

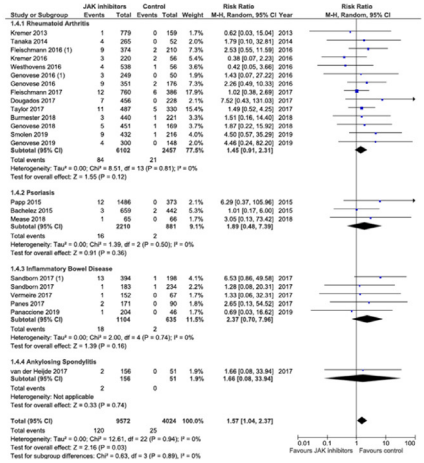


This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e18. Learning Objective: Upon completion of this CME activity, successful learners will be able to identify the safety profile of Janus Kinases (JAK) inhibitors in patients with Inflammatory Bowel Disease and other Immune-mediated Diseases.

Pooled analysis of serious infections



Pooled analysis of herpes zoster



Gastroenterology

**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 66,159 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 with patients given placebo or active

comparator (relative risk 0.72; 95% confidence interval 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% confidence interval 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.

*Keywords:* NMSC; IBD; Immunosuppression; Small Molecule.

**WHAT YOU NEED TO KNOW**

BACKGROUND AND CONTEXT

Inhibitors of Janus kinases (JAKs) are being developed for treatment of inflammatory bowel diseases and other immune-mediated diseases, but there are safety concerns.

NEW FINDINGS

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.

LIMITATIONS

Most studies evaluated the safety profile of tofacitinib and in patients with rheumatoid arthritis; further analyses of the safety of JAK inhibitors are needed.

IMPACT

JAK inhibitor therapy increases the risk of herpes zoster infection, but not other adverse events.

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

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.[6] These compounds can block several cytokines and inflammatory pathways simultaneously, thus inducing immunosuppression.[7] Tofacitinib has been the first JAK inhibitor to receive regulatory approval for the treatment of UC,[8] but there are currently other JAK inhibitory compounds in late stage of development in IBD, namely upadacitinib and filgotinib. 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).[9] Tofacitinib has been approved by the US Food and Drug Administration (FDA) for the treatment of moderately to severely active RA since late 2012,[10] and since 2017 for the treatment of active psoriatic arthritis.[11] Baricitinib has received regulatory approval from the FDA and European Medicines Agency for the treatment of moderately to severely active RA.[12,13] 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, particularity from RA, such as treat to target, tight control, early intervention, and disease-modifying interventions.[14] In addition, 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.[15] Finally, previous systematic reviews and meta-analyses have evaluated the safety of interventions in the myriad of IMIDs.[16,17]

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 (http://www.crd.york.ac.uk/prospero).[18] 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.

* Authors share co-first authorship.

***Abbreviations used in this paper:*** **AE, adverse event; AS, ankylosing spondylitis; CD, Crohn's disease; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease; JAK, Janus kinase; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PSO, psoriasis; RA, rheumatoid arthritis; RCT, randomized controlled trial; RR, relative risk; SAE, serious adverse event; TNF, tumor necrosis factor; UC, ulcerative colitis.**

Most current article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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. In addition, 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. In addition, 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 to 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 were 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 and SAEs, as well as AEs of interest were compared. RevMan software was used for this purpose (Version 5.3., The Nordic Cochrane Center, the Cochrane Collaboration, Copenhagen, Denmark, 2014). Heterogeneity among studies was evaluated by means of $\chi^2$ and $I^2$ 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 patients with RA,[19–70] 11 studies on patients with PSO,[71–81] 16 studies on patients with IBD,[82–93] and 2 studies on patients with AS.[94,95] 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 the included studies (74.39%) were phase 2 or phase 3 randomized controlled trials (RCTs), followed by observational cohort studies. Overall, 101,925 subjects were evaluated and 66,159 patients were exposed to a JAK inhibitor; 87.16% received tofacitinib. The studies included 86,308 patients with RA, 9311 patients with PSO, 5987 patients with IBD, and 319 patients with AS. Median time of JAK inhibitor exposure was 26 weeks (25%–75%, interquartile range 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 with IBD or PSO studies (Supplementary Table 1).

### AEs and SAEs

Supplementary Table 2 shows the proportion of patients who experienced AEs and SAEs. 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: 16,318 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 in which the comparator was not placebo: the pooled RRs

**Table 1.** Main Characteristics of Included Studies

| Author | Study design | No. of patients | Study duration | Exposure |
|---|---|---|---|---|
| **Rheumatoid arthritis** | | | | |
| Kremer 2009 | Phase 2a, randomized, double-blind, placebo-controlled, parallel-group study | 264 | 8 wk | Tofacitinib 5 mg BID; Tofacitinib 15 mg BID; Tofacitinib 30 mg BID; placebo |
| Cohen 2010 | Phase 1, open-label study | 12 | 9 d | Tofacitinib 30 mg |
| Tanaka 2011 | Phase 2, randomized, double-blind, placebo-controlled, parallel-group study | 136 | 12 wk | Tofacitinib 1 mg BID; Tofacitinib 3 mg BID; Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo |
| Fleischmann 2012 | Phase 2b, randomized, double-blind, placebo-controlled, active-comparator, parallel-group study | 384 | 24 wk | 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 |
| Fleischmann 2012 | Phase 3, randomized, double-blind, placebo-controlled, parallel group study | 611 | 26 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID |
| Kremer 2012 | Phase 2b, randomized, double-blind, placebo-controlled study | 507 | 24 wk | 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 |
| van Vollenhoven 2012 | Phase 3, randomized, double-blind, placebo-controlled study | 717 | 52 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; Adalimumab 40 mg EOW; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID |
| Burmester 2013 | Phase 3, randomized, double-blind, placebo-controlled, parallel-group study | 399 | 26 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID |
| Kremer 2013 | Phase 3, randomized, double-blind, placebo-controlled study | 792 | 52 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID |
| McInes 2013 | Phase 2, open-label for Tofacitinib and blinded for Atorvastatin | 111 | 12 wk | Tofacitinib 10 mg BID |
| van der Heijde 2013 | Phase 3, randomized, double-blind, parallel-group, placebo-controlled study | 797 | 26 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID |
| Lee 2014 | Phase 3, randomized, double-blind, parallel group study | 956 | 96 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; MTX |
| Sonomoto 2014 | Phase 2/3 randomized, double-blind, placebo-controlled with further open-label extension study | 44 | 52 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID |
| Tanaka 2014 | Phase 2, randomized, double-blind, placebo-controlled, parallel group study | 318 | 12 wk | Tofacitinib 1 mg BID; Tofacitinib 3 mg BID; Tofacitinib 5 mg BID; Tofacitinib 10 mg BID: Tofacitinib 15 mg BID; placebo |
| Wollenhaupt 2014 | Open-label, long-term extension study | 4102 | 76 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID |

**Table 1.** Continued

| Author | Study design | No. of patients | Study duration | Exposure |
|---|---|---|---|---|
| Keystone 2015 | Phase 2b, double-blind, placebo-controlled study | 301 | 24 wk | Baricitinib 1 mg QD; Baricitinib 2 mg QD; Baricitinib 4 mg QD; Baricitinib 8 mg QD; placebo |
| Kremer 2015 | Phase 1, randomized, placebo-controlled, parallel group study | 148 | 12 wk | Tofacitinib 10 mg BID; placebo |
| Curtis 2016 | Retrospective cohort study | 2526 | 313 wk | Tofacitinib at any dose |
| Fleischmann 2016 | Phase 3, randomized, double-blind, parallel-group study | 956 | 24 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo |
| Fleischmann 2016 | Phase 3, randomized, double-blind, active-controlled studies | 584 | 52 wk | MTX; Baricitinib 4 mg QD; Baricitinib 4 mg QD + MTX |
| Genovese 2016 | Phase 2b, randomized, placebo-controlled study | 299 | 12 wk | Upadacitinib 3 mg BID; Upadacitinib 6 mg BID; Upadacitinib 12 mg BID; Upadacitinib 18 mg BID; Upadacitinib 24 mg QD; Placebo |
| Genovese 2016 | Phase 3, randomized, double-blind, placebo-controlled study | 527 | 24 wk | Baricitinib 2 mg QD; Baricitinib 4 mg QD; placebo |
| Kavanaugh 2016 | Phase 2b, randomized, placebo-controlled study | 283 | 24 wk | Filgotinib 50 mg QD; Filgotinib 100 mg QD; Filgotinib 200 mg QD; placebo |
| Kremer 2016 | Phase 2b, randomized, placebo-controlled study | 276 | 12 wk | Upadacitinib 3 mg BID; Upadacitinib 6 mg BID; Upadacitinib 12 mg BID; Upadacitinib 18 mg BID; Placebo |
| Mohamed 2016 | Phase 1, randomized, placebo-controlled study | 114 | 4 wk | Upadacitinib 6 mg BID; Upadacitinib 12 mg BID; Upadacitinib 2 4mg BID; Placebo |
| Tanaka 2016 | Phase 2b, randomized, double-blind, placebo-controlled study | 145 | 12 wk | Baricitinib 1 mg QD; Baricitinib 2 mg QD; Baricitinib 4 mg QD; Baricitinib 8 mg QD; placebo |
| Westhovens 2016 | Phase 2b, randomized, placebo-controlled study | 594 | 24 wk | 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 |
| Yamanaka 2016 | Open-label, long-term extension study | 486 | 288 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID |
| Dougados 2017 | Phase 3, randomized, placebo-controlled study | 684 | 24 wk | Baricitinib 2 mg QD; Baricitinib 4 mg QD; Placebo |
| Fleischmann 2017 | Phase 3/4, head to head, non-inferiority, randomized, controlled study | 1146 | 52 wk | Tofacitinib 5 mg BID; tofacitinib 5 mg BID + MTX; adalimumab 40 mg EOW + MTX |
| Iwamoto 2017 | Prospective cohort study | 70 | 24 wk | Tofacitinib at any dose |
| Keystone 2017 | Open-label, long-term extension study | 133 | 128 wk | Previous exposure to Baricitinib or Placebo, then OLE with Baricitinib 4 mg QD |
| Mimori 2017 | Post-marketing study on safety | 2882 | 24 wk | Tofacitinib at any dose |
| Tanaka 2017 | Phase 2b, randomized, placebo-controlled study | 142 | 64 wk | Baricitinib 1 mg QD; baricitinib 2 mg QD; baricitinib 4 mg QD; baricitinib 8 mg QD or placebo. After 12 wk, baricitinib 4 mg or baricitinib 8 mg QD |

**Table 1.** Continued

| Author | Study design | No. of patients | Study duration | Exposure |
|---|---|---|---|---|
| Taylor 2017 | Phase 3, randomized, double-blind, placebo and active-controlled, parallel –group study | 1305 | 52 wk | Baricitinib 4 mg QD; Placebo then Baricitinib 4 mg QD; Adalimumab 40 mg EOW |
| Vanhoutte 2017 | Phase 2a, randomized, placebo-controlled study | 127 | 4 wk | 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 |
| Avila Machado 2018 | Retrospective cohort study | 21,832 (164 treated w/ Tofacitinib) | 260 wk | All patients treated with either MTX, DMARD, Tofacitinib |
| Burmester 2018 | Phase 3, randomized, double-blind, placebo-controlled study | 661 | 12 wk | Upadacitinib 15 mg QD; Upadactinib 30 mg QD; placebo |
| Cohen 2018 | Post-marketing surveillance study | 34,223 | 156 wk | Tofacitinib 5 mg BID |
| Desai 2018 | Retrospective cohort study | 2905 | 192 wk | Tofacitinib at any dose |
| Genovese 2018 | Phase 3, randomized, double-blind, placebo-controlled study | 499 | 24 wk | Weeks 0-12: Upadacitinib 15 mg QD; Upadacitinib 30 mg QD; Placebo. Weeks 12-24: Upadacitinib 15 mg QD; Upadacitinib 30 mg QD |
| Takeuchi 2018 | Phase 3, randomized, double-blind, placebo-controlled trial with open-label extension study | 559 | 48 wk | Baricitinib 4 mg QD; Baricitinib 2 mg QD. After having received Baricitinib 4 mg QD for >15 months |
| Tanaka 2018 | Phase 3, randomized, double-blind, double-dummy, parallel group, non-inferiority study | 209 | 12 wk | Tofacitinib MR 11 mg QD; Tofacitinib 5 mg BID |
| Yun 2018 | Retrospective cohort study | 2155 | 24 wk | Tofacitinib at any dose |
| Curtis 2019 | Retrospective cohort study | 8030 | 260 wk | Tofacitinib at any dose |
| Fleischmann 2019 | Long-term extension study | 423 | 24 wk | Baricitinib 4 mg QD |
| Genovese 2019 | Phase 3, randomized, double-blind, placebo-controlled study | 448 | 24 wk | Filgotinib 200 mg QD; Filgotinib 100 mg QD; placebo |
| Smolen 2019 | Phase 3, randomized, double-blind, double-dummy study | 648 | 14 wk | Upadacitinib 15 mg QD; Upadacitinib 30 mg QD; MTX |
| Takeuchi 2019 | Long-term extension study | 559 | 48 wk | Baricitinib 2 mg QD; Baricitinib 4 mg QD |
| Tanaka 2019 | Open-label study after phase 3 double-blind, placebo-controlled trial and follow up of baricitinib-rescued patients | 694 | 24 wk | Baricitinib 4 mg QD |
| Tanaka 2019 | Phase 3, randomized, double-dummy, parallel-group study | 209 | 12 wk | Tofacitinib 5 mg BID; Tofacitinib modified-release 11 mg QD |

**Table 1.** Continued

| Author | Study design | No. of patients | Study duration | Exposure |
|---|---|---|---|---|
| van der Heijde 2019 | Phase 3, randomized, placebo-controlled study | 797 | 104 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; Placebo then Tofacitinib 5 mg BID; Placebo then Tofacitinib 10 mg BID |
| Wollenhaupt 2019 | Open-label, long-term extension study | 4481 | 456 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID |
| Psoriasis | | | | |
| Papp 2012 | Phase 2b, randomized, double-blind, parallel-group, placebo-controlled study | 197 | 16 wk | Tofacitinib 2 mg BID; Tofacitinib 5 mg BID; Tofacitinib 15 mg BID; placebo |
| Ports 2013 | Phase 2a, randomized, double-blind, vehicle-controlled, parallel-group study | 71 | 4 wk | Topical Tofacitinib 2%; placebo |
| Bissonnette 2014 | Phase 3, randomized, double-blind, parallel-group, treatment withdrawal and re-treatment study | 674 | 56 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID |
| Bachelez 2015 | Phase 3, randomized, double-dummy, placebo-controlled, parallel-group study | 1106 | 16 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; Etanercept 50 mg twice/week; placebo |
| Papp 2015 | Phase 3, double-blind, placebo-controlled study | 1859 | 16 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo |
| Asahina 2016 | Phase 3, randomized, double-blind study | 99 | 52 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID |
| Papp 2016 | Phase 3, randomized, double-blind, placebo-controlled studies and open-label extension study | 1770 | 52 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID |
| Papp 2016 | Phase 2b, randomized, double-blind, placebo-controlled study | 271 | 24 wk | Baricitinib 2 mg QD; Baricitinib 4 mg QD; Baricitinib 8 mg QD; Baricitinib 10 mg QD; placebo |
| Zhang 2017 | Phase 3, randomized, placebo-controlled study | 266 | 52 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo then Tofacitinib 5 mg BID; placebo then Tofacitinib 10 mg BID |
| Mease 2018 | Phase 2, randomized, placebo-controlled study | 131 | 16 wk | Filgotinib 200 mg QD; placebo |
| Valenzuela 2018 | Open-label, long-term extension study | 2867 | 142 wk | Tofacitinib 10 mg BID |
| Inflammatory bowel disease | | | | |
| Sandborn 2012 | Phase 2, randomized, double-blind, placebo-controlled study | 194 | 12 wk | Tofacitinib 0.5 mg BID; Tofacitinib 3 mg BID; Tofacitinib 10 mg BID; Tofacitinib 15 mg BID; placebo |
| Sandborn 2014 | Phase 2, randomized, double-blind, placebo-controlled study | 239 | 8 wk | Tofacitinib 1 mg BID; Tofacitinib 5 mg BID; Tofacitinib 15 mg BID; placebo |
| Panes 2017 | Phase 2b randomized placebo-controlled study | 279 | 26 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo. Those on clinical response or remission after 8 wk = Tofacitinib 5 mg BID; Tofacitinib 10 mg BID |

**Table 1.** Continued

| Author | Study design | No. of patients | Study duration | Exposure |
|---|---|---|---|---|
| Sandborn 2017 | Phase 3, randomized, double-blind, placebo-controlled studies | 1139 | 8 wk | Tofacitinib 10 mg BID; placebo |
| Sandborn 2017 | Phase 3, randomized, double-blind, placebo-controlled study | 593 | 52 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo |
| Sandborn 2017 | Phase 2, randomized, double-blind, placebo-controlled study | 220 | 16 wk | Upadacitinib 3 mg BID; Upadacitinib 6 mg BID; Upadacitinib 12 mg BID; Upadacitinib 24 mg BID; Upadacitinib 24 mg QD; Placebo |
| Vermeire 2017 | Phase 2, randomized, placebo-controlled study | 174 | 20 wk | Filgotinib 200 mg QD; Placebo for 10 wk. Then, Filgotinib 100 mg QD; Filgotinib 200 mg QD; placebo |
| Lichtenstein 2018 | Phase 3, open-label, long-term extension study | 944 | 232 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID |
| Rubin 2018 | Post hoc analysis of Phase 3 randomized, placebo-controlled, double-blind study | 22 | 8 wk | Tofacitinib 15 mg BID |
| Sandborn 2018 | Phase 2b, double-blind, placebo-controlled, dose-ranging study | 250 | 8 wk | Upadacitinib 7.5 mg QD; Upadacitinib 15 mg QD; Upadacitinib 30 mg QD; Upadacitinib 45 mg QD; Placebo |
| Panes 2018 | Phase 2, randomized, double-blind study | 178 | 36 wk | Upadacitinib 3 mg BID; Upadacitinib 12 mg BID; Upadacitinib 24 mg QD |
| Deepak 2019 | Retrospective cohort study | 140 | 11 wk | Tofacitinib 10 mg BID |
| Panaccione 2019 | Phase 2b, randomized, double-blind study | 250 | 8 wk | Upadacitinib 7.5 mg QD; Upadacitinib 15 mg QD; Upadacitinib 30 mg QD; Upadacitinib 45 mg QD; placebo |
| Panes 2019 | Phase 2b, open-label extension study | 150 | 52 wk | Tofacitinib 5 mg BID; Tofacitinib 10 mg BID |
| Weisshof 2019 | Retrospective cohort study | 58 | 52 wk | Tofacitinib 5 mg BID or 10 mg BID |
| **Ankylosing spondylitis** | | | | |
| van der Heijde 2017 | Phase 2, randomized, placebo-controlled study | 207 | 16 wk | Tofacitinib 2 mg BID; Tofacitinib 5 mg BID; Tofacitinib 10 mg BID; placebo |
| van der Heijde 2018 | Phase 2, randomized, double-blind, placebo-controlled study | 112 | 12 wk | Filgotinib 200 mg QD; placebo |

BID, *bis in die* (twice a day); DMARD, disease-modifying antirheumatic drug; EOW, every other week; MTX, methotrexate; QD, *quaque die* (every day).

for AEs and SAEs were 1.02 (0.97–1.07) and 0.92 (0.78–1.09), respectively. Pooled analyses of the risk of AEs and SAEs stratified by JAK inhibitor dosage and JAK inhibitor type were performed (Supplementary Tables 5 and 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 42,646 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

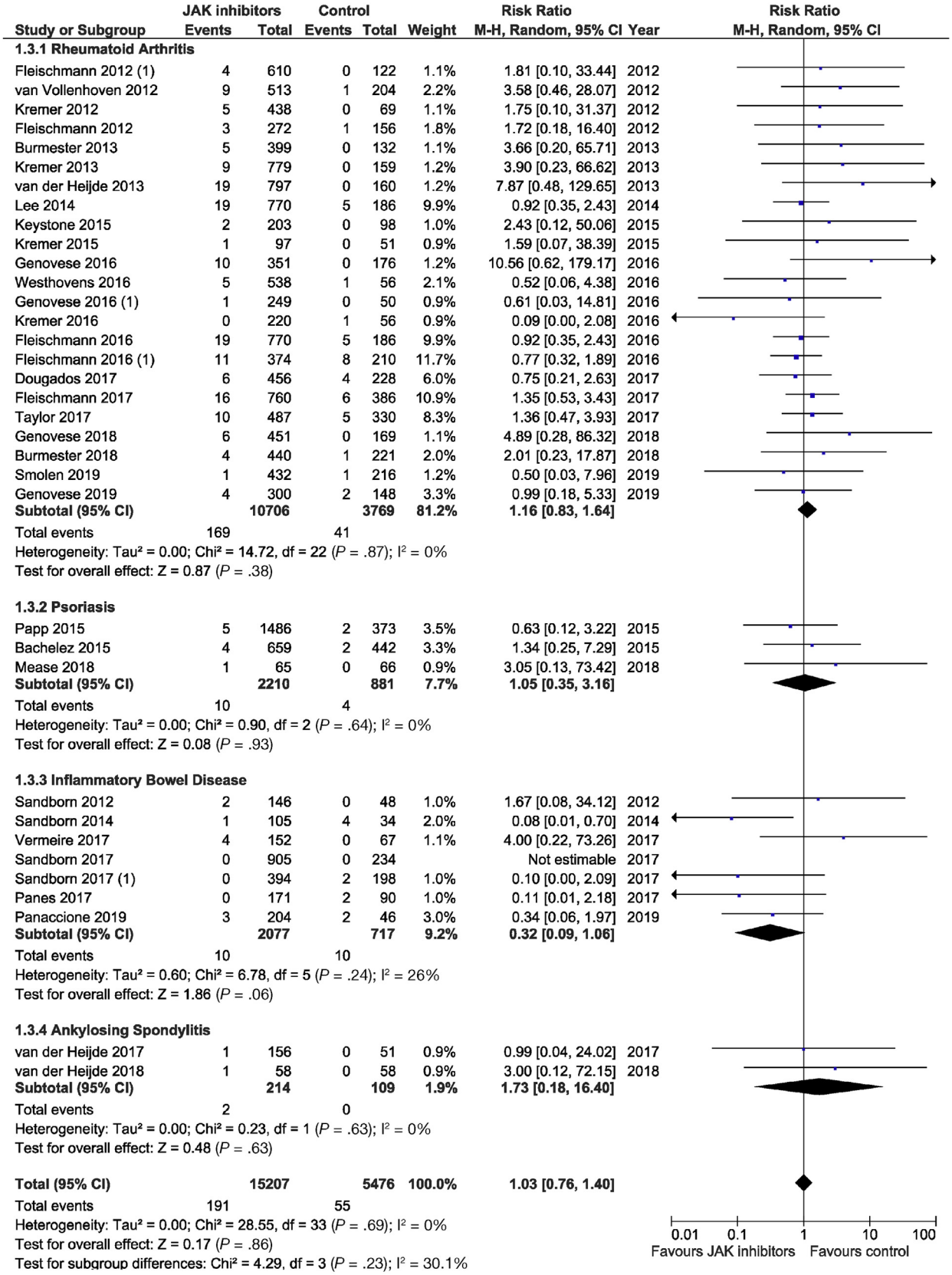


**Figure 1.** Pooled analysis of serious infections in controlled studies. CI, confidence interval.

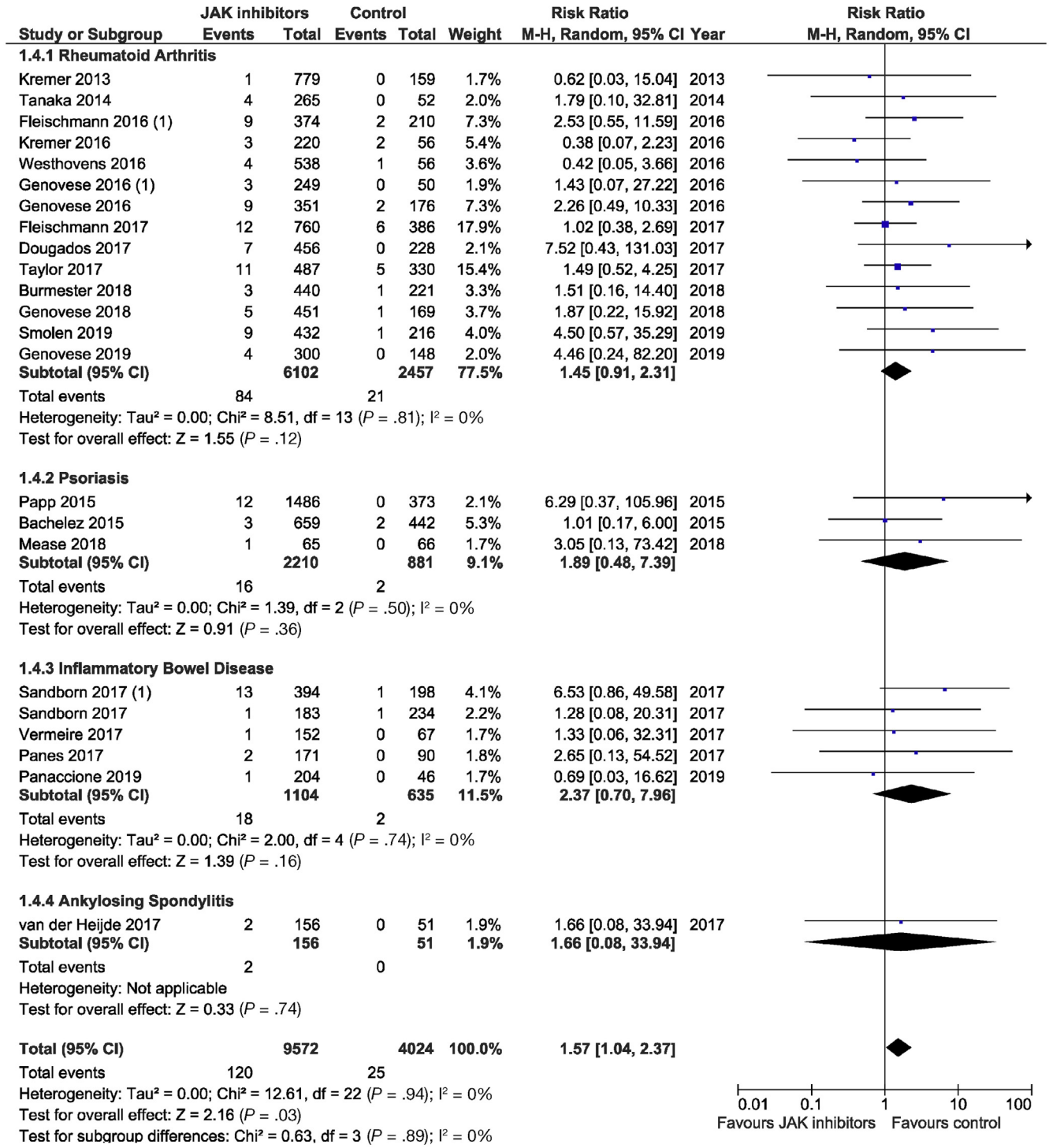


**Figure 2.** Pooled analysis of herpes zoster in controlled studies. CI, confidence interval.

analysis of 35 controlled studies, which included 15,207 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 48,093 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

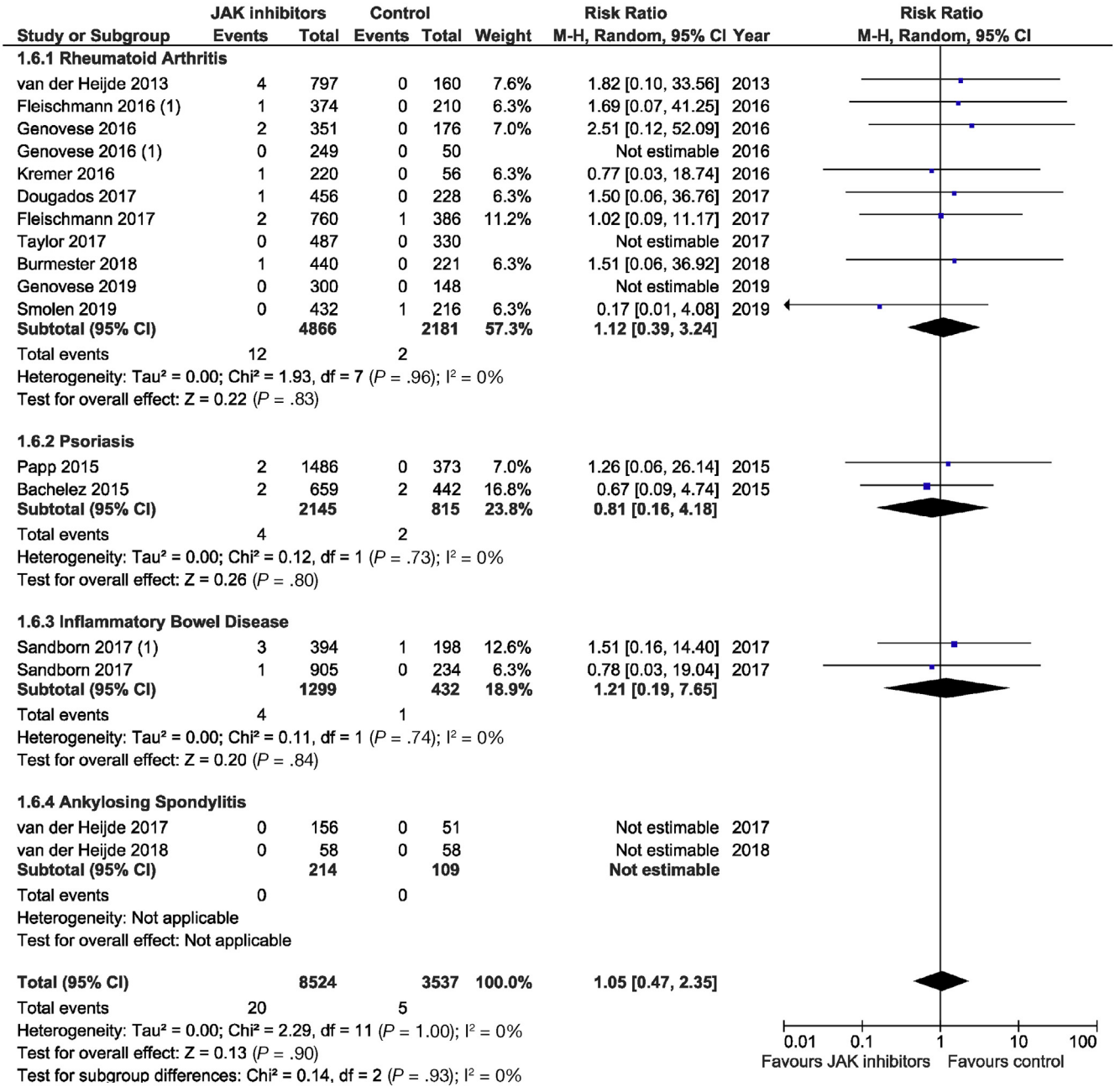


**Figure 3.** Pooled analysis of non-melanoma skin cancer in controlled studies. CI, confidence interval.

(1.57 [1.04–2.37]). The RR remained significant when analyzing placebo-controlled studies (1.72 [1.07–2.76]).

## *Malignancy and NMSC*

NMSC was assessed in 23 studies (13 tofacitinib studies, 4 baricitinib studies, 1 filgotinib study, and 5 upadacitinib studies), which included 26,334 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 32,131 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]).

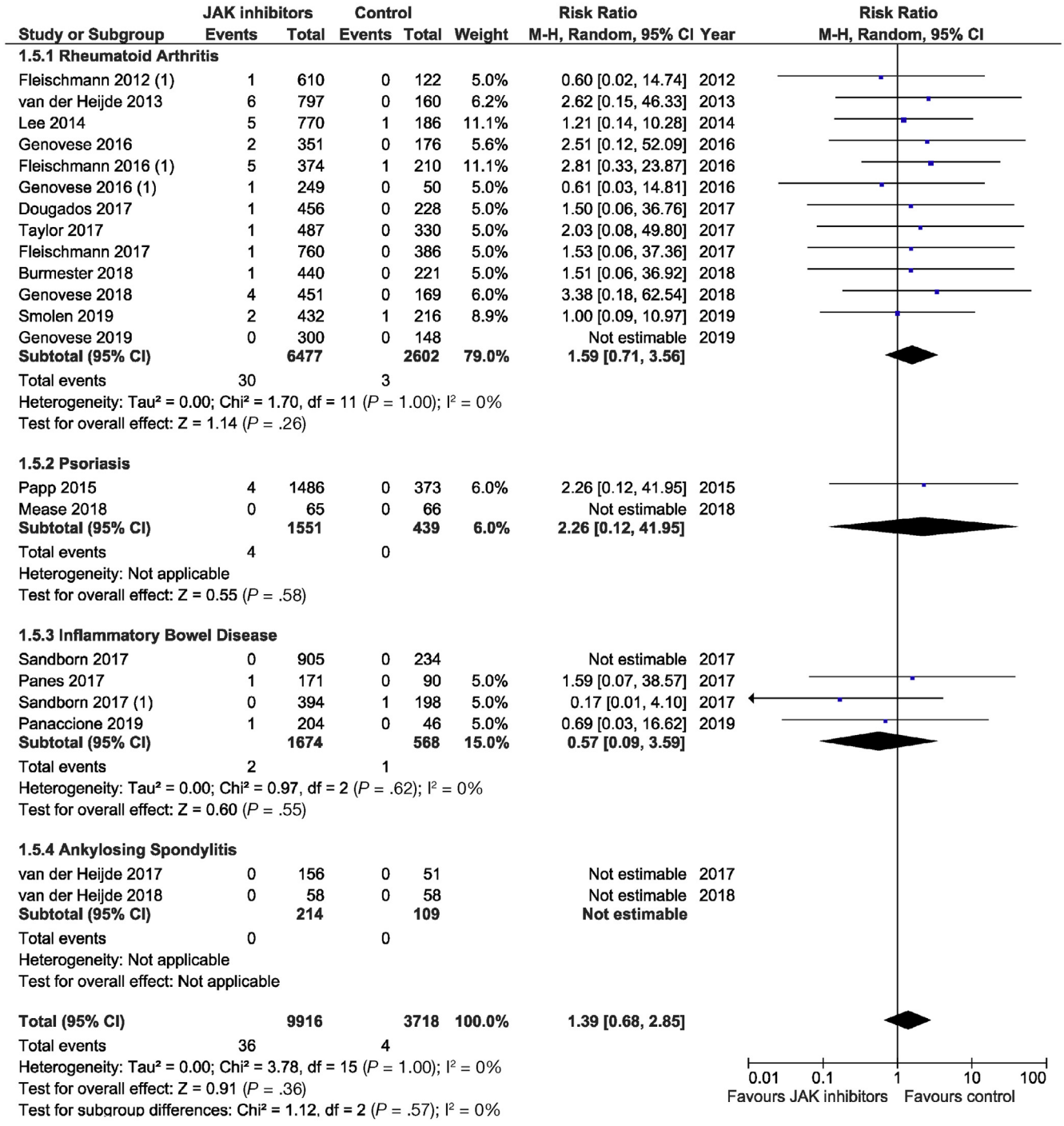


**Figure 4.** Pooled analysis of other malignancies in controlled studies. CI, confidence interval.

## *MACE*

Thirty studies assessed MACE on 32,765 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 (10,701 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

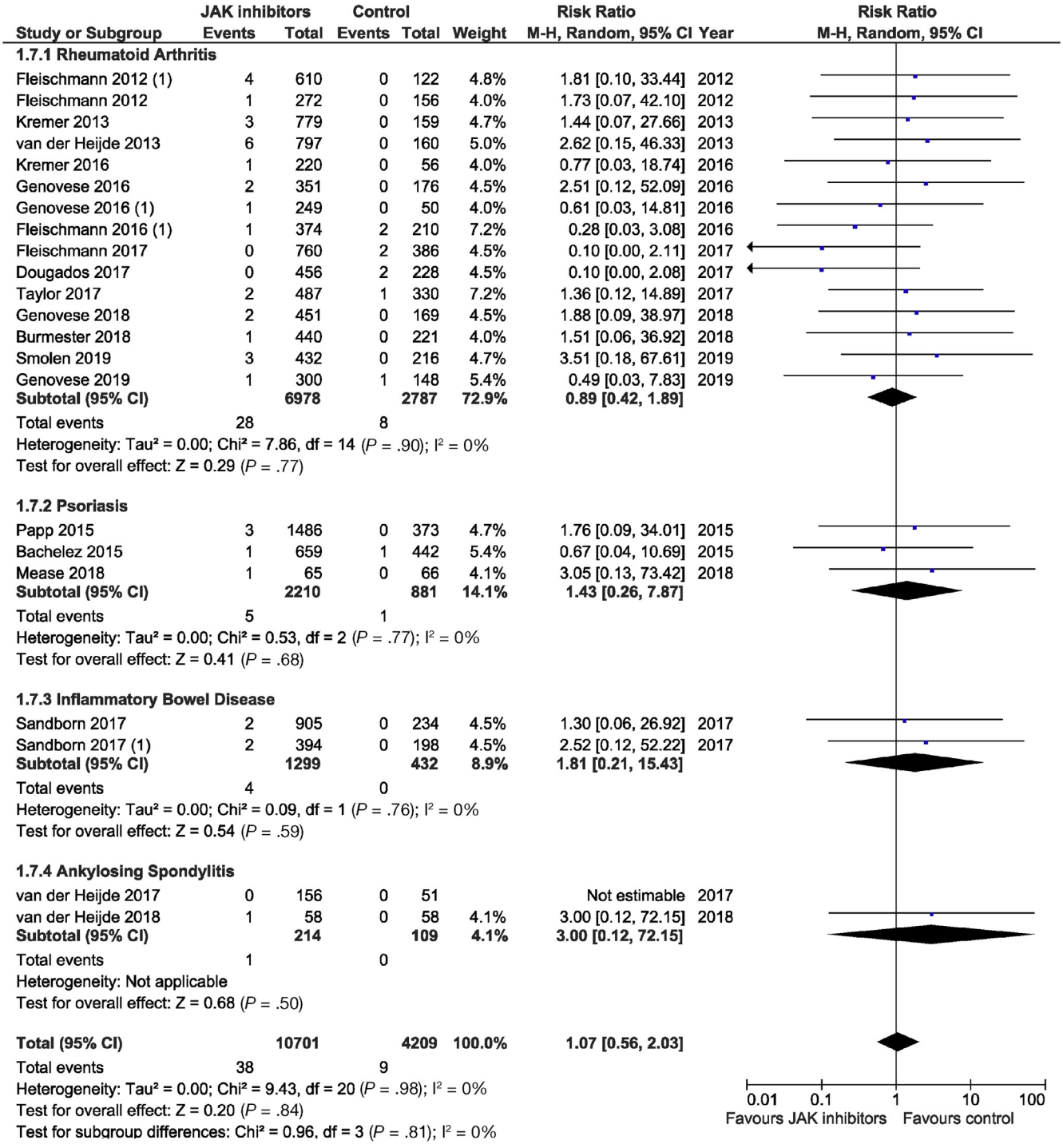


**Figure 5.** Pooled analysis of major cardiovascular events in controlled studies. CI, confidence interval.

included 24,128 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

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 4 IMIDs: IBD, RA, PSO, and AS. Evidence regarding occurrence of AEs, SAEs, and AEs of special interest (ie, infections, serious infections, herpes zoster, malignancy, and MACE) from 67 studies was 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

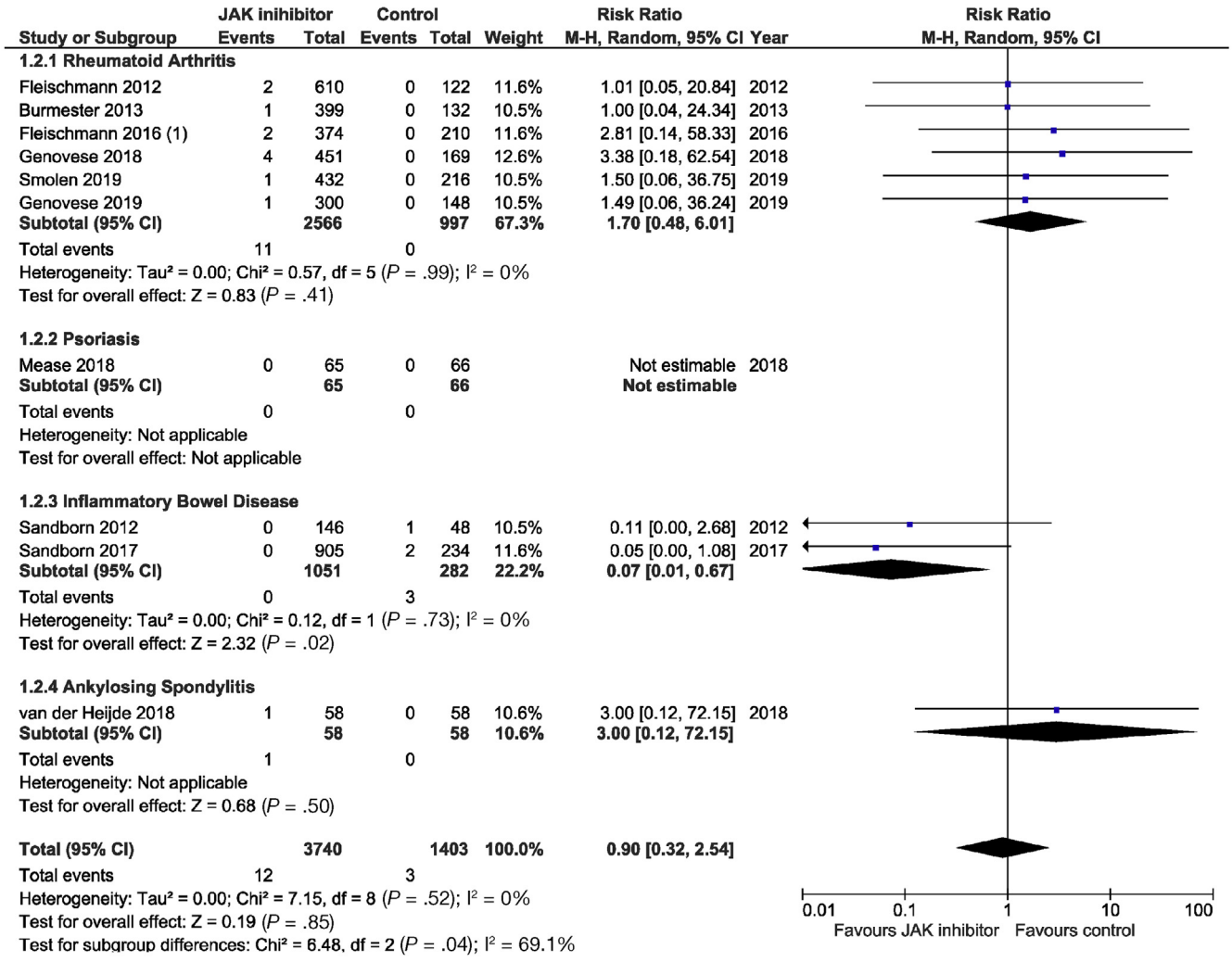


**Figure 6.** Pooled analysis of thromboembolic events in controlled studies. CI, confidence interval.

available in a foreseeable future, thus treatment algorithms will soon need to be updated.[5] The recent approval of tofacitinib in UC has opened the therapeutic avenue of JAK inhibition in IBD.[8] Tofacitinib has shown considerable efficacy in both biologic-naïve and -experienced patients with UC,[87] and is increasingly used in the clinic worldwide. However, defining the safety profile is paramount, because 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 of immunosuppressive effects of JAK inhibition, concerns about infections and 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.[96]

The JAK-STAT pathway has several key functions in inflammatory cytokines and immune response,[4] hence the risk of infections with the use of JAK inhibitors in IMIDs appears to be considerable.[97] 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 particularly high risk of viral infections, especially of herpes zoster. Patients with some IMIDs intrinsically have an increased risk of herpes zoster infection.[98,99] In addition, disease-modifying agents, immunosuppressants, and steroids increase the risk further,[100–102] and among biologics, non–anti-TNF agents appear to have a higher risk than anti-TNF agents. According to Marra et al,[102] 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 (RR 1.28 [0.69–2.40]).[102] 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.[102] Additional factors that influence the risk include increasing age, combination with steroids and methotrexate, and Asian population.[103] Although the exact pathogenic mechanism of the increased risk of herpes zoster in this context is unknown,[104] it is correlated with impairment in cell-mediated immunity.[97] Notably, most of the cases of herpes zoster associated with the use of JAK inhibitors are noncomplicated and with single dermatome involvement.[103] 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 with other therapies and/or placebo. In addition, 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/high-density lipoprotein cholesterol ratio usually stable, and with an overall low incidence of MACE in RCTs and observational studies.[105,106] On the other hand, the risk of thromboembolic events with the use of JAK inhibitors has been recently highlighted.[107,108] In an ongoing phase 3b/4 study (A3921133, NCT02092467) the safety of tofacitinib 5 mg twice a day and 10 mg twice a day versus adalimumab and etanercept in patients older than 50 years with RA 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 twice a day 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 twice a day, and a recommendation of the European Medicines Agency to practitioners to adhere to the 5 mg twice a day dosage approved for RA.[107] In addition, results of RCTs of baricitinib in RA pointed out a safety signal of increased risk of thromboembolic events, especially with at 4 mg every day.[109] Based on this finding, the FDA approved only baricitinib at 2 mg every day for RA in the United States.[12] Although it appears to be dose dependent, currently it 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 program showed that venous thromboembolism events occurred in 5 patients with UC exposed to tofacitinib 10 mg twice a day (1 patient had deep vein thrombosis and 4 had pulmonary embolism; all in the open-label extension phase).[110] Of note, patients who developed these events had at least 1 risk factor for venous thromboembolism[110]; however, we did not find an increased risk of thromboembolic events among patients exposed to JAK inhibitors in 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. In addition, 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,[110] 4 patients developed thromboembolic events in the induction and maintenance phase of the program, all of whom received placebo and none tofacitinib. Furthermore, the type of studies published so far, and thus included in our systematic review and meta-analysis, include mostly 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 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 4 selected for this systematic review. These 4 compounds were selected because tofacitinib and baricitinib are already FDA approved (tofacitinib for RA, psoriatic arthritis, and UC; baricitinib for RA) and are relatively nonselective (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 shows 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, most studies were conducted in RA, followed by psoriasis, IBD, and AS. Certainly there are disease-specific considerations that prevent 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 characteristics of patients. In addition, definitions of AEs and SAEs might have differed in observational studies, compared with RCTs, in which a standardized definition is used. This has probably influenced the marked difference in reported rates of some AEs, 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.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.01.001.

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**Correspondence**
Address correspondence to: Laurent Peyrin-Biroulet, MD, PhD, INSERM NGERE and Department of Hepatogastroenterology, Nancy University Hospital, Lorraine University, Allée du Morvan, F-54511 Vandoeuvre-lès-Nancy, France. e-mail: peyrinbiroulet@gmail.com; fax: + 33 383 153633.

**CRediT Authorship Contributions**
Pablo Andres Olivera, MD (Formal analysis: Supporting; Investigation: Lead; Methodology: Supporting; Project administration: Lead; Writing – original draft: Lead; Writing – review & editing: Lead). Juan Lasa, MD, MSc (Formal analysis: Lead; Investigation: Equal; Methodology: Lead; Writing – original draft: Supporting; Writing – review & editing: Supporting). Stefanos Bonovas, MD, PhD (Formal analysis: Supporting; Investigation: Supporting; Methodology: Supporting; Writing – review & editing: Supporting). Silvio Danese, MD, PhD (Conceptualization: Supporting; Project administration: Supporting; Supervision: Supporting; Writing – review & editing: Supporting). Laurent Peyrin-Biroulet, MD, PhD (Conceptualization: Lead; Investigation: Supporting; Methodology: Supporting; Project administration: Lead; Supervision: Lead; Writing – original draft: Supporting; Writing – review & editing: Lead).

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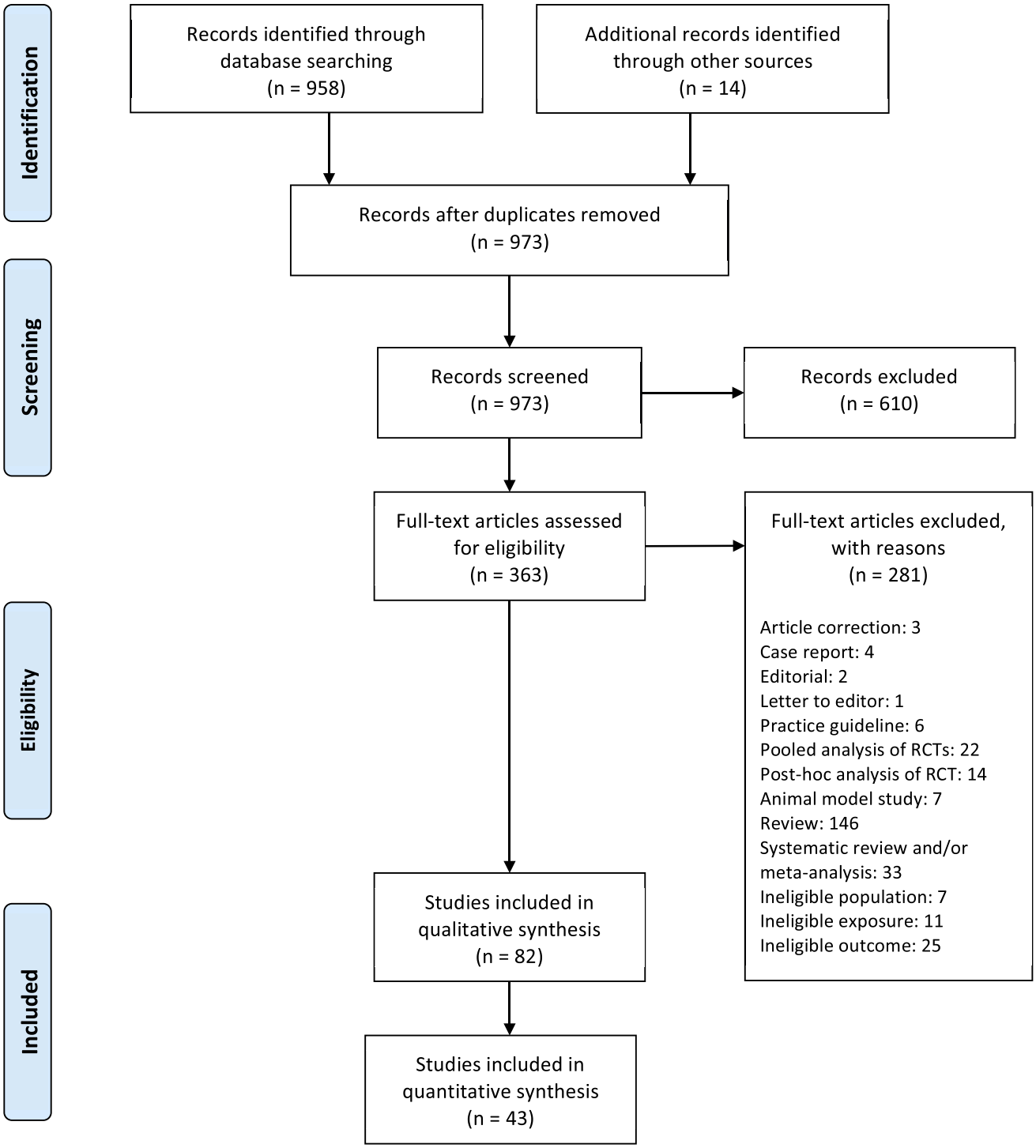
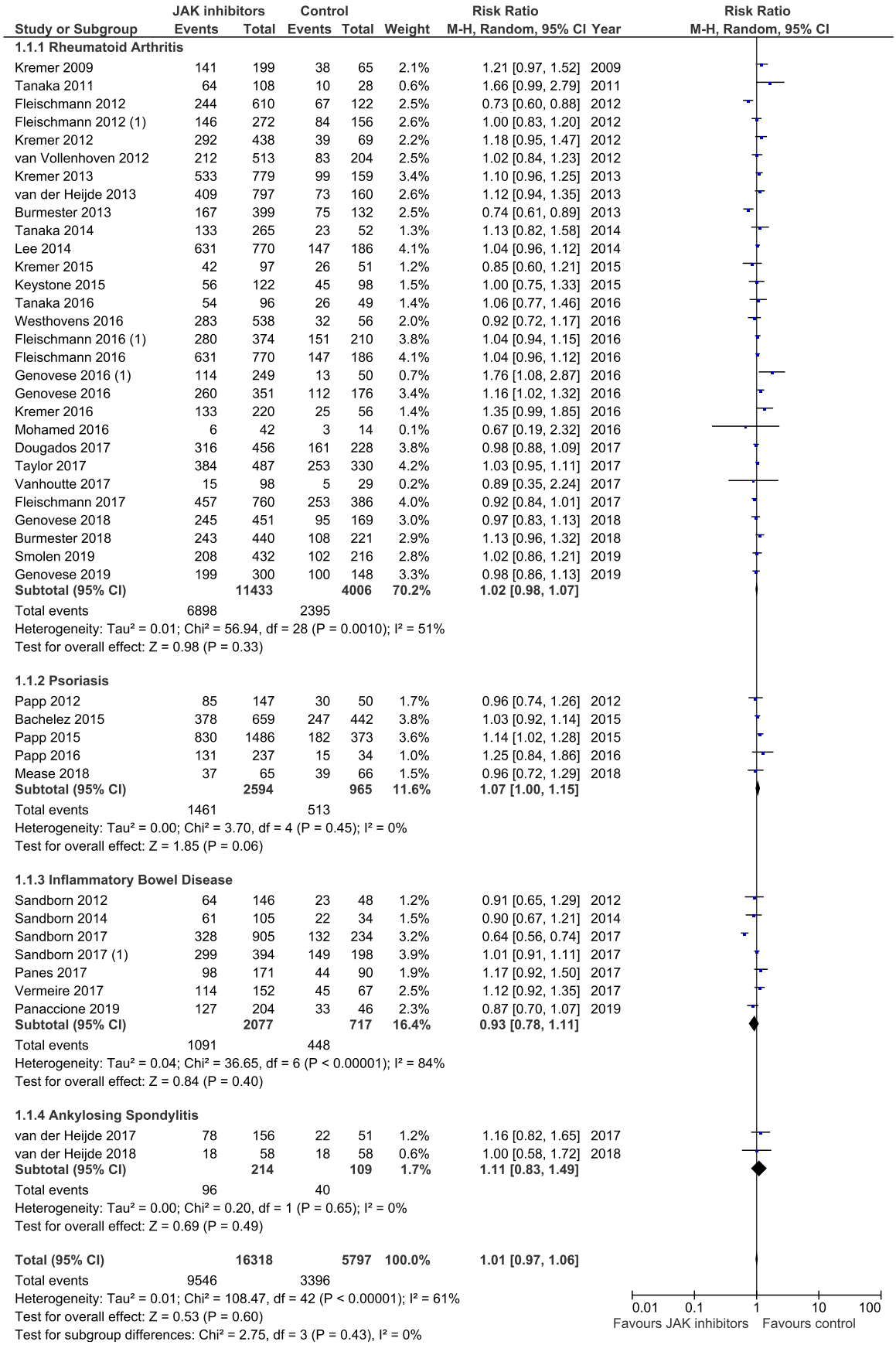
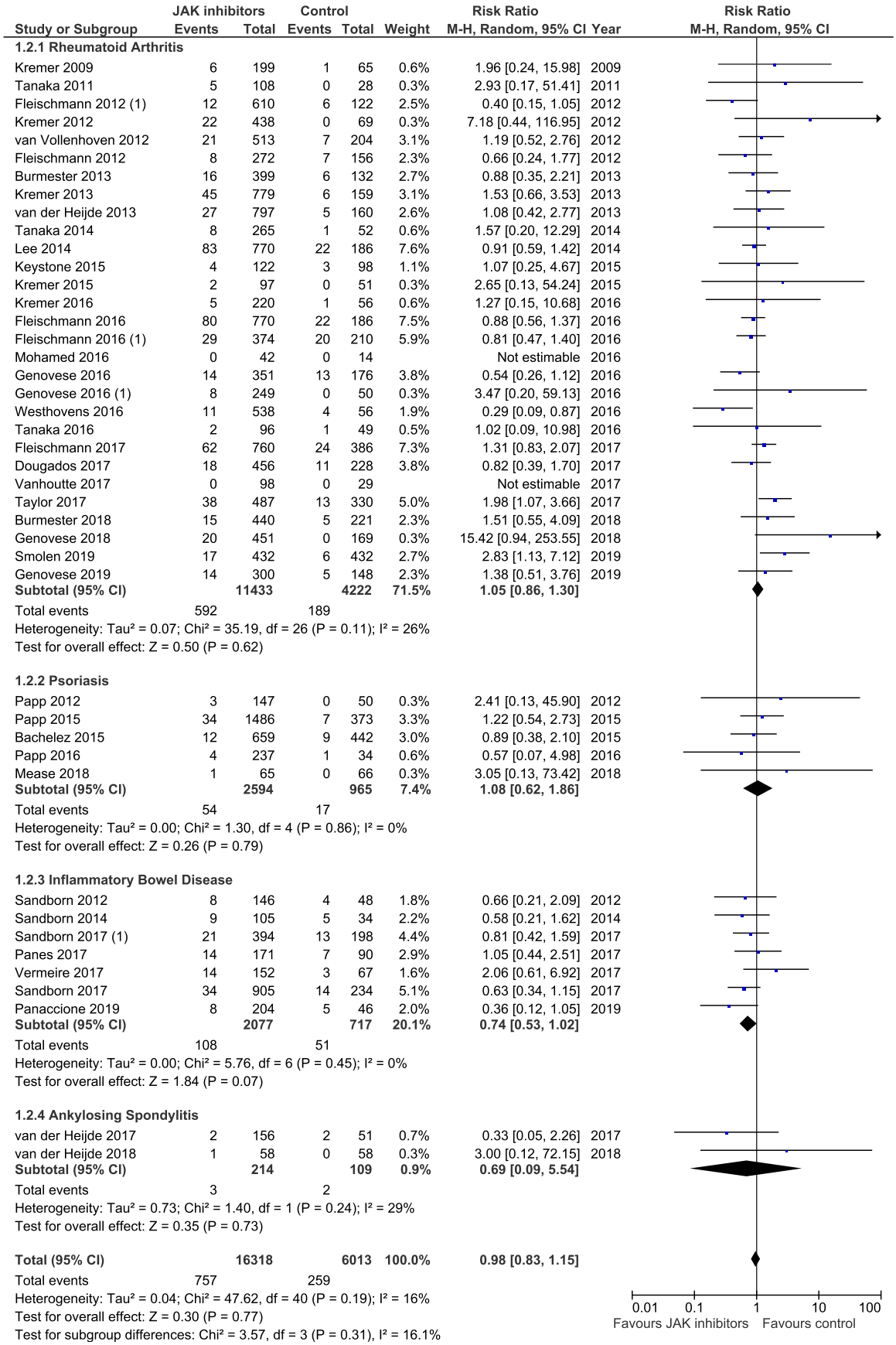
## Supplementary Material




**Supplementary Figure 1.** PRISMA flow diagram showing study selection.




**Supplementary Figure 2.** Pooled analysis of AEs in controlled studies.




**Supplementary Figure 3.** Pooled analysis of SAEs in controlled studies.

**Supplementary Table 1.** Main Clinical Features of Patients From Included Studies

| Study | Mean age (*y*) | Female (%, n/N) | White (%, n/N) | Concomitant treatments | Prior biologic use |
|---|---|---|---|---|---|
| **Rheumatoid arthritis** | | | | | |
| Kremer 2009 | 50.5 | 85.61 (226/264) | 68.18 (180/264) | Steroids: 62.87 (166/264) | 21.21 (56/264) |
| Cohen 2010 | 57.3 | 66.67 (9/12) | 66.67 (9/12) | MTX: 100 (12/12) | |
| Tanaka 2011 | 51.3 | 86.03 (117/136) | 0 (0/136) | Steroids: 59.55 (81/136) | |
| Fleischmann 2012 | 53.43 | 86.72 (333/384) | 68.75 (264/384) | Steroids: 55.73 (214/384)<br>Anti-Malarial agents: 10.93 (42/384) | 6.51 (25/384) |
| Fleischmann 2012 | 51.43 | 86.55 (528/610) | 67.05 (409/610) | Steroids: 59.83 (365/610)<br>Anti-Malarial agents: 16.55 (101/610) | 22.95 (140/610) |
| Kremer 2012 | 53.14 | 80.08 (406/507) | 86.19 (437/507) | Steroids: 58.18 (295/507)<br>MTX: 100 (507/507) | 6.11 (31/507) |
| van Vollenhoven 2012 | 53.16 | 81.72 (586/717) | 71.10 (517/717) | 63.04 (452/717) | 9.20 (66/717) |
| Burmester 2013 | 54.96 | 83.96 (335/399) | 83.21 (332/399) | Steroids: 62.40 (249/399)<br>MTX: 100 (399/399)<br>Anti-Malarial agents: 6.01 (24/399) | 100 (399/399) |
| Kremer 2013 | 52.17 | 81.43 (645/792) | 54.29 (430/792) | Steroids: 59.46 (471/792)<br>MTX: 79.04 (626/792) | 9.47 (75/792) |
| McInes 2013 | 52 | 89.69 (87/97) | 43.29 (42/97) | Not reported | |
| van der Heijde 2013 | 53 | 85.19 (679/797) | 46.17 (368/797) | MTX: 100 (797/797) | 20.57 (164/797) |
| Lee 2014 | 49.46 | 79.29 (758/956) | 66.11 (632/956) | Not reported | |
| Sonomoto 2014 | 54.3 | 79.5 (35/44) | 0 (0/44) | Steroids: 29.5 (13/44)<br>MTX: 81.8 (36/44) | |
| Tanaka 2014 | 53.38 | 83.28 (264/317) | 0 (0/318) | Not reported | |
| Wollenhaupt 2014 | 53.1 | 83.03 (3406/4102) | 56.80 (2330/4102) | 54.02 (2216/4102) | |
| Keystone 2015 | 51.8 | 83 (249/301) | Not reported | Steroids: 48.50 (146/301)<br>Hydroxychloroquine: 17.27 (52/301)<br>MTX: 99.66 (300/301) | 0 (0/301) |
| Kremer 2015 | 49.5 | 75 (111/148) | 93.91 (139/148) | Not reported | |
| Curtis 2016 | 55.4 | 83.21 (2102/2526) | Not reported | MTX: 39.39 (995/2526)<br>Steroids: 65.2 (1647/2526) | 85 (2147/2526) |
| Fleischmann 2016 | 49.56 | 79.29 (758/956) | 66.11 (632/956) | No reported | |
| Fleischmann 2016 | 50.33 | 72.77 (425/584) | Not reported | Steroids: 35.27 (206/584) | 0 (0/584) |
| Genovese 2016 | 55 | 79.26 (237/299) | Not reported | Steroids: 20.40 (61/299)<br>MTX: 100 (299/299) | |
| Genovese 2016 | 55.66 | 81.78 (431/527) | Not reported | Not reported | |
| Kavanaugh 2016 | 52.25 | 81.62 (231/283) | Not reported | Steroids: 59.01 (167/283)<br>Anti-Malarial agents: 4.24 (12/283) | 6.71 (19/283) |
| Kremer 2016 | 57.4 | 80.07 (221/276) | Not reported | MTX: 100 (276/276) | 100 (276/276) |
| Mohamed 2016 | 40.9 | 18.42 (21/114) | 74.56 (85/114) | MTX: 100 (RA subjects) | |
| Tanaka 2016 | 54.2 | 81.38 (118/145) | 0 (0/145) | Steroids: 58.62 (85/145)<br>MTX: 100 (145/145) | |
| Westhovens 2016 | 53.28 | 80.97 (481/594) | Not reported | Steroids: 59.26 (352/594)<br>MTX: 100 (594/594) | 8.41 (50/594) |
| Yamanaka 2016 | 52.6 | 83.12 (404/486) | 0 (0/486) | Steroids: 69.13 (336/486)<br>MTX: 45.68 (222/486) | |
| Dougados 2017 | 51.66 | 81.87 (560/684) | Not reported | MTX: 71.92 (492/684) | |
| Fleischmann 2017 | 50.13 | 82.89 (950/1146) | 76.35 (875/1146) | Steroids: 57.15 (655/1146) | |
| Iwamoto 2017 | 64.2 | 84.28 (59/70) | 0 (0/70) | Steroids: 52.85 (37/70)<br>MTX: 68.57 (48/70) | 68.57 (48/70) |
| Keystone 2017 | 53 | 83 (110/133) | Not reported | Steroids: 46 (61/133)<br>MTX: 75 (100/133)<br>MTX+DMARD: 24 (32/133) | |
| Mimori 2017 | 62.6 | 79.9 (2303/2882) | Not reported | Not reported | |
| Tanaka 2017 | 53.55 | 81.56 (115/141) | 0 (0/141) | Steroids: 58 (82/142)<br>MTX: 100 (142/142) | |
| Taylor 2017 | 53.33 | 77.24 (1008/1305) | Not reported | MTX: 100 (1305/1305) | |
| Vanhoutte 2017 | 50.56 | 84.8 (108/127) | 100 (127/127) | Steroids: 44.9 (57/127)<br>MTX: 100 (127/127) | 0 (0/127) |
| Avila Machado 2018 | 58 | 77 (16810/21832) | Not reported | Steroids: 67.69 (14780/21832) | |

**Supplementary Table 1.** Continued

| Study | Mean age (*y*) | Female (%, n/N) | White (%, n/N) | Concomitant treatments | Prior biologic use |
|---|---|---|---|---|---|
| Burmester 2018 | 55.7 | 78.66 (520/661) | Not reported | Steroids: 46.14 (305/661)<br>MTX: 60.36 (399/661)<br>MTX+DMARD: 20.42 (135/661) | 9.68 (64/661) |
| Cohen 2018 | 60 | 78.2 (7200/9209) | Not reported | Not reported | |
| Curtis 2018 | 60.3 | 83.3 (6689/8030) | 44.55 (3577/8030) | Not reported | |
| Desai 2018 | 60.5 | Not reported | Not reported | Not reported | |
| Genovese 2018 | 57.06 | 83.93 (418/498) | Not reported | Steroids: 48.89 (244/499)<br>MTX: 72.94 (364/499)<br>MTX+DMARD: 9.41 (47/499) | 100 (499/499) |
| Takeuchi 2018 | 54.05 | 75.67 (423/559) | 0 (0/559) | Steroids: 43.30 (242/559)<br>MTX: 82.11 (459/559) | 87.45 (489/559) |
| Tanaka 2018 | 58 | 77.03 (161/209) | 0 (0/209) | Steroids: 49.28 (103/209)<br>MTX: 100(209/209) | 22.9 (48/209) |
| Yun 2018 | Not reported | Not reported | Not reported | Not reported | |
| Curtis 2019 | 60.45 | 81.74 (6564/8030) | Not reported | Not reported | |
| Fleischmann 2019 | 50.6 | 73.04 (309/423) | 61 (258/423) | Steroids: 30.49 (129/423) | |
| Genovese 2019 | 55.66 | 80.35 (360/448) | 70.53 (316/448) | MTX: 81.92 (367/448) | |
| Smolen 2019 | 54.3 | 80.71 (523/648) | Not reported | Steroids: 50.46 (327/648)<br>Prior MTX: 100 (648/648) | |
| Takeuchi 2019 | 54.05 | 75.67 (423/559) | Not reported | Steroids: 43.29 (242/559)<br>MTX: 82.11 (459/559) | 12.52 (70/559) |
| Tanaka 2019 | 52.65 | 77.01 (687/892) | Not reported | MTX: 100 (892/892) | |
| Tanaka 2019 | 58 | 77.03 (161/209) | 0 (0/209) | Steroids: 49.28 (103/209)<br>MTX: 100 (209/209) | 14.35 (30/209) |
| van der Heijde 2019 | 52.75 | 85.07 (678/797) | 46.17 (368/797) | MTX: 100 (797/797) | |
| Wollenhaupt 2019 | 53.3 | 81.92 (3671/4481) | 70.85 (3175/4481) | Not reported | |
| Psoriasis | | | | | |
| Papp 2012 | 44.3 | 36.54 (72/197) | 80.7 (159/197) | Not reported | 25.89 (51/197) |
| Ports 2013 | 49.8 | 39.43 (28/71) | Not reported | Not reported | |
| Bachelez 2015 | 44 | 29.33 (323/1101) | 86.83 (956/1101) | Not permitted | 10.26 (113/1101) |
| Bissonnette 2015 | 46 | 31.23 (208/666) | 92.19 (614/666) | Not reported | 28.07 (187/666) |
| Papp 2015 | 45.5 | 30.55 (568/1859) | 82.46 (1533/1859) | Not permitted | 27.70 (515/1859) |
| Asahina 2016 | 49.25 | 17.17 (17/99) | 0 (0/99) | Steroids: 6.06 (6/99) | 15.15 (15/99) |
| Papp 2016 | 45.5 | 29.55 (523/1770) | 82.15 (1454/1770) | Not reported | |
| Papp 2016 | 47.3 | 27.30 (76/271) | 79.33 (215/271) | Not reported | |
| Zhang 2017 | 41.1 | 27.06 (72/266) | 0 (0/266) | Not permitted | 14.66 (39/266) |
| Mease 2018 | 49.5 | 50.38 (66/131) | Not reported | Steroids: 25.19 (33/131)<br>MTX: 54.19 (71/131)<br>DMARD: 74.04 (97/131) | 15.26 (20/131) |
| Valenzuela 2018 | 46 | 29.40 (843/2867) | 86.53 (2480/2867) | Not reported | |
| Inflammatory bowel disease | | | | | |
| Sandborn 2012 | 42.64 | 42.36 (88/194) | 90.72 (176/194) | Steroids: 34.02 (66/194)<br>Mesalamine: 62.88 (122/194) | 30.41 (59/194) |
| Sandborn 2014 | 37.27 | 50.36 (70/139) | 89.92 (125/139) | Steroids: 43.88 (61/139) | 7.19 (10/139) |
| Panes 2017 | 39.5 | 52.32 (146/279) | 82.07 (229/279) | Steroids: 35.48 (99/279) | 77.06 (215/279) |
| Sandborn 2017 | 41.15 | 41.35 (471/1139) | Not reported | Steroids: 46.09 (525/1139) | 54.25 (618/1139) |
| Sandborn 2017 | 42.73 | 44.52 (264/593) | Not reported | Steroids: 48.56 (288/593) | 47.72 (283/593) |
| Sandborn 2017 | 40.7 | Not reported | Not reported | Not reported | 95.91 (211/220) |
| Vermeire 2017 | 36.25 | 55.74 (97/174) | Not reported | Steroids: 50.57 (88/174) | 58.04 (101/174) |
| Lichtenstein 2018 | 41.2 | 41.21 (389/944) | Not reported | Not reported | |
| Rubin 2018 | 38.4 | 45.45 (10/22) | Not reported | Not reported | 45.45 (10/22) |
| Sandborn 2018 | 42.3 | Not reported | Not reported | Not reported | 77.60 (194/250) |
| Panes 2018 | 40.7 | Not reported | Not reported | Not reported | |
| Deepak 2019 | 36 | 22.85 (32/140) | 58.57(82/140) | Not reported | |
| Panaccione 2019 | 41.4 | 40 (100/250) | Not reported | Steroids: 52 (130/250) | 77.6 (194/250) |
| Panes 2019 | 39.6 | 47.33 (71/150) | 80 (120/150) | Steroids: 16 (24/150) | 74 (111/150) |
| Sandborn 2019 | 41.3 | 41.31 (478/1157) | 80.12 (927/1157) | Steroids: 45.2 (523/1157) | 51.9 (583/1157) |

**Supplementary Table 1.** Continued

| Study | Mean age (*y*) | Female (%, n/N) | White (%, n/N) | Concomitant treatments | Prior biologic use |
|---|---|---|---|---|---|
| Weisshof 2019 | 39.7 | 37.93 (22/58) | Not reported | Steroids: 46.55 (27/58)<br>Immunomodulators: 8.62 (5/58)<br>Vedolizumab: 5.17 (3/58) | Anti TNF: 93.1 (54/58)<br>Vedolizumab: 81.03 (47/58)<br>Ustekinumab: 3.45 (2/58) |
| Ankylosing spondylitis | | | | | |
| van der Heijde 2017 | 41.62 | 30.91 (64/207) | 81.16 (168/207) | Steroids: 8.21 (17/207)<br>DMARD: 33.33 (69/207) | |
| van der Heijde 2018 | 41.5 | 25.86 (30/116) | Not reported | Steroids: 14.65 (17/116)<br>MTX: 11.20 (13/116)<br>DMARD: 38.79 (45/116) | 9.48 (11/116) |

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate.

**Supplementary Table 2.** Prevalence of Adverse Events and Serious Adverse Events in the Included Studies

| Study | AE (%, n/N) JAK inhibitors patients | AE (%, n/N) comparator patients | SAE (%, n/N) JAK inhibitors patients | SAE (%, n/N) comparator patients |
|---|---|---|---|---|
| **Rheumatoid arthritis** | | | | |
| Kremer 2009 | 70.85 (141/199) | 58.46 (38/65) | 3.01 (6/199) | 1.53 (1/65) |
| Cohen 2010 | 41.66 (5/12) | | 0 (0/12) | |
| Tanaka 2011 | 59.26 (64/108) | 35.71 (10/28) | 4.63 (5/108) | 0 (0/28) |
| Fleischmann 2012 | 53.67 (146/272) | 53.84 (84/156) | 2.94 (8/272) | 4.48 (7/156) |
| Fleischmann 2012 | 0–3 months: 53.89 (263/488)<br>3–6 months: 40 (244/610) | 0–3 months: 54.91 (67/122) | 0–3 months: 1.23 (6/488)<br>3–6 months: 1.96 (12/610) | 0–3 months: 4.92 (6/122) |
| Kremer 2012 | 66.67 (292/438) | 56.52 (39/69) | 5.02 (22/438) | 0 (0/69) |
| van Vollenhoven 2012 | 0–3 months: 49.38(200/405)<br>3–6 months: 31.93 (145/454)<br>6–12 months: 41.32 (212/513) | 0–3 months: 50 (156/312)<br>3–6 months: 31.94 (84/263)<br>6–12 months: 40.68 (83/204) | 0–3 months: 5.43 (22/405)<br>3–6 months: 3.74 (17/454)<br>6–12 months: 4.09 (21/513) | 0–3 months: 2.24 (7/312)<br>3–6 months: 3.04 (8/263)<br>6–12 months: 3.43 (7/204) |
| Burmester 2013 | 0–3 months: 55.05 (147/267)<br>3–6 months: 41.85 (167/399) | 0–3 months: 56.81 (75/132) | 0–3 months: 1.49 (4/267)<br>3–6 months: 4.01 (16/399) | 0–3 months: 4.54 (6/132) |
| Kremer 2013 | 68.42 (533/779) | 62.26 (99/159) | 5.77 (45/779) | 3.77 (6/159) |
| McInes 2013 | 46.84 (52/111) | | 1.80 (2/111) | |
| van der Heijde 2013 | 51.31 (409/797) | 45.62 (73/160) | 3.38 (27/797) | 3.12 (5/160) |
| Lee 2014 | 81.94 (631/770) | 79.03 (147/186) | 10.78 (83/770) | 11.82 (22/186) |
| Sonomoto 2014 | 52.27 (23/44) | | 0 (0/44) | |
| Tanaka 2014 | 50.19 (133/265) | 44.23 (23/52) | 3.01 (8/265) | 1.92 (1/52) |
| Wollenhaupt 2014 | 76.84 (3152/4102) | | 15.35 (630/4102) | |
| Keystone 2015 | 0–12 weeks: 45.32 (92/203)<br>12–24 weeks: 45.90 (56/122) | 45.91 (45/98) | 0–12 weeks:1.97 (4/203)<br>12–24 weeks: 3.27 (4/122) | 3.06 (3/98) |
| Kremer 2015 | 43.29 (42/97) | 50.98 (26/51) | 2.06 (2/97) | 0 (0/51) |
| Curtis 2016 | 2.93 (74/2526) | | | |
| Fleischmann 2016 | 81.94 (631/770) | 79.03 (147/186) | 10.39 (80/770) | 11.82 (22/186) |
| Fleischmann 2016 | 74.86 (280/374) | 71.90 (151/210) | 7.75 (29/374) | 9.52 (20/210) |
| Genovese 2016 | 74.07 (260/351) | 63.63 (112/176) | 7.12 (14/351) | 7.38 (13/176) |
| Genovese 2016 | 45.78 (114/249) | 26 (13/50) | 3.21 (8/249) | 0 (0/50) |
| Kavanaugh 2016 | 39.85 (110/276) | | 2.89 (8/276) | |
| Kremer 2016 | 60.45 (133/220) | 44.36 (25/56) | 2.27 (5/220) | 1.78 (1/56) |
| Mohamed 2016 | 14.28 (6/42) | 21.42 (3/14) | | |
| Tanaka 2016 | 56.25 (54/96) | 53.06 (26/49) | 2.08 (2/96) | 2.04 (1/49) |
| Westhovens 2016 | 52.60 (283/538) | 57.14 (32/56) | 2.04 (11/538) | 7.14 (4/56) |
| Yamanaka 2016 | 97.94 (476/486) | | 28.60 (139/486) | |
| Dougados 2017 | 69.29 (316/456) | 70.61 (161/228) | 3.94 (18/456) | 4.82 (11/228) |
| Fleischmann 2017 | 60.13 (457/760) | 65.54 (253/386) | 8.15 (62/760) | 6.21 (24/386) |
| Iwamoto 2017 | 21.43 (15/70) | | | |
| Keystone 2017 | 52.63 (70/133) | | 6 (8/133) | |
| Mimori 2017 | 33.48 (965/2882) | | 7.67 (221/2882) | |
| Tanaka 2017 | 95.03 (134/141) | | 14.18 (20/141) | |
| Taylor 2017 | 78.85 (384/487) | 76.66 (253/330) | 7.80 (38/487) | 3.94 (13/330) |
| Vanhoutte 2017 | 15.30 (15/98) | 17.24 (5/29) | 0 | 0 |
| Avila Machado 2018 | 10.36 (17/164) | | | |
| Burmester 2018 | 55.22 (243/440) | 48.87 (108/221) | 3.41 (15/440) | 2.26 (5/221) |
| Cohen 2018 | 77.3/100 patient-year | | 12.7/100 patient-year | |
| Curtis 2018 | 6/100 patient-year | | | |
| Desai 2018 | 0.51 (15/2905) | | | |
| Genovese 2018 | 0–12 weeks: 61.39 (202/329)<br>12–24 weeks: 54.32 (245/451) | 56.21 (95/169) | 0–12 weeks: 6.08 (20/329)<br>12–24 weeks: 4.43 (20/451) | 0 (0/169) |
| Takeuchi 2018 | 55.45 (310/559) | | 6.08 (34/559) | |
| Tanaka 2018 | 52.15 (109/209) | | 4.31 (9/209) | |
| Yun 2018 | 0.93 (20/2155) | | | |
| Fleischmann 2019 | 41.13 (174/423) | | 3.78 (16/423) | |
| Genovese 2019 | 66.33 (199/300) | 67.56 (100/148) | 4.66 (14/300) | 3.37 (5/148) |
| Smolen 2019 | 48.15 (208/432) | 47.22 (102/216) | 3.93 (17/432) | 1.39 (6/432) |
| Takeuchi 2019 | 55.45 (310/559) | | 6.08 (34/559) | |
| Tanaka 2019 | 54.32 (377/694) | | 6.48 (45/694) | |
| Tanaka 2019 | 52.15 (109/209) | | 4.30 (9/209) | |

**Supplementary Table 2.** Continued

| Study | AE (%, n/N) JAK inhibitors patients | AE (%, n/N) comparator patients | SAE (%, n/N) JAK inhibitors patients | SAE (%, n/N) comparator patients |
|---|---|---|---|---|
| van der Heijde 2019 | 84.56 (674/797) | | 25.47 (203/797) | |
| Wollenhaupt 2019 | 90.07 (4036/4481) | | 29.97 (1343/4481) | |
| Psoriasis | | | | |
| Papp 2012 | 57.82 (85/147) | 60 (30/50) | 2.04 (3/147) | 0 (0/50) |
| Ports 2013 | 35 (25/71) –overall | | 0 (0/71)- overall | |
| Bissonnette 2014 | 65.91 (439/666) | | 2.55 (17/666) | |
| Bachelez 2015 | 57.36 (378/659) | 55.88 (247/442) | 1.82 (12/659) | 2.03 (9/442) |
| Papp 2015 | 55.85 (830/1486) | 48.79 (182/373) | 2.29 (34/1486) | 1.87 (7/373) |
| Asahina 2016 | 85.10 (78/94) | | 4.25 (4/94) | |
| Papp 2016 | 65.65 (1162/1770) | | 5.31 (94/1770) | |
| Papp 2016 | 55.27 (131/237) | 44.11 (15/34) | 1.68 (4/237) | 2.94 (1/34) |
| Zhang 2017 | 68.85 (168/244) | | 2.05 (5/244) | |
| Mease 2018 | 56.92 (37/65) | 59.09 (39/66) | 1.54 (1/65) | 0 (0/66) |
| Valenzuela 2018 | 82.52 (2366/2867) | | 13.67 (392/2867) | |
| Inflammatory bowel disease | | | | |
| Sandborn 2012 | 43.83 (64/146) | 47.91 (23/48) | 5.48 (8/146) | 8.33 (4/48) |
| Sandborn 2014 | 58.09 (61/105) | 64.70 (22/34) | 8.57 (9/105) | 14.70 (5/34) |
| Panes 2017 | Induction: 59.65 (102/171)<br>Maintenance: 57.31 (98/171) | Induction: 61.11 (55/90)<br>Maintenance: 48.89 (44/90) | Induction: 7.60 (13/171)<br>Maintenance: 8.18 (14/171) | Induction: 3.33 (3/90)<br>Maintenance: 7.77 (7/90) |
| Sandborn 2017 | 36.24 (328/905) | 56.41 (132/234) | 3.76 (34/905) | 5.98 (14/234) |
| Sandborn 2017 | 75.88 (299/394) | 75.25 (149/198) | 5.33 (21/394) | 6.56 (13/198) |
| Vermeire 2017 | 75 (114/152) | 67.16 (45/67) | 9.21 (14/152) | 4.47 (3/67) |
| Lichtenstein 2018 | 78.92 (745/944) | | 14.83 (140/944) | |
| Rubin 2018 | 72.72 (16/22) | | 0 (0/22) | |
| Sandborn 2018 | Not reported | Not reported | 3.91 (8/204) | 10.86 (5/46) |
| Panes 2018 | 70.22 (125/178) | | 14.60 (26/178) | |
| Deepak 2019 | 13.57 (19/140) | | 5.71 (8/140) | |
| Panaccione 2019 | 62.25 (127/204) | 71.74 (33/46) | 3.92 (8/204) | 10.87 (5/46) |
| Panes 2019 | 77.33 (116/150) | | 14.66 (22/150) | |
| Sandborn 2019 | 75.88 (299/394) | 75.3 (149/198) | 7.7 (15/196) | 6.6 (13/198) |
| Weisshof 2019 | 22.41 (13/58) | | | |
| Ankylosing spondylitis | | | | |
| van der Heijde 2017 | 50 (78/156) | 43.13 (22/51) | 1.28 (2/156) | 3.92 (2/51) |
| van der Heijde 2018 | 31.03 (18/58) | 31.03 (18/58) | 1.72 (1/58) | 0 (0/58) |

**Supplementary Table 3.** Proportion of Patients Showing Adverse Events of Interest

| Study | Serious infections (%, n/N) | Herpes zoster (%, n/N) | NMSC (%, n/N) | Other malignancy (%, n/N) | MACE (%, n/N) | DVT/PE (%, n/N) |
|---|---|---|---|---|---|---|
| **Rheumatoid arthritis** | | | | | | |
| Fleischmann 2012 | 0.65 (4/610) | | | 0.16 (1/610) | 0.65 (4/610) | 0.33 (2/610) |
| Fleischmann 2012 | 1.10 (3/272) | | | | 0.36 (1/272) | |
| Kremer 2012 | 1.14 (5/438) | | | | | |
| van Vollenhoven 2012 | 1.75 (9/513) | | | | | |
| Burmester 2013 | 1.25 (5/399) | | | | | 0.25 (1/399) |
| Kremer 2013 | 1.15 (9/779) | 0.13 (1/779) | | | 0.38 (3/779) | |
| McInes 2013 | 1.80 (2/111) | | | | | |
| van der Heijde 2013 | 2.38 (19/797) | | 0.51 (4/797) | 0.75 (6/797) | 0.75 (6/797) | |
| Lee 2014 | 2.46 (19/770) | | | 0.65 (5/770) | | |
| Sonomoto 2014 | | 15.9 (7/44) | | | | |
| Tanaka 2014 | | 1.51 (4/265) | | | | |
| Wollenhaupt 2014 | 3.24 (133/4102) | 4.41 (181/4102) | | | 0.29 (12/4102) | |
| Keystone 2015 | 0.98 (2/203) | | | | | |
| Kremer 2015 | 1.03 (1/97) | | | | | |
| Curtis 2016 | | 2.93 (74/2526) | | | | |
| Fleischmann 2016 | 2.46 (19/770) | | | | | |
| Fleischmann 2016 | 2.94 (11/374) | 2.40 (9/374) | 0.26 (1/374) | 1.33 (5/374) | 0.26 (1/374) | 0.26 (1/374) |
| Genovese 2016 | 0.40 (1/249) | 1.20 (3/249) | 0 (0/249) | 0.40 (1/249) | 0.40 (1/249) | |
| Genovese 2016 | 2.85 (10/351) | 2.56 (9/351) | 0.57 (2/351) | 0.57 (2/351) | 0.57 (2/351) | 0.28 (1/351) |
| Kavanaugh 2016 | 1.45 (4/276) | 1.31 (1/276) | | | | |
| Kremer 2016 | 0 (0/220) | 1.36 (3/220) | 0.45 (1/220) | | 0.45 (1/220) | 0.91 (2/220) |
| Westhovens 2016 | 0.93 (5/538) | 0.74 (4/538) | | | | |
| Yamanaka 2016 | | 19.3 (94/486) | | 3.9 (19/486) | | |
| Dougados 2017 | 1.31 (6/456) | 1.53 (7/456) | 0.22 (1/456) | 0.22 (1/456) | 0 (0/456) | 0.22 (1/456) |
| Fleischmann 2017 | 2.10 (16/760) | 1.58 (12/760) | 0.26 (2/760) | 0.13 (1/760) | 0 (0/760) | |
| Iwamoto 2017 | | 7.14 (5/70) | | 1.43 (1/70) | | |
| Keystone 2017 | 3 (4/133) | 0.7 (1/133) | | | | |
| Mimori 2017 | 3.50 (101/2882) | 3.40 (98/2882) | | 0.73 (21/2882) | | |
| Tanaka 2017 | 5 (7/142) | 8.4 (12/142) | | 0.7 (1/142) | | |
| Taylor 2017 | 2.05 (10/487) | 2.26 (11/487) | 0 (0./487) | 0.20 (1/487) | 0.41 (2/487) | |
| Burmester 2018 | 0.91 (4/440) | 0.68 (3/440) | 0.23 (1/440) | 0.23 (1/440) | 0.23 (1/440) | |
| Cohen 2018 | 9.46 (879/9291) | 0.07 (7/9291) | 0.17(16/9291) | 0.72 (67/9291) | 1.58 (147/9291) | 0.16 (15/9291) |
| Desai 2018 | | | | | | 0.51 (15/2905) |
| Genovese 2018 | 0-12 weeks: 1.52 (5/329) 12-24 weeks: 1.33 (6/451) | 0-12 weeks: 1.52 (5/329) 12-24 weeks: 1.1 (5/451) | | 0-12 weeks: 0.91 (3/329) 12-24 weeks: 0.22 (1/451) | 0.-12 weeks: 0.3 (1/329) 12-24 weeks: 0.22 (1/451) | 0-12 weeks: 0.30 (1/329) 12-24 weeks: 0.66 (3/451) |
| Takeuchi 2018 | 1.96 (11/59) | | | | | |
| Tanaka 2018 | 2.87 (6/209) | 0.95 (2/209) | | 0.95 (2/209) | | |
| Yun 2018 | | | | | | 0.93 (20/2155) |
| Curtis 2019 | | 2.76 (222/8030) | | | | |
| Fleischmann 2019 | 1.42 (6/423) | | | | | |
| Genovese 2019 | 1.33 (4/300) | 1.33 (4/300) | 0 (0/300) | 0 (0/300) | 0.33 (1/300) | 0.33 (1/300) |
| Smolen 2019 | 0.23 (1/432) | 2.08 (9/432) | 0 (0/432) | 0.46 (2/432) | 0.69 (3/432) | 0.23 (1/432) |
| Takeuchi 2019 | 1.61 (9/559) | | | | | |
| Tanaka 2019 | 1.73 (12/694) | 1.73 (12/694) | | | | |
| van der Heijde 2019 | 5.52 (44/797) | 7.9 (63/797) | 1.25 (10/797) | 2.51 (20/797) | 2.01 (16/797) | |
| Wollenhaupt 2019 | (395/4481) | (526/4481) | (116/4481) | (138/4481) | (62/4481) | 0.98 (44/4481) |
| Psoriasis | | | | | | |
| Bachelez 2015 | 0.61 (4/659) | 0.45 (3/659) | 0.30 (2/659) | 0.15 (1/659) | 0.15 (1/659) | |
| Papp 2015 | 0.33 (5/1486) | 0.81 (12/1486) | 0.13 (2/1486) | 0.27 (4/1486) | 0.20 (3/1486) | |
| Asahina 2016 | | 17.02 (16/94) | | | | |
| Papp 2016 | 1.64 (29/1770) | 1.13 (20/1770) | 0.62 (11/1770) | 0.79 (14/1770) | 0.28 (5/1770) | |
| Zhang 2017 | 1.1 (3/266) | 4.5 (12/266) | | 1.1 (3/266) | 0 (0/266) | |
| Avila Machado 2018 | 10.36 (17/164) | | | | | |
| Mease 2018 | 1.54 (1/65) | 1.54 (1/65) | | 0 (0/65) | 1.54 (1/65) | 0 (0/65) |
| Inflammatory Bowel Disease | | | | | | |
| Sandborn 2012 | 1.37 (2/146) | | | | | |
| Sandborn 2014 | 0.95 (1/105) | | | | | |

**Supplementary Table 3.** Continued

| Study | Serious infections (%, n/N) | Herpes zoster (%, n/N) | NMSC (%, n/N) | Other malignancy (%, n/N) | MACE (%, n/N) | DVT/PE (%, n/N) |
|---|---|---|---|---|---|---|
| Panes 2017 | | 1.17 (2/171) | | 0.58 (1/171) | | |
| Sandborn 2017 | | 3.29 (13/394) | 0.76 (3/394) | 0 (0/394) | 0.51 (2/394) | |
| Sandborn 2017 | | 0.54 (1/183) | 0.54 (1/183) | | 1.09 (2/183) | |
| Vermeire 2017 | 2.63 (4/152) | 0.66 (1/152) | | | | |
| Lichtenstein 2018 | 2.96 (28/944) | 6.03 (57/944) | 1.38 (13/944) | 1.38 (13/944) | 0.21 (2/944) | |
| Panes 2018 | | | | 1.12 (2/178) | | |
| Deepak 2019 | | 3.57 (5/140) | | | | |
| Panaccione 2019 | 1.47 (3/204) | 0.49 (1/204) | | 0.49 (1/204) | | |
| Panes 2019 | 2.66 (4/150) | 2 (3/150) | 0.66 (1/150) | 0 (0/150) | | |
| Sandborn 2019 | 2.85 (33/1157) | 5.62 (65/1157) | 0.95 (11/1157) | 0.95 (11/1157) | 0.34 (4/1157) | 0.43 (5/1157) |
| **Ankylosing spondylitis** | | | | | | |
| van der Heijde 2017 | 0.64 (1/156) | 1.28 (2/156) | 0 (0/156) | 0 (0/156) | 0 (0/156) | |
| van der Heijde 2018 | 1.72 (1/58) | N/A | 0 (0/58) | 0 (0/58) | 1.72 (1/58) | 1.72 (1/58) |

DVT, deep vein thrombosis; PE, pulmonary embolism.

**Supplementary Table 4.** Incidence Rates (per 100 Person/y) of JAK Inhibitors Adverse Events

| | All patients (n = 66,159) | Tofacitinib patients (n = 57,667) | Baricitinib patients (n = 4632) | Upadacitinib patients (n = 2373) | Filgotinib patients (n = 1487) |
|---|---|---|---|---|---|
| AEs | 42.69 | 32.35 | 71.69 | 133.52 | 144.96 |
| SAEs | 9.98 | 9.06 | 6.67 | 12.66 | 8.61 |
| Serious infections | 3.36 | 3.91 | 2.15 | 2.16 | 3.33 |
| Herpes zoster | 2.11 | 1.62 | 2.16 | 3.92 | 1.83 |
| Malignancy | 0.75 | 0.62 | 0.64 | 1.01 | 0 |
| NMSC | 0.51 | 0.37 | 0.32 | 0.73 | 0 |
| MACE | 0.67 | 0.48 | 0.40 | 1.47 | 1.97 |
| DVT/PE | 0.31 | 0.15 | 0.50 | 1.81 | 1.31 |

DVT/PE, deep vein thrombosis /pulmonary embolism.

**Supplementary Table 5.** Pooled Analysis of AEs and SAEs Stratified by JAK Inhibitor Dosage

| | AEs [RR (95%CI)] | SAEs [RR (95%CI)] |
|---|---|---|
| **Tofacitinib** | | |
| 5 mg BID | 1 | 1 |
| 10 mg BID | 1.03 (0.99-1.07) | 0.99 (0.9-1.08) |
| 15 mg BID | 1.12 (1-1.26) | 0.57 (0.12-2.64) |
| **Baricitinib** | | |
| 2 mg | 1 | 1 |
| 4 mg | 1.07 (0.99-1.16) | 1.43 (0.62-3.32) |
| 8 mg | 1.25 (1.01-1.53) | 1.05 (0.35-3.12) |
| **Upadacitinib** | | |
| 15 mg | 1 | 1 |
| 30 mg | 1 (0.89-1.13) | 0.68 (0.36-1.31) |
| **Filgotinib** | | |
| 100 mg | 1 | 1 |
| 200 mg | 1.16 (1.03-1.31) | 1.16 (.35-3.77) |

AE, adverse event; RR, risk ratio; SAE, serious adverse event.

**Supplementary Table 6.** Pooled Risk of AE According to Type of JAK Inhibitor (Controlled Studies)

| | Tofacitinib, RR (95% CI) | Baricitinib, RR (95% CI) | Upadacitinib, RR (95% CI) | Filgotinib, RR (95% CI) |
|---|---|---|---|---|
| AEs | 0.99 (0.93–1.06) | 1.04 (0.99–1.09) | 1.07 (0.97–1.19) | 1 (0.91–1.10) |
| SAEs | 0.93 (0.79–1.13) | 0.94 (0.63–1.40) | 1.11 (0.59–2.09) | 1.11 (0.42–2.90) |
| SI | 1.03 (0.68–1.54) | 1.11 (0.58–2.14) | 0.68 (0.24–1.93) | 1.76 (0.52–5.99) |
| HZ | 1.50 (0.76–2.96) | 2.05 (0.99–4.24) | 1.09 (0.41–2.86) | 1.28 (0.32–5.07) |
| Malignancy | 1.15 (0.39–3.40) | 2.30 (0.58–9.16) | 1.18 (0.32–4.36) | Not estimable |
| NMSC | 1.05 (0.38–2.93) | 1.88 (0.31–11.48) | 0.58 (0.09–3.67) | Not estimable |
| MACE | 1.19 (0.44–3.19) | 0.57 (0.15–2.16) | 1.41 (0.35–5.67) | 1.47 (0.26–8.41) |
| DVT/PE | 0.27 (0.06–1.29) | 2.81 (0.14–58.33) | 2.34 (0.27–20.19) | 2.11 (0.22–20.13) |

CI, confidence interval; DVT/PE, deep vein thrombosis/pulmonary embolism; HZ, herpes zoster; SI, serious infections.