# **CLINICAL—ALIMENTARY TRACT**

## 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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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.



**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 personyears, 2.67 per 100 person-years, 0.89 per 100 personyears, 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.

Inflammatory bowel disease (IBD) comprises 2 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 (ie, anti-tumor necrosis factor [TNF] agents, vedolizumab, and ustekinumab).<sup>3</sup> 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.<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, 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 filgotinib. Some of these compounds and others have been approved or are currently being tested in other immunemediated inflammatory diseases (IMIDs), such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriasis (PSO).<sup>9</sup> Tofacitinib has been approved by the 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 the FDA and European Medicines Agency for the treatment of moderately to severely active RA.<sup>12,13</sup> IAK 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.<sup>14</sup> 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.<sup>15</sup> Finally, previous

#### 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.

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).<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 nonrandomized) 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.

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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, psoriasi; RA, rheumatoid arthritis; RCT, randomized controlled trial; RR, relative risk; SAE, serious adverse event; TNF, tumor necrosis factor; UC, ulcerative colitis.

Most current article

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,<sup>19–70</sup> 11 studies on patients with PSO,<sup>71–81</sup> 16 studies on patients with IBD,<sup>82-93</sup> and 2 studies on patients with AS.<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 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 personyears 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,	264	8 wk	Tofacitinib 5 mg BID; Tofacitinib 15 mg BID; Tofacitinib 30 mg BID; placebo
Cohen 2010	Phase 1, open-label	12	9 d	Tofacitinib 30 mg
Tanaka 2011	Phase 2, randomized, double-blind, placebo-controlled,	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
McIness 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	301	24 wk	Baricitinib 1 mg QD; Baricitinib 2 mg QD; Baricitinib 4 mg QD; Baricitinib 8 mg QD;
Kremer 2015	study Phase 1, randomized, placebo-controlled,	148	12 wk	piacebo 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 BlD; Filgotinib 100 mg BlD; Filgotinib 200 mg BlD; 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	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	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	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	2155	24 wk	Tofacitinib at any dose
Curtis 2019	Retrospective cohort study	8030	260 wk	Tofacitinib at any dose
Fleischmann 2019	Long-term extension	423	24 wk	Baricitinib 4 mg QD
Genovese 2019	Phase 3, randomized, double-blind, placebo-controlled	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	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

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## Table 1. Continued

Author	Study design	No. of patients	Study duration	Exposure
van der Heijde 2019	Phase 3, randomized, placebo-controlled	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	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-	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	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
Рарр 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	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	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 dis	sease			
Sandborn 2012	Phase 2, randomized, double-blind, placebo-controlled	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
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

	JAK inhi	ibitors	Contr	ol		<b>Risk Ratio</b>		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	l Year	M-H, Random, 95% Cl
1.3.1 Rheumatoid Arthu	ritis							
Fleischmann 2012 (1)	4	610	0	122	1.1%	1.81 [0.10, 33.44]	2012	· · · · · · · · · · · · · · · · · · ·
van Vollenhoven 2012	9	513	1	204	2.2%	3.58 [0.46, 28.07]	2012	· · · · · · · · · · · · · · · · · · ·
Kremer 2012	5	438	0	69	1.1%	1.75 [0.10, 31.37]	2012	
Fleischmann 2012	3	272	1	156	1.8%	1.72 [0.18, 16.40]	2012	
Burmester 2013	5	399	0	132	1.1%	3.66 [0.20, 65.71]	2013	
Kremer 2013	9	779	0	159	1.2%	3.90 [0.23, 66.62]	2013	
van der Heijde 2013	19	797	0	160	1.2%	7.87 [0.48, 129.65]	2013	
Lee 2014	19	770	5	186	9.9%	0.92 [0.35, 2.43]	2014	
Keystone 2015	2	203	0	98	1.0%	2.43 [0.12, 50.06]	2015	
Kremer 2015	1	97	0	51	0.9%	1.59 [0.07, 38.39]	2015	· · · · · · · · · · · · · · · · · · ·
Genovese 2016	10	351	0	176	1.2%	10.56 [0.62, 179.17]	2016	· · · · · · · · · · · · · · · · · · ·
Westhovens 2016	5	538	1	56	2.1%	0.52 [0.06, 4.38]	2016	
Genovese 2016 (1)	1	249	0	50	0.9%	0.61 [0.03, 14.81]	2016	
Kremer 2016	0	220	1	56	0.9%	0.09 [0.00, 2.08]	2016	• • • • • • • • • • • • • • • • • • •
Fleischmann 2016	19	770	5	186	9.9%	0.92 [0.35, 2.43]	2016	
Fleischmann 2016 (1)	11	374	8	210	11.7%	0.77 [0.32, 1.89]	2016	
Dougados 2017	6	456	4	228	6.0%	0 75 [0 21, 2 63]	2017	
Eleischmann 2017	16	760	6	386	10.9%	1.35 [0.53, 3.43]	2017	·
Taylor 2017	10	487	5	330	8.3%	1.36 [0.47 3 03]	2017	· · · · · ·
Genovese 2018	6	451	0	169	1 1%	4 80 10 28 86 221	2018	
Rumester 2018	4	40	1	221	2 0%	2 01 10 22 17 27	2010	
Smolen 2010	4	440	1	216	1 2%	0.50 10.23, 17.07]	2010	
	1	402	י ס	1/0	2 20/	0.00 [0.03, 7.90]	2019	
Subtotal (95% CI)	4	10706	2	3769	81 2%	1 16 10 83 1 641	2019	· •
Tatal aventa	100	10700	44	5705	01.270	1.10 [0.00, 1.04]		T
lotal events	109 00. Chi2 - 1	14 70 df	- 22 (D	07), 1	2 00/			
Test for overall effect: Z	= 0.87 (P =	= .38)	- 22 (r =	.07), 1	- = 070			
1.3.2 Psoriasis	_							
Papp 2015	5	1486	2	373	3.5%	0.63 [0.12, 3.22]	2015	
Bachelez 2015	4	659	2	442	3.3%	1.34 [0.25, 7.29]	2015	
Mease 2018 Subtotal (95% CI)	1	65 2210	0	66 <b>881</b>	0.9% 7.7%	3.05 [0.13, 73.42] 1.05 [0.35, 3.16]	2018	•
Total events	10		4					
Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z	00; Chi² = 0 = 0.08 (P =	0. <b>90</b> , df = = .93)	<b>2</b> (P = .6	64); l² =	0%			
1.3.3 Inflammatory Bov	vel Diseas	е						
Sandborn 2012	2	146	0	48	1.0%	1.67 [0.08, 34.12]	2012	
Sandborn 2014	1	105	4	34	2.0%	0.08 [0.01, 0.70]	2014	· •
Vermeire 2017	4	152	0	67	1.1%	4.00 [0.22, 73.26]	2017	· · · · · · · · · · · · · · · · · · ·
Sandborn 2017	0	905	0	234		Not estimable	2017	,
Sandborn 2017 (1)	0	394	2	198	1.0%	0.10 [0.00, 2.09]	2017	· •
Panes 2017	0	171	2	90	1.0%	0.11 [0.01, 2.18]	2017	· •
Panaccione 2019	3	204	2	46	3.0%	0.34 [0.06, 1.97]	2019	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		2077		717	9.2%	0.32 [0.09, 1.06]		
Total events	10		10					
Heterogeneity: Tau² = 0. Test for overall effect: Z	60; Chi² = 0 = 1.86 ( <i>P</i> =	6. <b>78</b> , df = = .06)	5 (P = .2	24); I <sup>2</sup> =	26%			
1.3.4 Ankylosing Spon	dylitis							
van der Heijde 2017	1	156	0	51	0.9%	0.99 [0.04, 24.02]	2017	·
van der Heijde 2018 Subtotal (95% CI)	1	58 214	0	58 <b>109</b>	0.9% 1 <b>.9%</b>	3.00 [0.12, 72.15] 1.73 [0.18, 16.40]	2018	
Total events	2		0					
Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z	00; Chi² = 0 = 0.48 (P =	0.23, df = 63)	• 1 (P = .6	63); I² =	0%			
Total (95% CI)		15207		5476	100.0%	1.03 [0.76, 1.40]		
Total events	191		55					
Heterogeneity: Tau <sup>2</sup> = 0.	00; Chi <sup>2</sup> = 2	28.55, df	= 33 (P =	.69); I	<sup>2</sup> = 0%			
Test for overall effect: Z	= 0.17 (P =	= .86)						OUT U.T T TU 100
Test for subgroup differe	nces: Chi <sup>2</sup>	= 4.29, d	f = 3 (P =	.23); F	<sup>2</sup> = 30.1%	, )	Г	avours JAK IIIIIDILOIS FAVOUIS CONTO

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

	JAK inhi	bitors	Contr	ol		<b>Risk Ratio</b>		Risk Ratio	
Study or Subgroup	Events	Total	<b>Events</b>	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl	
1.4.1 Rheumatoid Arthr	itis								
Kremer 2013	1	779	0	159	1.7%	0.62 [0.03, 15.04]	2013 -		
Tanaka 2014	4	265	0	52	2.0%	1.79 [0.10, 32.81]	2014		
Fleischmann 2016 (1)	9	374	2	210	7.3%	2.53 [0.55, 11.59]	2016		
Kremer 2016	3	220	2	56	5.4%	0.38 [0.07, 2.23]	2016		
Westhovens 2016	4	538	1	56	3.6%	0.42 [0.05, 3.66]	2016		
Genovese 2016 (1)	3	249	0	50	1.9%	1.43 [0.07, 27,22]	2016		
Genovese 2016	9	351	2	176	7.3%	2.26 [0.49, 10.33]	2016		
Fleischmann 2017	12	760	6	386	17.9%	1.02 [0.38, 2.69]	2017	_ <b>+</b> _	
Dougados 2017	7	456	0	228	2.1%	7.52 [0.43, 131.03]	2017		→
Taylor 2017	11	487	5	330	15.4%	1.49 [0.52, 4.25]	2017		
Burmester 2018	3	440	1	221	3.3%	1.51 [0.16, 14.40]	2018		
Genovese 2018	5	451	1	169	3.7%	1.87 [0.22, 15.92]	2018		
Smolen 2019	9	432	1	216	4.0%	4.50 [0.57, 35,29]	2019		
Genovese 2019	4	300	O	148	2.0%	4 46 [0 24 82 20]	2019		-
Subtotal (95% CI)	т	6102	0	2457	77.5%	1.45 [0.91, 2.31]	2010	•	
Total events	84		21						
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>2</sup> = 8	3.51, df =	= <b>13</b> (P =	.81); l <sup>2</sup>	= 0%				
Test for overall effect: Z =	= 1.55 (P =	.12)	,	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,					
	,	,							
1.4.2 Psoriasis									
Papp 2015	12	1486	0	373	2.1%	6.29 [0.37, 105.96]	2015		•
Bachelez 2015	3	659	2	442	5.3%	1.01 [0.17, 6.00]	2015		
Mease 2018	1	65	0	66	1.7%	3.05 [0.13, 73.42]	2018		
Subtotal (95% CI)		2210		881	9.1%	1.89 [0.48, 7.39]			
Total events	16		2						
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>2</sup> = 1	1.39, df =	= 2 (P = .	50); l² =	: 0%				
Test for overall effect: Z =	<b>= 0.91</b> (P =	: .36)							
1 4 3 Inflammatory Bow	al Diease	a							
O-mails and 0047 (4)	el Discas			400	4 40/	0 50 10 00 40 501	0047		
Sandborn 2017 (1)	13	394	1	198	4.1%	6.53 [0.86, 49.58]	2017		
Sandborn 2017	1	183	1	234	2.2%	1.28 [0.08, 20.31]	2017		
Vermeire 2017	1	152	0	67	1.7%	1.33 [0.06, 32.31]	2017		
Panes 2017	2	1/1	0	90	1.8%	2.65 [0.13, 54.52]	2017		
Panaccione 2019 Subtotal (95% CI)	1	204	U	40	1.7%	0.69 [0.03, 16.62]	2019		
Subtotal (95% CI)	40	1104	•	035	11.570	2.37 [0.70, 7.90]			
I otal events	10 00. 01:2 - 4		- <b>A</b> (D	7 4) . 12	00/				
Heterogeneity: Tau <sup>2</sup> = 0.0	JU; Cnr = /	2.00, dr =	= 4 (P = .	(4); 1-=	= 0%				
Test for overall effect: Z -	= 1.39 (P =	:.10)							
1.4.4 Ankylosing Spond	lvlitis								
van der Heijde 2017	2	156	n	51	1 9%	1 66 [0 08 33 04]	2017		
Subtotal (95% CI)	2	156	Ŭ	51	1.9%	1.66 [0.08, 33.94]	2011		
Total events	2		0			•			
Heterogeneity: Not applic	able								
Test for overall effect: Z	= <b>0.33</b> (P =	.74)							
								•	
Total (95% CI)		9572		4024	100.0%	1.57 [1.04, 2.37]		-	
Total events	120		25					,	
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>2</sup> =	12.61, df	= 22 (P =	= .94); I	<sup>2</sup> = 0%		0.01	0.1 1 10 10	0
Test for overall effect: Z =	<b>= 2.16</b> ( <i>P</i> =	: .03)					Favours	JAK inhibitors Favours control	5
Test for subgroup differe	nces: Chi <sup>2</sup>	= 0.63, d	lf=3 (P=	= .89); I	<sup>∠</sup> = 0%				

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Figure 2. Pooled analysis of herpes zoster in controlled studies. Cl, 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

	JAK inhi	ibitors	Contr	ol		<b>Risk Ratio</b>		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	Year	M-H, Random, 95% Cl
1.6.1 Rheumatoid Arth	ritis							
van der Heijde 2013	4	797	0	160	7.6%	1.82 [0.10, 33.56]	2013	
Fleischmann 2016 (1)	1	374	0	210	6.3%	1.69 [0.07, 41.25]	2016	
Genovese 2016	2	351	0	176	7.0%	2.51 [0.12, 52.09]	2016	
Genovese 2016 (1)	0	249	0	50		Not estimable	2016	
Kremer 2016	1	220	0	56	6.3%	0.77 [0.03, 18.74]	2016	
Dougados 2017	1	456	0	228	6.3%	1.50 [0.06, 36.76]	2017	
Fleischmann 2017	2	760	1	386	11.2%	1.02 [0.09, 11.17]	2017	
Taylor 2017	0	487	0	330		Not estimable	2017	
Burmester 2018	1	440	0	221	6.3%	1.51 [0.06, 36.92]	2018	
Genovese 2019	0	300	0	148		Not estimable	2019	
Smolen 2019	0	432	1	216	6.3%	0.17 [0.01, 4.08]	2019	• • •
Subtotal (95% CI)		4866		2181	57.3%	1.12 [0.39, 3.24]		$\bullet$
Total events	12		2					
Heterogeneity: Tau <sup>2</sup> = 0.	00; Chi² =	1.93, df =	<b>7</b> (P = .9	96); l² =	= 0%			
Test for overall effect: Z	= 0.22 (P =	= .83)						
1.6.2 Psoriasis								
Papp 2015	2	1486	0	373	7.0%	1.26 [0.06, 26.14]	2015	
Bachelez 2015	2	659	2	442	16.8%	0.67 [0.09, 4.74]	2015	
Subtotal (95% CI)		2145		815	23.8%	0.81 [0.16, 4.18]		
Total events	4		2					
Heterogeneity: Tau <sup>2</sup> = 0.	00; Chi² =	0.12, df =	= 1 (P = .:	73); l² =	= 0%			
Test for overall effect: Z	= 0.26 (P =	= .80)						
1.6.3 Inflammatory Boy	vel Diseas	e						
Sandborn 2017 (1)	3	394	1	198	12.6%	1 51 [0 16 14 40]	2017	
Sandborn 2017 (1)	1	905	'n	234	6.3%		2017	
Subtotal (95% CI)		1299	0	432	18.9%	1.21 [0.19, 7.65]	2011	
Total events	4		1					
Heterogeneity: $Tau^2 = 0$ .	00: Chi <sup>2</sup> =	0.11. df =	= 1 (P = )	74)· 1² =	= 0%			
Test for overall effect: 7	= 0.20 (P)	= 84)			- 070			
	0.20 () -	04)						
1.6.4 Ankylosing Spon	dylitis							
van der Heijde 2017	0	156	0	51		Not estimable	2017	
van der Heijde 2018	0	58	0	58		Not estimable	2018	
Subtotal (95% CI)		214		109		Not estimable		
Total events	0		0					
Heterogeneity: Not appli	cable							
Test for overall effect: No	ot applicab	le						
Total (95% CI)		8524		3537	100.0%	1.05 [0.47. 2.35]		•
Total events	20		5					Ť
Heterogeneity: $Tau^2 = 0$	$00^{\circ}$ Chi <sup>2</sup> =	2.29 df=	= 11 (P -	1 00).	$^{2} = 0\%$		ł	
Test for overall effect: 7	= 0.13 (P -	= .90)			- 070		_ '	0.01 0.1 1 10 100
Test for subaroun differe	nces: Chi <sup>2</sup>	= 0.14	f = 2 (P =	93) · I	$^{2} = 0\%$		Fav	vours JAK Inhibitors Favours control
				,,	0,0			

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]).

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	JAK inhib	itors	Contr	ol		<b>Risk Ratio</b>		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	Year	M-H, Random, 95% Cl
1.5.1 Rheumatoid Arthr	itis							
Fleischmann 2012 (1)	1	610	0	122	5.0%	0.60 [0.02, 14.74]	2012	
van der Heijde 2013	6	797	0	160	6.2%	2.62 [0.15, 46.33]	2013	· · · · · · · · · · · · · · · · · · ·
Lee 2014	5	770	1	186	11.1%	1.21 [0.14, 10.28]	2014	
Genovese 2016	2	351	0	176	5.6%	2.51 [0.12, 52.09]	2016	
Fleischmann 2016 (1)	5	374	1	210	11.1%	2.81 [0.33, 23.87]	2016	
Genovese 2016 (1)	1	249	0	50	5.0%	0.61 [0.03, 14.81]	2016	
Dougados 2017	1	456	0	228	5.0%	1.50 [0.06, 36.76]	2017	
Taylor 2017	1	487	0	330	5.0%	2.03 [0.08, 49.80]	2017	
Fleischmann 2017	1	760	0	386	5.0%	1.53 [0.06, 37.36]	2017	
Burmester 2018	1	440	0	221	5.0%	1.51 [0.06, 36.92]	2018	
Genovese 2018	4	451	0	169	6.0%	3.38 [0.18, 62.54]	2018	
Smolen 2019	2	432	1	216	8.9%	1.00 [0.09, 10.97]	2019	
Genovese 2019	0	300	0	148		Not estimable	2019	
Subtotal (95% CI)		6477		2602	79.0%	1.59 [0.71, 3.56]		
Total events	30		3					
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>2</sup> = 1	.70, df =	= 11 (P =	1.00);	<sup>2</sup> = 0%			
Test for overall effect: Z =	= 1.14 (P =	.26)						
1.5.2 Psoriasis								
Papp 2015	4	1486	0	373	6.0%	2.26 [0.12, 41.95]	2015	
Mease 2018	0	65	0	66		Not estimable	2018	
Subtotal (95% CI)		1551		439	6.0%	2.26 [0.12, 41.95]		
Total events	4		0					
Heterogeneity: Not applic	able							
Test for overall effect: Z =	= 0.55 (P =	.58)						
1.5.3 Inflammatory Bow	el Disease	)						
Sandborn 2017	0	905	0	234		Not estimable	2017	
Panes 2017	1	171	0	90	5.0%	1.59 [0.07, 38.57]	2017	
Sandborn 2017 (1)	0	394	1	198	5.0%	0.17 [0.01, 4.10]	2017	• • • • • • • • • • • • • • • • • • • •
Panaccione 2019	1	204	0	46	5.0%	0.69 [0.03, 16.62]	2019	
Subtotal (95% CI)		1674		568	15.0%	0.57 [0.09, 3.59]		
Total events	2		1					
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>2</sup> = 0	.97, df =	• 2 (P = .6	52); l <sup>2</sup> =	= 0%			
Test for overall effect: Z =	= 0. <b>60</b> ( <i>P</i> =	.55)						
1.5.4 Ankylosing Spong	lulitis							
van der Heijde 2017	0	156	n	51		Not estimable	2017	
van der Heijde 2017	0	59	0	59		Not estimable	2017	
Subtotal (95% CI)	U	214	U	109		Not estimable	2010	
Total events	٥		0					
Heterogeneity: Not applic	vahle		U					
Test for overall effect. No	applicable	<del>,</del>						
	- approable	-						
Total (95% CI)		9916		3718	100.0%	1.39 [0.68, 2.85]		
Total events	36		4					
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi² = 3	.78, df =	= 15 (P =	1.00);	<sup>2</sup> = 0%			
Test for overall effect: Z =	= 0.91 (P =	.36)					F	avours IAK inhibitors Eavours control
Test for subgroup differen	nces: Chi <sup>2</sup> =	= 1.12, c	lf = 2 (P =	= .57); I	<sup>2</sup> = 0%		1.0	

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 patientyears). 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 **CLINICAL AT** 

	JAK inhit	oitors	Contr	ol		<b>Risk Ratio</b>		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
1.7.1 Rheumatoid Arthr	itis							
Fleischmann 2012 (1)	4	610	0	122	4.8%	1.81 [0.10, 33.44]	2012	· · · ·
Fleischmann 2012	1	272	0	156	4.0%	1.73 [0.07, 42.10]	2012	
Kremer 2013	3	779	0	159	4.7%	1.44 [0.07, 27.66]	2013	
van der Heijde 2013	6	797	0	160	5.0%	2.62 [0.15, 46.33]	2013	
Kremer 2016	1	220	0	56	4.0%	0.77 [0.03, 18.74]	2016	
Genovese 2016	2	351	0	176	4.5%	2.51 [0.12, 52.09]	2016	
Genovese 2016 (1)	1	249	0	50	4.0%	0.61 [0.03, 14.81]	2016	
Fleischmann 2016 (1)	1	374	2	210	7.2%	0.28 [0.03, 3.08]	2016	
Fleischmann 2017	0	760	2	386	4.5%	0.10 [0.00, 2.11]	2017	· · · · · · · · · · · · · · · · · · ·
Dougados 2017	0	456	2	228	4.5%	0.10 [0.00, 2.08]	2017	←
Taylor 2017	2	487	1	330	7.2%	1.36 [0.12, 14.89]	2017	
Genovese 2018	2	451	0	169	4.5%	1.88 [0.09, 38.97]	2018	
Burmester 2018	1	440	0	221	4.0%	1.51 [0.06, 36.92]	2018	•
Smolen 2019	3	432	0	216	4.7%	3.51 [0.18, 67.61]	2019	
Genovese 2019	1	300	1	148	5.4%	0.49 [0.03, 7.83]	2019	
Subtotal (95% CI)		6978		2787	72.9%	0.89 [0.42, 1.89]		
Total events	28		8					
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>2</sup> = 7	7.86, df =	= <b>14</b> (P =	.90); l²	= 0%			
Test for overall effect: Z :	= 0.29 (P =	.77)	¢					
	(	,						
1.7.2 Psoriasis								
Papp 2015	3	1486	0	373	4.7%	1.76 [0.09, 34.01]	2015	
Bachelez 2015	1	659	1	442	5.4%	0.67 [0.04, 10.69]	2015	
Mease 2018	1	65	0	66	4.1%	3.05 [0.13, 73.42]	2018	
Subtotal (95% CI)		2210		881	14.1%	1.43 [0.26, 7.87]		
Total events	5		1					
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi <sup>2</sup> = 0	).53, df =	<b>2</b> (P = .	77); l <sup>2</sup> =	: 0%			
Test for overall effect: Z =	= 0.41 (P =	.68)						
		,						
1.7.3 Inflammatory Bow	el Disease	9						
Sandborn 2017	2	905	0	234	4.5%	1.30 [0.06, 26.92]	2017	
Sandborn 2017 (1)	2	394	0	198	4.5%	2.52 [0.12, 52.22]	2017	
Subtotal (95% CI)		1299		432	8.9%	1.81 [0.21, 15.43]		
Total events	4		0					
Heterogeneity: Tau <sup>2</sup> = 0.0	00; $Chi^2 = 0$	).09, df =	= 1 (P = .)	76); l <sup>2</sup> =	0%			
Test for overall effect: Z :	= 0.54 (P =	.59)						
1.7.4 Ankylosing Spond	dylitis							
van der Heijde 2017	0	156	0	51		Not estimable	2017	
van der Heijde 2018	1	58	0	58	4.1%	3.00 [0.12, 72.15]	2018	
Subtotal (95% CI)		214		109	4.1%	3.00 [0.12, 72.15]		
Total events	1		0					
Heterogeneity: Not applie	cable							
Test for overall effect: Z =	= 0.68 (P =	.50)						
Total (95% CI)		10701		4209	100.0%	1.07 [0.56, 2.03]		<b>—</b>
Total events	38		9					
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi² = 9	9.43, df =	<b>= 20</b> (P =	.98); l²	= 0%			
Test for overall effect: Z	= 0.20 (P =	.84)					F	avours JAK inhibitors Favours control
Test for subgroup differe	nces: Chi <sup>2</sup> :	= 0.96, c	lf = 3 (P =	= .81); l	$^{2} = 0\%$			

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

	JAK inih	ibitor	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
1.2.1 Rheumatoid Arthr	itis							
Fleischmann 2012	2	610	0	122	11.6%	1.01 [0.05, 20.84]	2012	
Burmester 2013	1	399	0	132	10.5%	1.00 [0.04, 24.34]	2013	
Fleischmann 2016 (1)	2	374	0	210	11.6%	2.81 [0.14, 58.33]	2016	
Genovese 2018	4	451	0	169	12.6%	3.38 [0.18, 62.54]	2018	
Smolen 2019	1	432	0	216	10.5%	1.50 [0.06, 36.75]	2019	
Genovese 2019	1	300	0	148	10.5%	1.49 [0.06, 36.24]	2019	
Subtotal (95% CI)		2566		997	67.3%	1.70 [0.48, 6.01]		
Total events	11		0					
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi² =	0.57, df	= 5 (P =	.99); l²	<sup>2</sup> = 0%			
Test for overall effect: Z =	= 0.83 (P =	= .41)						
4.2.2 Desciencia								
1.2.2 PSoriasis	•	05	•	~~		N		
Mease 2018 Subtotal (95% CI)	U	65	U	66		Not estimable	2018	
Sublotal (95% CI)	0	05	0	00		Notestimable		
lotal events	0		U					
Heterogeneity: Not applic	able							
lest for overall effect: No	applicabl	le						
1.2.3 Inflammatory Bow	el Diseas	e						
Sandborn 2012	0	146	1	48	10.5%	0.11 [0.00, 2.68]	2012	• • •
Sandborn 2017	0	905	2	234	11.6%	0.05 [0.00, 1.08]	2017	←
Subtotal (95% CI)		1051		282	22.2%	0.07 [0.01, 0.67]		
Total events	0		3					
Heterogeneity: Tau <sup>2</sup> = 0.0	00; Chi² = 0	0.12, df	= 1 (P =	.73); l <sup>2</sup>	<sup>2</sup> = 0%			
Test for overall effect: Z =	= 2.32 (P =	= .02)						
1.2.4 Ankylosing Spond	lylitis							
van der Heijde 2018	1	58	0	58	10.6%	3.00 [0.12, 72.15]	2018	
Subtotal (95% CI)		58		58	10.6%	3.00 [0.12, 72.15]		
Total events	1		0					
Heterogeneity: Not applic	cable							
Test for overall effect: Z =	= 0.68 (P =	= .50)						
Total (95% CI)		3740		1403	100.0%	0.90 [0.32, 2 54]		
Total events	12	0140	2			0100 [0104, 2104]		
Hotorogonoity: Tau <sup>2</sup> = 0.0	12 10: Chi² - 1	7 15 df	-9(D_	52).12	2 - 0%			
Test for overall effect: 7 -	= 0 19 (P -	- 85)	-0(F=	.JZJ, F	- 070			0.01 0.1 1 10 100
Test for subgroup differen	- 0.19 (/* = nces: Chi²	= 6 48	df = 2 (P	- 04)	· 12 – 69 1	%		Favours JAK inhibitor Favours control
Test for subgroup differen	nces: Chi²	= 6.48,	df = 2 (P	= .04)	; l <sup>2</sup> = 69.1	%		Favours JAK Inhibitor Favours control

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

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 patients with UC,<sup>87</sup> 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.<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 particularly 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> In addition, 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,<sup>102</sup> the pooled risk of herpes zoster among patients with IMIDs exposed to nonanti-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]).<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 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.<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 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.<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 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.<sup>107</sup> 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.<sup>109</sup> Based on this finding, the FDA approved only baricitinib at 2 mg every day for RA in the United States.<sup>12</sup> Although it appears to be dose dependent, currently it is unknown whether this risk is modulated by IAK 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 openlabel extension phase).<sup>110</sup> Of note, patients who developed these events had at least 1 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 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,<sup>110</sup> 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.

## References

- 1. Torres J, Mehandru S, Colombel J-F, et al. Crohn's disease. Lancet 2016;2:37–41.
- 2. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. Lancet 2017;389:1756–1770.
- **3.** Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. Nat Rev Gastroenterol Hepatol 2015;12:537–545.
- Olivera P, Danese S, Peyrin-Biroulet L. JAK inhibition in inflammatory bowel disease. Expert Rev Clin Immunol 2017;13:693–703.
- 5. Olivera P, Danese S, Peyrin-Biroulet L. Next generation of small molecules in inflammatory bowel disease. Gut 2017;66:199–209.
- O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med 2013;368:161–170.
- Danese S, Grisham M, Hodge J, et al. JAK inhibition using tofacitinib for inflammatory bowel disease treatment: a hub for multiple inflammatory cytokines. Am J Physiol Gastrointest Liver Physiol 2016;310:G155–G162.
- 8. US Food and Drug Administration. FDA approves new treatment for moderately to severely active ulcerative colitis. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-moderately-severely-active-ulcerative-colitis. Accessed December 12, 2018.
- **9.** Baker KF, Isaacs JD. Novel therapies for immunemediated inflammatory diseases: what can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis? Ann Rheum Dis 2018; 77:175–187.
- US Food and Drug Administration. FDA approves Xeljanz for rheumatoid arthritis. 2012. Available at: http:// www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ ucm327152.htm. Accessed December 12, 2018.
- 11. US Food and Drug Administration. Xeljanz (tofacitinib citrate) 5 mg tablets for the treatment of psoriatic arthritis. 2017. Available at: https://www.fda.gov/media/ 106625/download. Accessed February 1, 2019.
- 12. US Food and Drug Administration. FDA briefing document Arthritis Advisory Committee meeting NDA 207924 baricitinib janus kinase (JAK) inhibitor for RA Eli Lilly and Company (Lilly). 2018. Available at: https://www.fda.gov/media/112372/download. Accessed February 1, 2019.
- 13. European Medicines Agency. Olumiant. 2018. Available at: https://www.ema.europa.eu/en/documents/overview/ olumiant-epar-medicine-overview\_en.pdf. Accessed February 1, 2019.
- 14. Allen PB, Olivera P, Emery P, et al. Review article: moving towards common therapeutic goals in Crohn's

disease and rheumatoid arthritis. Aliment Pharmacol Ther 2017;45:1058–1072.

- Danese S, Bonovas S, Peyrin-Biroulet L. Biosimilars in IBD: from theory to practice. Nat Rev Gastroenterol Hepatol 2017;14:22–31.
- Capogrosso Sansone A, Mantarro S, Tuccori M, et al. Safety profile of certolizumab pegol in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis. Drug Saf 2015;38:869–888.
- 17. Souto A, Maneiro JR, Salgado E, et al. Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases treated with biologics and tofacitinib: a systematic review and meta-analysis of randomized controlled trials and long-term extension studies. Rheumatology (Oxford) 2014;53:1872–1885.
- 18. Olivera P, Peyrin-Biroulet L, Danese S, et al. Safety of janus kinase inhibitors in inflammatory bowel disease and other immune-mediated diseases: a systematic review. PROSPERO: International prospective register of systematic reviews 2019. CRD42019121662. Available at: https://www.crd.york.ac.uk/prospero/display\_record. php?ID=CRD42019121662. Accessed June 20, 2019.
- **19.** Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebocontrolled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum 2009; 60:1895–1905.
- Cohen S, Zwillich SH, Chow V, et al. Co-administration of the JAK inhibitor CP-690,550 and methotrexate is well tolerated in patients with rheumatoid arthritis without need for dose adjustment. Br J Clin Pharmacol 2010; 69:143–151.
- 21. McInnes IB, Kim H-Y, Lee S-H, et al. Open-label tofacitinib and double-blind atorvastatin in rheumatoid arthritis patients: a randomised study. Ann Rheum Dis 2014;73:124–131.
- Sonomoto K, Yamaoka K, Kubo S, et al. Effects of tofacitinib on lymphocytes in rheumatoid arthritis: relation to efficacy and infectious adverse events. Rheumatology (Oxford) 2014;53:914–918.
- 23. Wollenhaupt J, Silverfield J, Lee EB, et al. Safety and efficacy of tofacitinib, an oral janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. J Rheumatol 2014;41:837–852.
- Lee EB, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014; 370:2377–2386.
- 25. Keystone EC, Taylor PC, Drescher E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis 2015;74:333–340.
- 26. Kremer JM, Kivitz AJ, Simon-Campos JA, et al. Evaluation of the effect of tofacitinib on measured glomerular filtration rate in patients with active rheumatoid arthritis: results from a randomised controlled trial. Arthritis Res Ther 2015;17:95.
- 27. Tanaka Y, Takeuchi T, Yamanaka H, et al. Efficacy and safety of tofacitinib as monotherapy in Japanese

Gastroenterology Vol. 158, No. 6

patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. Mod Rheumatol 2015; 25:514–521.

- 28. Yamanaka H, Tanaka Y, Takeuchi T, et al. Tofacitinib, an oral Janus kinase inhibitor, as monotherapy or with background methotrexate, in Japanese patients with rheumatoid arthritis: an open-label, long-term extension study. Arthritis Res Ther 2016;18:34.
- 29. Tanaka Y, Emoto K, Cai Z, et al. Efficacy and safety of baricitinib in Japanese patients with active rheumatoid arthritis receiving background methotrexate therapy: a 12-week, double-blind, randomized placebo-controlled study. J Rheumatol 2016;43:504–511.
- **30.** Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med 2016;374:1243–1252.
- Tanaka Y, Suzuki M, Nakamura H, et al. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken) 2011;63:1150–1158.
- **32.** Fleischmann RM, Huizinga TWJ, Kavanaugh AF, et al. Efficacy of tofacitinib monotherapy in methotrexatenaive patients with early or established rheumatoid arthritis. RMD Open 2016;2:1–10.
- **33.** Curtis JR, Xie F, Yun H, et al. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016;75:1843–1847.
- 34. Mohamed M-EF, Camp HS, Jiang P, et al. Pharmacokinetics, safety and tolerability of ABT-494, a novel selective JAK 1 inhibitor, in healthy volunteers and subjects with rheumatoid arthritis. Clin Pharmacokinet 2016; 55:1547–1558.
- **35.** Kremer JM, Emery P, Camp HS, et al. A phase IIb study of ABT-494, a selective JAK-1 inhibitor, in patients with rheumatoid arthritis and an inadequate response to antitumor necrosis factor therapy. Arthritis Rheumatol (Hoboken) 2016;68:2867–2877.
- **36.** Genovese MC, Smolen JS, Weinblatt ME, et al. Efficacy and safety of ABT-494, a selective JAK-1 inhibitor, in a phase IIb study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Rheumatol (Hoboken) 2016;68:2857–2866.
- 37. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis 2017;76:88–95.
- **38.** Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med 2017;376:652–662.
- **39.** Fleischmann R, Schiff M, van der Heijde D, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior diseasemodifying antirheumatic drug treatment. Arthritis Rheumatol (Hoboken) 2017;69:506–517.
- 40. Iwamoto N, Tsuji S, Takatani A, et al. Efficacy and safety at 24 weeks of daily clinical use of tofacitinib in patients with rheumatoid arthritis. PLoS One 2017;12:e0177057.

- 41. Kavanaugh A, Kremer J, Ponce L, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). Ann Rheum Dis 2017;76:1009–1019.
- 42. Fleischmann R, Cutolo M, Genovese MC, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum 2012;64:617–629.
- **43.** Westhovens R, Taylor PC, Alten R, et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). Ann Rheum Dis 2017; 76:998–1008.
- 44. Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet 2017;390:457–468.
- 45. Vanhoutte F, Mazur M, Voloshyn O, et al. Efficacy, safety, pharmacokinetics, and pharmacodynamics of filgotinib, a selective JAK-1 inhibitor, after short-term treatment of rheumatoid arthritis: results of two randomized phase Ila trials. Arthritis Rheumatol (Hoboken) 2017;69:1949–1959.
- 46. Tanaka Y, Ishii T, Cai Z, et al. Efficacy and safety of baricitinib in Japanese patients with active rheumatoid arthritis: A 52-week, randomized, single-blind, extension study. Mod Rheumatol 2018;28:20–29.
- Machado MAÁ, Moura CS, Guerra SF, et al. Effectiveness and safety of tofacitinib in rheumatoid arthritis: a cohort study. Arthritis Res Ther 2018;20:60.
- Genovese MC, Kremer JM, Kartman CE, et al. Response to baricitinib based on prior biologic use in patients with refractory rheumatoid arthritis. Rheumatology (Oxford) 2018;57:900–908.
- 49. Cohen S, Curtis JR, DeMasi R, et al. Worldwide, 3-year, post-marketing surveillance experience with tofacitinib in rheumatoid arthritis. Rheumatol Ther 2018;5:283–291.
- **50.** Burmester GR, Kremer JM, van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018; 391:2503–2512.
- **51.** Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet 2018;391:2513–2524.
- 52. Tanaka Y, Sugiyama N, Toyoizumi S, et al. Modifiedversus immediate-release tofacitinib in Japanese

rheumatoid arthritis patients: a randomized, phase III, non-inferiority study. Rheumatology (Oxford) 2019; 58:70–79.

- 53. Kremer JM, Cohen S, Wilkinson BE, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum 2012;64:970–981.
- 54. Takeuchi T, Genovese MC, Haraoui B, et al. Dose reduction of baricitinib in patients with rheumatoid arthritis achieving sustained disease control: results of a prospective study. Ann Rheum Dis 2019;78:171–178.
- 55. van der Heijde D, Strand V, Tanaka Y, et al. Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: clinical efficacy, radiographic, and safety outcomes from a twenty-four-month, phase III study. Arthritis Rheumatol (Hoboken) 2019;71:878–891.
- 56. Wollenhaupt J, Lee EB, Curtis JR, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther 2019; 21:89.
- **57.** Tanaka Y, Fautrel B, Keystone EC, et al. Clinical outcomes in patients switched from adalimumab to baricitinib due to non-response and/or study design: phase III data in patients with rheumatoid arthritis. Ann Rheum Dis 2019;78:890–898.
- 58. Smolen JS, Pangan AL, Emery P, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. Lancet 2019;393:2303– 2311.
- 59. Genovese MC, Kalunian K, Gottenberg JE, et al. Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomized clinical trial. JAMA 2019;322:315– 325.
- 60. Fleischmann R, Takeuchi T, Schiff M, et al. Efficacy and safety of long-term baricitinib with and without methotrexate for the treatment of rheumatoid arthritis: experience with baricitinib monotherapy continuation or after switching from methotrexate monotherapy or baricitinib plus methotrexate [published online ahead of print June 24, 2019]. Arthritis Care Res (Hoboken) https://doi.org/ 10.1002/acr.24007.
- 61. Mimori T, Harigai M, Atsumi T, et al. Post-marketing surveillance of tofacitinib in Japanese patients with rheumatoid arthritis: an interim report of safety data [abstract]. Arthritis Rheumatol 2017;69: 585(suppl).
- 62. Desai RJ, Pawar A, Weinblatt ME, et al. Comparative risk of venous thromboembolism with tofacitinib versus tumor necrosis factor inhibitors: a cohort study of rheumatoid arthritis patients [abstract]. Arthritis Rheumatol 2018;70:3395(suppl).
- 63. Yun H, Xie F, Chen L, et al. Risk of venous thrombotic events in rheumatoid arthritis patients initiating

tofacitinib or adalimumab [abstract]. Arthritis Rheumatol 2018;70:236(suppl).

- 64. Fleischmann R, Kremer J, Cush J, et al. Placebocontrolled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012;367:495–507.
- **65.** Keystone EC, Genovese MC, Schlichting DE, et al. Safety and efficacy of baricitinib through 128 weeks in an open-label, longterm extension study in patients with rheumatoid arthritis. J Rheumatol 2018;45:14–21.
- **66.** Curtis JR, Xie F, Yang S, et al. Risk for herpes zoster in tofacitinib-treated rheumatoid arthritis patients with and without concomitant methotrexate and glucocorticoids. Arthritis Care Res (Hoboken) 2019;71:1249–1254.
- **67.** van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508–519.
- **68.** Burmester GR, Blanco R, Charles-Schoeman C, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet 2013; 381:451–460.
- **69.** van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum 2013;65:559–570.
- **70.** Kremer J, Li ZG, Hall S, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med 2013;159:253–261.
- 71. Papp KA, Menter A, Strober B, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phase 2b randomized placebocontrolled dose-ranging study. Br J Dermatol 2012; 167:668–677.
- 72. Ports WC, Khan S, Lan S, et al. A randomized phase 2a efficacy and safety trial of the topical Janus kinase inhibitor tofacitinib in the treatment of chronic plaque psoriasis. Br J Dermatol 2013;169:137–145.
- **73.** Mease P, Coates LC, Helliwell PS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. Lancet 2018;392:2367–2377.
- 74. Bissonnette R, Iversen L, Sofen H, et al. Tofacitinib withdrawal and retreatment in moderate-to-severe chronic plaque psoriasis: a randomized controlled trial. Br J Dermatol 2015;172:1395–1406.
- 75. Bachelez H, van de Kerkhof PCM, Strohal R, et al. Tofacitinib versus, etanercept or placebo in moderateto-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet 2015;386:552–561.
- 76. Papp KA, Menter MA, Abe M, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebocontrolled, phase III trials. Br J Dermatol 2015; 173:949–961.
- 77. Papp KA, Krueger JG, Feldman SR, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic

plaque psoriasis: long-term efficacy and safety results from 2 randomized phase-III studies and 1 open-label long-term extension study. J Am Acad Dermatol 2016; 74:841–850.

- **78.** Papp KA, Menter MA, Raman M, et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/ JAK2 inhibitor, in patients with moderate-to-severe psoriasis. Br J Dermatol 2016;174:1266–1276.
- 79. Asahina A, Etoh T, Igarashi A, et al. Oral tofacitinib efficacy, safety and tolerability in Japanese patients with moderate to severe plaque psoriasis and psoriatic arthritis: a randomized, double-blind, phase 3 study. J Dermatol 2016; 43:869–880.
- **80.** Zhang JZ, Tsai TF, Lee MG, et al. The efficacy and safety of tofacitinib in Asian patients with moderate to severe chronic plaque psoriasis: a Phase 3, randomized, double-blind, placebo-controlled study. J Dermatol Sci 2017;88:36–45.
- 81. Valenzuela F, Korman NJ, Bissonnette R, et al. Tofacitinib in patients with moderate-to-severe chronic plaque psoriasis: long-term safety and efficacy in an open-label extension study. Br J Dermatol 2018;179:853–862.
- 82. Sandborn WJ, Ghosh S, Panes J, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med 2012;367:616–624.
- 83. Sandborn WJ, Ghosh S, Panes J, et al. A phase 2 study of tofacitinib, an oral Janus kinase inhibitor, in patients with Crohn's disease. Clin Gastroenterol Hepatol 2014; 12:1485–1493.e2.
- 84. Panaccione R, D'Haens GR, Sandborn WJ, et al. Efficacy of upadacitinib as an induction therapy for patients with moderately to severely active ulcerative colitis, with or without previous treatment failure of biologic therapy: data from the dose-ranging phase 2B Study U-Achieve (abstract). Gastroenterology 2019;156:S-170.
- 85. Deepak P, Khatiwada A, Christophi GP, et al. Real-world safety of tofacitinib in inflammatory bowel diseases: a multi-center study (abstract). Gastroenterology 2019; 156:S-169.
- **86.** Vermeire S, Schreiber S, Petryka R, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. Lancet 2017;389:266–275.
- Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2017;376:1723–1736.
- 88. Panés J, Sandborn WJ, Schreiber S, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. Gut 2017;66:1049–1059.
- **89.** Panés J, D'Haens GR, Higgins PDR, et al. Long-term safety and tolerability of oral tofacitinib in patients with Crohn's disease: results from a phase 2, open-label, 48-week extension study. Aliment Pharmacol Ther 2019; 49:265–276.
- **90.** Sandborn WJ, Feagan BG, Panes J, et al. Safety and efficacy of upadacitinib (ABT-494) an oral JAK 1 inhibitor, as induction therapy in patients with Crohn's

disease: results from CELEST. Gastroenterology 2017; 152:S1308–S1309.

- 91. Panes J, Sandborn WJ, Loftus EV, et al. Efficacy and safety of upadacitinib maintenance treatment for moderate to severe Crohn's disease: results from the CEL-EST study. Gastroenterology 2018;154:S178–S179.
- 92. Sandborn WJ, Schreiber S, Lee SD, et al. Efficacy and safety of upadacitinib as an induction therapy for patients with moderately-to-severely active ulcerative colitis: data from the phase 2b study U-ACHIEVE. Eur J Gastroenterol Hepatol 2018;6(Supplement 1):74.
- **93.** Weisshof R, Aharoni Golan M, Sossenheimer PH, et al. Real-world experience with tofacitinib in IBD at a tertiary center. Dig Dis Sci 2019;64:1945–1951.
- 94. van der Heijde D, Baraliakos X, Gensler LS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebocontrolled, phase 2 trial. Lancet 2018;392:2378–2387.
- **95.** van der Heijde D, Deodhar A, Wei JC, et al. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. Ann Rheum Dis 2017;76:1340–1347.
- **96.** Choy EH. Clinical significance of Janus Kinase inhibitor selectivity. Rheumatology (Oxford) 2019;58:953–962.
- 97. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol 2017; 13:234–243.
- **98.** Chen SY, Suaya JA, Li Q, et al. Incidence of herpes zoster in patients with altered immune function. Infection 2014;42:325–334.
- 99. Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum 2007;57:1431–1438.
- 100. Winthrop KL, Baddley JW, Chen L, et al. Association between the initiation of anti-tumor necrosis factor therapy and the risk of herpes zoster. JAMA 2013; 309:887–895.
- 101. Long MD, Martin C, Sandler RS, et al. Increased risk of herpes zoster among 108 604 patients with inflammatory bowel disease. Aliment Pharmacol Ther 2013;37:420– 429.
- 102. Marra F, Lo E, Kalashnikov V, et al. Risk of herpes zoster in individuals on biologics, disease-modifying antirheumatic drugs, and/or corticosteroids for autoimmune diseases: a systematic review and meta-analysis. Open Forum Infect Dis 2016;3:ofw205.
- **103.** Winthrop KL, Melmed GY, Vermeire S, et al. Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. Inflamm Bowel Dis 2018;24:2258–2265.
- **104.** Colombel JF. Herpes zoster in patients receiving JAK inhibitors for ulcerative colitis: mechanism, epidemiology, management, and prevention. Inflamm Bowel Dis 2018;24:2173–2182.
- **105.** Charles-Schoeman C, Wicker P, Gonzalez-Gay MA, et al. Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus

kinase inhibitor. Semin Arthritis Rheum 2016;46:261-271.

- 106. Wu JJ, Strober BE, Hansen PR, et al. Effects of tofacitinib on cardiovascular risk factors and cardiovascular outcomes based on phase III and long-term extension data in patients with plaque psoriasis. J Am Acad Dermatol 2016;75:897–905.
- 107. European Medicines Agency. Increased risk of blood clots in lungs and death with higher dose of Xeljanz (tofacitinib) for rheumatoid arthritis. 2019. Available at: https://www.ema.europa.eu/en/news/increased-risk-bloodclots-lungs-death-higher-dose-xeljanz-tofacitinibrheumatoid-arthritis. Accessed April 1, 2019.
- 108. US Food and Drug Administration. Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate. 2019. Available at: https:// www.fda.gov/drugs/drug-safety-and-availability/safetytrial-finds-risk-blood-clots-lungs-and-death-higher-dosetofacitinib-xeljanz-xeljanz-xr. Accessed April 1, 2019.
- 109. Xie W, Huang Y, Xiao S, et al. Impact of Janus kinase inhibitors on risk of cardiovascular events in patients with rheumatoid arthritis: systematic review and metaanalysis of randomised controlled trials. Ann Rheum Dis 2019;78:1043–1054.
- 110. Sandborn WJ, Panés J, Sands BE, et al. Venous thromboembolic events in the tofacitinib ulcerative colitis clinical development programme. Aliment Pharmacol Ther 2019; 50:1068–1076.

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#### **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).

#### Conflicts of interest

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## **Supplementary Material**



Supplementary Figure 1. PRISMA flow diagram showing study selection.

	Events	Total	Events	Total	Weight	M-H, Random. 95% C	Year	M-H, Random. 95% Cl
1.1.1 Rheumatoid Arth	ritis					,,,,		
Kremer 2009	141	199	38	65	2 1%	1 21 [0 97 1 52]	2009	-
Tanaka 2011	64	100	10	200	2.170	1.21 [0.37, 1.32]	2009	
Tallaka 2011	04	100	10	20	0.0%	1.00 [0.99, 2.79]	2011	-
Fleischmann 2012	244	010	67	122	2.5%	0.73 [0.60, 0.88]	2012	1
Fleischmann 2012 (1)	146	272	84	156	2.6%	1.00 [0.83, 1.20]	2012	I. I
Kremer 2012	292	438	39	69	2.2%	1.18 [0.95, 1.47]	2012	
van Vollenhoven 2012	212	513	83	204	2.5%	1.02 [0.84, 1.23]	2012	Ť
Kremer 2013	533	779	99	159	3.4%	1.10 [0.96, 1.25]	2013	-
van der Heijde 2013	409	797	73	160	2.6%	1.12 [0.94, 1.35]	2013	<u>+</u>
Burmester 2013	167	399	75	132	2.5%	0.74 [0.61, 0.89]	2013	-
Tanaka 2014	133	265	23	52	1.3%	1.13 [0.82, 1.58]	2014	
Lee 2014	631	770	147	186	4.1%	1.04 [0.96, 1.12]	2014	÷
Kremer 2015	42	97	26	51	1.2%	0.85 [0.60, 1.21]	2015	
Keystone 2015	56	122	45	98	1.5%	1 00 [0 75 1 33]	2015	+
Tanaka 2016	54	96	26	10	1.0%		2016	+
Woothovong 2016	202	529	20		2.0%		2010	↓
Flaigehmenn 2016 (1)	200	274	151	210	2.0 /0	0.92 [0.72, 1.17]	2010	Ļ
Fleischmann 2016 (1)	280	374	151	210	3.8%	1.04 [0.94, 1.15]	2016	[
Fielschmann 2016	631	//0	147	186	4.1%	1.04 [0.96, 1.12]	2016	Ĩ
Genovese 2016 (1)	114	249	13	50	0.7%	1.76 [1.08, 2.87]	2016	- <b>-</b> -
Genovese 2016	260	351	112	176	3.4%	1.16 [1.02, 1.32]	2016	-
Kremer 2016	133	220	25	56	1.4%	1.35 [0.99, 1.85]	2016	
Mohamed 2016	6	42	3	14	0.1%	0.67 [0.19, 2.32]	2016	
Dougados 2017	316	456	161	228	3.8%	0.98 [0.88, 1.09]	2017	+
Taylor 2017	384	487	253	330	4.2%	1.03 [0.95, 1.11]	2017	ł
Vanhoutte 2017	15	98	5	29	0.2%	0.89 [0.35, 2.24]	2017	— <del>,</del>
Eleischmann 2017	457	760	253	386	4.0%	0.92 [0.84 1.01]	2017	4
Genovese 2018	245	451	95	169	3.0%	0.97 [0.83, 1.13]	2018	4
Burmester 2019	240	110	100	221	2 00/	1 13 10 06 1 201	2018	L.
Smolon 2010	240	440	100	221	2.3/0 200/	1 02 0 06 1 241	2010	Ļ
	200	432	102	210	2.0%		2019	Ţ
Genovese 2019 Subtotal (95% CI)	199	300	100	148	ა.პ% 70.2%	0.90 [0.86, 1.13]	2019	1
Subtotal (95 % CI)		11455		4000	10.2 /0	1.02 [0.30, 1.07]		
l otal events	6898		2395					
Test for overall effect: Z	= 0.98 (P =	= 0.33)	- 20 (1 -	0.0010	,, r <i>–</i> 017	U		
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012	= 0.98 (P =	= 0.33) 147	30	50	1.7%	0.96 [0.74, 1.26]	2012	+
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015	= 0.98 (P = 85 378	147 659	30 247	50 442	1.7% 3.8%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14]	2012 2015	ţ
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015	= 0.98 (P = 85 378 830	147 659 1486	30 247 182	50 442 373	1.7% 3.8% 3.6%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28]	2012 2015 2015	+
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2016	= 0.98 (P = 85 378 830 131	147 659 1486 237	30 247 182 15	50 442 373 34	1.7% 3.8% 3.6% 1.0%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86]	2012 2015 2015 2016	+
Test for overall effect: Z <b>1.1.2 Psoriasis</b> Papp 2012 Bachelez 2015 Papp 2015 Papp 2016 Mease 2018	= 0.98 (P = 85 378 830 131 37	147 659 1486 237 65	30 247 182 15 39	50 442 373 34 66	1.7% 3.8% 3.6% 1.0% 1.5%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29]	2012 2015 2015 2016 2018	+ + + + + + + + + + + + + + + + + + + +
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI)	85 378 830 131 37	147 659 1486 237 65 <b>2594</b>	30 247 182 15 39	50 442 373 34 66 <b>965</b>	1.7% 3.8% 3.6% 1.0% 1.5% <b>11.6</b> %	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15]	2012 2015 2015 2016 2018	
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events	85 378 830 131 37 1461	147 659 1486 237 65 <b>2594</b>	30 247 182 15 39 513	50 442 373 34 66 <b>965</b>	1.7% 3.8% 3.6% 1.0% 1.5% <b>11.6%</b>	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15]	2012 2015 2015 2016 2018	+ * * + *
Test for overall effect: Z <b>1.1.2 Psoriasis</b> Papp 2012 Bachelez 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0	85 378 830 131 37 1461 .00; Chi <sup>2</sup> =	147 659 1486 237 65 <b>2594</b> 3.70, df =	30 247 182 15 39 513 4 (P = 0	50 442 373 34 66 <b>965</b> 45);   <sup>2</sup> :	1.7% 3.8% 3.6% 1.0% 1.5% <b>11.6%</b> = 0%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] <b>1.07 [1.00, 1.15</b> ]	2012 2015 2015 2016 2018	+ + + + +
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z	85 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P =	147 659 1486 237 65 <b>2594</b> 3.70, df = 0.06)	30 247 182 15 39 513 4 (P = 0.	50 442 373 34 66 <b>965</b> .45); I <sup>2</sup> =	1.7% 3.8% 3.6% 1.0% 1.5% <b>11.6</b> % = 0%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15]	2012 2015 2015 2016 2018	
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.3 Inflammatory Boo	85 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P = wel Diseas	147 659 1486 237 65 <b>2594</b> 3.70, df = = 0.06)	30 247 182 15 39 513 4 (P = 0.	50 442 373 34 66 <b>965</b> (45); 1 <sup>2</sup> =	1.7% 3.8% 3.6% 1.0% 1.5% 11.6% = 0%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15]	2012 2015 2015 2016 2018	
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.3 Inflammatory Box Sandborn 2012	85 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P = wel Diseas 64	147 659 1486 237 65 <b>2594</b> 3.70, df = 0.06) e 146	30 247 182 15 39 513 4 (P = 0	50 442 373 34 66 <b>965</b> (45);   <sup>2</sup> =	1.7% 3.8% 3.6% 1.0% 1.5% 11.6% = 0%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] <b>1.07 [1.00, 1.15]</b>	2012 2015 2015 2016 2018 2018	
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Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.3 Inflammatory Box Sandborn 2012 Sandborn 2014 Sandborn 2017	85 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P = wel Diseas 64 61 328	e 0.33) 147 659 1486 237 65 2594 3.70, df = 0.06) e 146 105 905	30 247 182 15 39 513 4 (P = 0. 23 22 132	50 442 373 34 66 <b>965</b> (45); 1 <sup>2</sup> = 48 34 234	1.7% 3.8% 3.6% 1.0% 1.5% 11.6% = 0%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15] 0.91 [0.65, 1.29] 0.90 [0.67, 1.21] 0.64 [0.56, 0.74]	2012 2015 2016 2018 2018	- - - - - - -
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Test for overall effect: Z <b>1.1.2 Psoriasis</b> Papp 2012 Bachelez 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z <b>1.1.3 Inflammatory Bon</b> Sandborn 2012 Sandborn 2017 Sandborn 2017 (1) Panes 2017 Vermeire 2017	85 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P = wel Diseas 64 61 328 299 98 114	e 0.33) 147 659 1486 237 65 2594 3.70, df = 0.06) e 146 105 905 394 171 152	30 247 182 15 39 513 4 (P = 0 23 22 132 149 44 5	50 442 373 34 66 <b>965</b> .(45);   <sup>2</sup> = 48 34 234 234 198 90 67	1.7% 3.8% 3.6% 1.0% 1.5% 11.6% = 0% 1.2% 1.5% 3.2% 1.9% 2.5%	<ul> <li>0.96 [0.74, 1.26]</li> <li>1.03 [0.92, 1.14]</li> <li>1.14 [1.02, 1.28]</li> <li>1.25 [0.84, 1.86]</li> <li>0.96 [0.72, 1.29]</li> <li>1.07 [1.00, 1.15]</li> <li>0.90 [0.65, 1.29]</li> <li>0.90 [0.67, 1.21]</li> <li>0.64 [0.56, 0.74]</li> <li>1.01 [0.91, 1.11]</li> <li>1.17 [0.92, 1.50]</li> <li>1.12 [0.92, 1.35]</li> </ul>	2012 2015 2015 2016 2018 2018 2012 2014 2017 2017 2017 2017	
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.3 Inflammatory Box Sandborn 2012 Sandborn 2014 Sandborn 2017 Sandborn 2017 (1) Panes 2017 Vermeire 2017 Panaccione 2019	85 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P = wel Diseas 64 61 328 299 98 114 127	e 147 659 1486 237 65 2594 3.70, df = e 146 105 905 394 171 152 204	30 247 182 15 39 513 4 (P = 0 23 22 132 149 44 45 33	50 442 373 34 66 <b>965</b> .(45); I <sup>2</sup> = 48 34 234 198 90 67 46	1.7% 3.8% 3.6% 1.0% 1.5% 11.6% = 0% 1.2% 1.5% 3.2% 3.9% 1.9% 2.5% 2.3%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15] 0.90 [0.67, 1.21] 0.64 [0.56, 0.74] 1.01 [0.91, 1.11] 1.17 [0.92, 1.50] 1.12 [0.92, 1.35] 0.87 [0.70, 1.07]	2012 2015 2016 2018 2018 2012 2014 2017 2017 2017 2017 2017 2019	
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Test for overall effect: Z <b>1.1.2 Psoriasis</b> Papp 2012 Bachelez 2015 Papp 2015 Papp 2016 Mease 2018 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z <b>1.1.3 Inflammatory Bov</b> Sandborn 2012 Sandborn 2014 Sandborn 2017 Sandborn 2017 Sandborn 2017 Vermeire 2017 Panes 2017 Vermeire 2017 Panes 2017 Vermeire 2019 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z	85, 378 85 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P = wel Diseas 64 61 328 299 98 114 127 1091 .04; Chi <sup>2</sup> = = 0.84 (P =	147 659 1486 237 65 <b>2594</b> 3.70, df = = 0.06) e 146 105 905 394 171 152 204 2077 36.65, df = 0.40)	30 247 182 15 39 513 4 (P = 0 23 22 132 149 44 45 33 448 = 6 (P < 1	50 442 373 34 66 <b>965</b> (45); I <sup>2</sup> = 48 34 234 198 90 67 46 717 0.00001	1.7% 3.8% 3.6% 1.0% 1.5% 11.6% = 0% 1.2% 1.5% 3.2% 3.9% 1.9% 2.5% 2.3% 16.4% );   <sup>2</sup> = 84%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15] 0.90 [0.67, 1.21] 0.64 [0.56, 0.74] 1.01 [0.91, 1.11] 1.17 [0.92, 1.50] 1.12 [0.92, 1.35] 0.87 [0.70, 1.07] 0.93 [0.78, 1.11]	2012 2015 2016 2018 2018 2012 2014 2017 2017 2017 2017 2019	
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Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.3 Inflammatory Box Sandborn 2012 Sandborn 2014 Sandborn 2017 Sandborn 2017 Sandborn 2017 Panaes 2017 Vermeire 2017 Panaes 2017 Vermeire 2017 Panaccione 2019 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.4 Ankylosing Spon van der Heijde 2017 van der Heijde 2018 Subtotal (95% CI)	85 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P = wel Diseas 64 61 328 299 98 114 127 1091 .04; Chi <sup>2</sup> = = 0.84 (P = 78 18	147 659 1486 237 655 2594 3.70, df = = 0.06) e 146 105 905 394 171 152 204 2077 36.65, df = 0.40)	30 247 182 15 39 513 4 (P = 0. 23 22 132 149 44 45 33 448 = 6 (P < 1 22 18	50 442 373 34 66 965 (45); l <sup>2</sup> = 48 34 234 198 90 67 46 717 0.00001 51 58 109	1.7% 3.8% 3.6% 1.5% 11.6% = 0% 1.2% 1.5% 3.2% 3.9% 1.9% 2.5% 2.3% 16.4% );   <sup>2</sup> = 849 1.2% 0.6% 1.7%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15] 0.90 [0.65, 1.29] 0.90 [0.67, 1.21] 0.64 [0.56, 0.74] 1.01 [0.91, 1.11] 1.17 [0.92, 1.50] 1.12 [0.92, 1.35] 0.87 [0.70, 1.07] 0.93 [0.78, 1.11] 4 1.16 [0.82, 1.65] 1.00 [0.58, 1.72] 1.11 [0.83, 1.49]	2012 2015 2016 2018 2018 2017 2017 2017 2017 2017 2019	
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.3 Inflammatory Box Sandborn 2012 Sandborn 2017 Sandborn 2017 Sandborn 2017 Vermeire 2017 Panes 2017 Vermeire 2017 Panes 2017 Vermeire 2017 Panes 2017 Vermeire 2017 Panes 2017 Vermeire 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.4 Ankylosing Spon van der Heijde 2017 van der Heijde 2018 Subtotal (95% CI) Total events	85, 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P = wel Diseas 64 61 328 299 98 114 127 1091 .04; Chi <sup>2</sup> = = 0.84 (P = dylitis 78 18 96	147 659 1486 237 655 2594 3.70, df = = 0.06) e 146 105 905 394 171 152 204 2077 36.65, df = 0.40) 156 58 214	30 247 182 15 39 513 4 (P = 0. 23 22 132 149 44 45 33 448 = 6 (P < 1 22 18 40	50 442 373 36 <b>965</b> (45); 1 <sup>2</sup> = 48 34 234 198 90 67 46 717 0.00001 51 58 <b>109</b>	1.7% 3.8% 3.6% 1.0% 11.6% = 0% 1.2% 3.2% 3.9% 1.9% 2.5% 2.3% 16.4% );   <sup>2</sup> = 84% 1.2% 0.6% 1.7%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15] 0.90 [0.67, 1.21] 0.64 [0.56, 0.74] 1.01 [0.91, 1.11] 1.17 [0.92, 1.50] 1.12 [0.92, 1.35] 0.87 [0.70, 1.07] 0.93 [0.78, 1.11] 6 1.16 [0.82, 1.65] 1.00 [0.58, 1.72] 1.11 [0.83, 1.49]	2012 2015 2016 2018 2018 2012 2014 2017 2017 2017 2017 2019 2019	
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.3 Inflammatory Box Sandborn 2012 Sandborn 2017 Sandborn 2017 Sandborn 2017 Sandborn 2017 Panaccione 2017 Panaccione 2017 Panaccione 2017 Panaccione 2017 Panaccione 2017 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.4 Ankylosing Spon van der Heijde 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z	85 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P = wel Diseas 64 61 328 299 98 114 127 1091 .04; Chi <sup>2</sup> = = 0.84 (P = dylitis 78 18 96 .00; Chi <sup>2</sup> = = 0.69 (P =	147 659 1486 237 655 2594 3.70, df = 0.06) e 146 105 905 394 171 152 204 2077 36.65, df = 0.40) 156 58 214 0.20, df = 0.20, df =	30 247 182 15 39 513 4 (P = 0. 23 22 132 149 44 45 33 448 = 6 (P < 1 22 18 40 1 (P = 0.	50 442 373 36 965 (45); 1 <sup>2</sup> = 48 34 234 198 90 67 46 717 0.00001 51 58 109 (65); 1 <sup>2</sup> =	1.7% 3.8% 3.6% 1.5% 11.6% = 0% 1.2% 1.5% 3.2% 3.9% 1.9% 2.5% 2.3% 16.4% 1.2% 0.6% 1.7% = 0%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15] 0.90 [0.67, 1.21] 0.64 [0.56, 0.74] 1.01 [0.91, 1.11] 1.17 [0.92, 1.50] 1.12 [0.92, 1.35] 0.87 [0.70, 1.07] 0.93 [0.78, 1.11] 6 1.16 [0.82, 1.65] 1.00 [0.58, 1.72] 1.11 [0.83, 1.49]	2012 2015 2016 2018 2018 2012 2014 2017 2017 2017 2017 2019 2017	
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.3 Inflammatory Bon Sandborn 2012 Sandborn 2014 Sandborn 2017 Sandborn 2017 Vermeire 2017 Panaccione 2019 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.4 Ankylosing Spon van der Heijde 2017 van der Heijde 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.4 Ankylosing Spon van der Heijde 2017 van der Heijde 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z Total eys% CI)	85 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P = wel Diseas 64 61 328 299 98 114 127 1091 .04; Chi <sup>2</sup> = = 0.84 (P = dylitis 78 18 96 .00; Chi <sup>2</sup> = = 0.69 (P =	147 659 1486 237 65 2594 3.70, df = e 0.06) e 146 105 905 394 171 152 204 2077 36.65, df = 0.40) 156 58 214 0.20, df = e 0.20, df =	30 247 182 15 39 513 4 (P = 0 23 22 132 149 44 45 33 448 = 6 (P < 1 22 18 40 1 (P = 0.	50 442 373 34 66 965 (45); l <sup>2</sup> = 48 34 234 198 90 67 17 0.00001 51 58 109 (65); l <sup>2</sup> = 5797	1.7% 3.8% 3.6% 1.0% 1.5% 11.6% = 0% 1.2% 3.9% 1.5% 3.2% 3.9% 1.9% 2.5% 2.3% 16.4% );   <sup>2</sup> = 84% 1.2% 0.6% 1.7% = 0%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15] 0.90 [0.67, 1.21] 0.64 [0.56, 0.74] 1.01 [0.91, 1.11] 1.17 [0.92, 1.50] 1.12 [0.92, 1.35] 0.87 [0.70, 1.07] 0.93 [0.78, 1.11] 6 1.16 [0.82, 1.65] 1.00 [0.58, 1.72] 1.11 [0.83, 1.49] 1.01 [0.97, 1.06]	2012 2015 2016 2018 2018 2012 2014 2017 2017 2017 2017 2019 2017 2017	
Test for overall effect: Z 1.1.2 Psoriasis Papp 2012 Bachelez 2015 Papp 2015 Papp 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.3 Inflammatory Box Sandborn 2012 Sandborn 2014 Sandborn 2017 Sandborn 2017 Sandborn 2017 Panes 2017 Vermeire 2017 Panes 2017 Vermeire 2019 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.1.4 Ankylosing Spon van der Heijde 2017 van der Heijde 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z Total (95% CI) Total events	85 378 830 131 37 1461 .00; Chi <sup>2</sup> = = 1.85 (P = wel Diseas 64 61 328 299 98 114 127 1091 .04; Chi <sup>2</sup> = = 0.84 (P = 0.4; Chi <sup>2</sup> = = 0.84 (P = 0.69 (P = 9546	147 659 1486 2594 3.70, df = = 0.06) e 146 105 905 394 171 152 204 2077 36.65, df = 0.40) 156 58 214 0.20, df = = 0.49)	30 247 182 15 39 513 4 (P = 0. 23 22 132 149 44 45 33 448 = 6 (P < 1 22 18 40 1 (P = 0. 3396	50 442 373 34 66 965 (45); l <sup>2</sup> = 48 34 234 198 90 67 46 717 0.00001 51 58 109 65); l <sup>2</sup> = 5797	1.7% 3.8% 3.6% 1.5% 11.6% = 0% 1.2% 1.5% 3.2% 3.9% 1.9% 2.5% 2.3% 16.4% 1);   <sup>2</sup> = 849 1.2% 0.6% 1.7% = 0%	0.96 [0.74, 1.26] 1.03 [0.92, 1.14] 1.14 [1.02, 1.28] 1.25 [0.84, 1.86] 0.96 [0.72, 1.29] 1.07 [1.00, 1.15] 0.90 [0.67, 1.21] 0.64 [0.56, 0.74] 1.01 [0.91, 1.11] 1.17 [0.92, 1.50] 1.12 [0.92, 1.35] 0.87 [0.70, 1.07] 0.93 [0.78, 1.11] 1.16 [0.82, 1.65] 1.00 [0.58, 1.72] 1.11 [0.83, 1.49] 1.01 [0.97, 1.06]	2012 2015 2016 2018 2018 2017 2017 2017 2017 2017 2019 2017 2017 2018	

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

	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	Year	M-H. Random. 95% CI
1.2.1 Rheumatoid Arth	ritis	Total	=vonta		mangin			
Kromor 2000	6	100	1	65	0.6%	1 06 [0 24 15 08]	2000	
Tanaka 2011	5	109	0	28	0.0%		2003	
Flaigabrann 2012 (1)	10	610	6	100	0.5%	2.93 [0.17, 31.41]	2011	
Fleischmann 2012 (1)	12	010	0	122	2.5%		2012	
Kremer 2012	22	438	0	69	0.3%	7.18 [0.44, 116.95]	2012	
van Vollenhoven 2012	21	513	1	204	3.1%	1.19 [0.52, 2.76]	2012	
Fleischmann 2012	8	272	7	156	2.3%	0.66 [0.24, 1.77]	2012	
Burmester 2013	16	399	6	132	2.7%	0.88 [0.35, 2.21]	2013	
Kremer 2013	45	779	6	159	3.1%	1.53 [0.66, 3.53]	2013	
van der Heijde 2013	27	797	5	160	2.6%	1.08 [0.42, 2.77]	2013	
Tanaka 2014	8	265	1	52	0.6%	1.57 [0.20, 12.29]	2014	
Lee 2014	83	770	22	186	7.6%	0.91 [0.59, 1.42]	2014	-
Kevstone 2015	4	122	3	98	1.1%	1.07 [0.25, 4.67]	2015	
Kremer 2015	2	97	0	51	0.3%	2.65 [0.13, 54,24]	2015	
Kremer 2016	5	220	1	56	0.6%	1.27 [0.15, 10.68]	2016	
Eleischmann 2016	80	770	22	186	7.5%	0.88 [0.56, 1.37]	2016	
Eloischmann 2016 (1)	20	374	20	210	5.0%	0.81 [0.47, 1.40]	2010	
Mehamod 2016 (1)	29	374	20	210	5.9%	0.01 [0.47, 1.40]	2010	
Nonamed 2016	0	42	10	14	0.00/		2016	
Genovese 2016	14	351	13	176	3.8%	0.54 [0.26, 1.12]	2016	
Genovese 2016 (1)	8	249	0	50	0.3%	3.47 [0.20, 59.13]	2016	
Westhovens 2016	11	538	4	56	1.9%	0.29 [0.09, 0.87]	2016	
Tanaka 2016	2	96	1	49	0.5%	1.02 [0.09, 10.98]	2016	
Fleischmann 2017	62	760	24	386	7.3%	1.31 [0.83, 2.07]	2017	+
Dougados 2017	18	456	11	228	3.8%	0.82 [0.39, 1.70]	2017	
Vanhoutte 2017	0	98	0	29		Not estimable	2017	
Taylor 2017	38	487	13	330	5.0%	1.98 [1.07, 3.66]	2017	
Burmester 2018	15	440	5	221	2.3%	1.51 [0.55, 4.09]	2018	
Genovese 2018	20	451	0	169	0.3%	15.42 [0.94, 253,55]	2018	· · · · · · · · · · · · · · · · · · ·
Smolen 2019	17	432	6	432	2.7%	2.83 [1.13, 7,12]	2019	
Genovese 2019	14	300	5	148	2.3%	1 38 [0 51 3 76]	2019	
Subtotal (95% CI)		11433	Ŭ	4222	71.5%	1.05 [0.86, 1.30]	2010	•
	502		100			. / .		ĺ
1.2.2 Psoriasis	0	4.47		50	0.00/		0040	
Papp 2012	3	1/1/		50	0.3%		2012	
D	-	147	-	070	0.070	2.41 [0.13, 45.90]	2012	
Papp 2015	34	1486	7	373	3.3%	2.41 [0.13, 45.90] 1.22 [0.54, 2.73]	2015	
Papp 2015 Bachelez 2015	34 12	1486 659	7 9	373 442	3.3% 3.0%	2.41 [0.13, 43.90] 1.22 [0.54, 2.73] 0.89 [0.38, 2.10]	2015 2015	
Papp 2015 Bachelez 2015 Papp 2016	34 12 4	1486 659 237	7 9 1	373 442 34	3.3% 3.0% 0.6%	2.41 [0.13, 45.90] 1.22 [0.54, 2.73] 0.89 [0.38, 2.10] 0.57 [0.07, 4.98]	2015 2015 2016	
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018	34 12 4 1	1486 659 237 65	7 9 1 0	373 442 34 66	3.3% 3.0% 0.6% 0.3%	2.41 [0.13, 45.90] 1.22 [0.54, 2.73] 0.89 [0.38, 2.10] 0.57 [0.07, 4.98] 3.05 [0.13, 73.42]	2015 2015 2016 2018	
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI)	34 12 4 1	1486 659 237 65 <b>2594</b>	7 9 1 0	373 442 34 66 <b>965</b>	3.3% 3.0% 0.6% 0.3% <b>7.4%</b>	2.41 [0.13, 43.90] 1.22 [0.54, 2.73] 0.89 [0.38, 2.10] 0.57 [0.07, 4.98] 3.05 [0.13, 73.42] 1.08 [0.62, 1.86]	2015 2015 2015 2016 2018	
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events	34 12 4 1	1486 659 237 65 <b>2594</b>	7 9 1 0	373 442 34 66 <b>965</b>	3.3% 3.0% 0.6% 0.3% <b>7.4%</b>	1.22 [0.54, 2.73] 0.89 [0.38, 2.10] 0.57 [0.07, 4.98] 3.05 [0.13, 73.42] 1.08 [0.62, 1.86]	2012 2015 2015 2016 2018	•••••
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0	34 12 4 1 54 .00; Chi <sup>2</sup> =	1486 659 237 65 <b>2594</b> 1.30, df =	7 9 1 0 17 4 (P = 0.	373 442 34 66 <b>965</b> 86); 1 <sup>2</sup> =	0.3% 3.3% 3.0% 0.6% 0.3% 7.4%	1.22 [0.54, 2.73] 0.89 [0.38, 2.10] 0.57 [0.07, 4.98] 3.05 [0.13, 73.42] 1.08 [0.62, 1.86]	2012 2015 2015 2016 2018	••••••••••••••••••••••••••••••••••••••
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z	34 12 4 1 54 .00; Chi <sup>2</sup> = = 0.26 (P =	147 1486 659 237 65 <b>2594</b> 1.30, df = : 0.79)	7 9 1 0 17 4 (P = 0.	373 442 34 66 <b>965</b> 86); 1 <sup>2</sup> :	0.3% 3.3% 3.0% 0.6% 0.3% 7.4%	2.41 [0.13, 43.90] 1.22 [0.54, 2.73] 0.89 [0.38, 2.10] 0.57 [0.07, 4.98] 3.05 [0.13, 73.42] 1.08 [0.62, 1.86]	2012 2015 2015 2016 2018	
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.2.3 Inflammatory Box	34 12 4 1 .00; Chi <sup>2</sup> = = 0.26 (P = wel Diseas	1486 659 237 65 <b>2594</b> 1.30, df = : 0.79)	7 9 1 0 17 4 (P = 0.	373 442 34 66 <b>965</b> 86); I <sup>2</sup> =	0.3% 3.3% 3.0% 0.6% 0.3% 7.4%	1.22 [0.54, 2.73] 0.89 [0.38, 2.10] 0.57 [0.07, 4.98] 3.05 [0.13, 73.42] 1.08 [0.62, 1.86]	2015 2015 2016 2018	
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.2.3 Inflammatory Box Sandborn 2012	34 12 4 1 .00; Chi <sup>2</sup> = = 0.26 (P = wel Diseas 8	1486 659 237 65 <b>2594</b> 1.30, df = : 0.79) e 146	7 9 1 0 4 (P = 0.	373 442 34 66 <b>965</b> 86); I <sup>2</sup> =	0.3% 3.3% 3.0% 0.6% 0.3% 7.4% = 0%	2.41 [0.13, 43.90] 1.22 [0.54, 2.73] 0.89 [0.38, 2.10] 0.57 [0.07, 4.98] 3.05 [0.13, 73.42] 1.08 [0.62, 1.86]	2015 2015 2016 2018 2018	• • • •
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z <b>1.2.3 Inflammatory Bo</b> v Sandborn 2012 Sandborn 2014	34 12 4 1 .00; Chi <sup>2</sup> = = 0.26 (P = wel Diseas 8 9	147 1486 659 237 65 <b>2594</b> 1.30, df = : 0.79) e 146 105	7 9 1 0 17 4 (P = 0.	373 442 34 66 <b>965</b> 86); I <sup>2</sup> = 48 34	0.3% 3.3% 3.0% 0.6% 0.3% 7.4% = 0%	2.41 [0.13, 43.90] 1.22 [0.54, 2.73] 0.89 [0.38, 2.10] 0.57 [0.07, 4.98] 3.05 [0.13, 73.42] 1.08 [0.62, 1.86] 0.66 [0.21, 2.09] 0.58 [0.21, 1.62]	2015 2015 2016 2018 2018 2012 2012 2014	• • • •
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z <b>1.2.3 Inflammatory Bot</b> Sandborn 2012 Sandborn 2014 Sandborn 2017 (1)	34 12 4 1 .00; Chi <sup>2</sup> = = 0.26 (P = wel Diseas 8 9 21	1486 659 237 65 <b>2594</b> 1.30, df = : 0.79) e 146 105 394	7 9 1 0 17 4 (P = 0. 4 5 13	373 442 34 66 <b>965</b> 86); I <sup>2</sup> = 48 34 198	1.8% 2.2% 4.4%	0.66 [0.21, 2.09] 0.58 [0.21, 2.09] 0.68 [0.38, 2.10] 0.57 [0.07, 4.98] 0.057 [0.07, 4.98] 0.062, 1.86] 0.66 [0.21, 2.09] 0.58 [0.21, 1.62] 0.81 [0.42, 1.59]	2012 2015 2015 2016 2018 2018 2018	
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.2.3 Inflammatory Box Sandborn 2012 Sandborn 2014 Sandborn 2017 (1) Panes 2017	34 12 4 1 .00; Chi <sup>2</sup> = = 0.26 (P = wel Diseas 8 9 21 14	1486 659 237 65 2594 1.30, df = : 0.79) e 146 105 394 171	7 9 1 0 17 4 (P = 0. 4 5 13 7	373 442 34 66 <b>965</b> 86); I <sup>2</sup> = 48 34 198 90	1.8% 2.2% 4.4% 2.9%	0.66 [0.21, 2.09] 0.58 [0.21, 2.09] 0.58 [0.21, 2.09] 0.58 [0.21, 2.09] 0.58 [0.21, 2.09] 0.58 [0.21, 1.62] 0.81 [0.42, 1.59] 1.05 [0.44, 2.51]	2015 2015 2016 2018 2018 2018 2012 2014 2017 2017	
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z <b>1.2.3 Inflammatory Bot</b> Sandborn 2012 Sandborn 2014 Sandborn 2017 Panes 2017 Vermeire 2017	34 12 4 1 54 .00; Chi <sup>2</sup> = = 0.26 (P = wel Diseas 8 9 21 14 14	1486 659 237 65 <b>2594</b> 1.30, df = • 0.79) e 146 105 394 171 152	7 9 1 0 17 4 (P = 0. 4 5 13 7 3	373 442 34 66 <b>965</b> 86); I <sup>2</sup> = 48 34 198 90 67	1.8% 2.2% 4.4% 2.9% 1.6%	2.41 [0.13, 43.90] 1.22 [0.54, 2.73] 0.89 [0.38, 2.10] 0.57 [0.07, 4.98] 3.05 [0.13, 73.42] 1.08 [0.62, 1.86] 0.66 [0.21, 2.09] 0.58 [0.21, 1.62] 0.81 [0.42, 1.59] 1.05 [0.44, 2.51] 2.06 [0.61, 6.92]	2015 2015 2016 2018 2018 2018 2018 2012 2014 2017 2017 2017	
Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z 1.2.3 Inflammatory Bot Sandborn 2012 Sandborn 2014 Sandborn 2014 Sandborn 2017 Vermeire 2017 Sandborn 2017	34 12 4 1 .00; Chi <sup>2</sup> = = 0.26 (P = wel Diseas 8 9 21 14 14 34	146 659 237 65 2594 1.30, df = : 0.79) e 146 105 394 171 152 905	7 9 1 0 17 4 (P = 0. 4 5 13 7 3 14	373 442 34 66 <b>965</b> 86); I <sup>2</sup> = 48 34 198 90 67 234	1.8% 2.2% 4.4% 2.9% 1.6% 5.1%	0.66 [0.21, 2.09] 0.58 [0.21, 2.09] 0.58 [0.21, 2.09] 0.58 [0.21, 2.09] 0.58 [0.21, 2.09] 0.58 [0.21, 1.62] 0.81 [0.42, 1.59] 1.05 [0.44, 2.51] 2.06 [0.61, 6.92] 0.63 [0.34 1 15]	2015 2015 2016 2018 2018 2018 2018 2017 2017 2017 2017	
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Papp 2015 Bachelez 2015 Papp 2016 Mease 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z <b>1.2.3 Inflammatory Bov</b> Sandborn 2012 Sandborn 2017 Sandborn 2017 Vermeire 2017 Vermeire 2017 Sandborn 2017 Panas 2017 Vermeire 2017 Sandborn 2017 Data events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z <b>1.2.4 Ankylosing Spon</b> van der Heijde 2017 van der Heijde 2017 van der Heijde 2017 van der Heijde 2017 van der Heijde 2018 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: Z Total (95% CI)	34 12 4 12 4 1 54 .00; Chi <sup>2</sup> = = 0.26 (P = wel Diseas 8 9 21 14 14 14 34 8 .00; Chi <sup>2</sup> = = 1.84 (P = dylitis 2 1 3 .73; Chi <sup>2</sup> = = 0.35 (P =	1446 659 237 65 2594 1.30, df = 0.79) e 146 105 394 171 152 905 204 2077 5.76, df = 0.07) 156 58 214 1.40, df = 0.73)	7 9 1 0 17 4 (P = 0. 4 5 13 7 3 14 5 5 1 6 (P = 0. 2 0 2 1 (P = 0.	373 373 442 34 66 965 86);   <sup>2</sup> : 48 34 198 90 67 234 46 717 45);   <sup>2</sup> : 51 58 109 24);   <sup>2</sup> : 51 58 109	0.5% 3.3% 3.0% 0.6% 0.3% 7.4% = 0% 1.8% 2.2% 4.4% 2.9% 1.6% 5.1% 2.0% 20.1% = 0% 0.7% 0.3% 0.9% = 29% 100.0%	0.66 [0.21, 2.09] 0.57 [0.07, 4.98] 3.05 [0.13, 73.42] 1.08 [0.62, 1.86] 0.58 [0.21, 2.09] 0.58 [0.21, 1.62] 0.58 [0.21, 1.62] 0.63 [0.44, 2.51] 2.06 [0.61, 6.92] 0.63 [0.34, 1.15] 0.36 [0.12, 1.05] 0.74 [0.53, 1.02] 0.33 [0.05, 2.26] 3.00 [0.12, 72.15] 0.69 [0.09, 5.54]	2012 2015 2016 2018 2018 2018 2017 2017 2017 2017 2017 2017 2019 2017 2018	

Test for subgroup differences:  $\dot{Chi^2} = 3.57$ , df = 3 (P = 0.31), l<sup>2</sup> = 16.1%

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

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

	Mean	Female	White	Concomitant	Prior
Study	age (y)	(%, n/N)	(%, n/N)	treatments	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)	6.51 (25/384)
				Anti-Malarial agents: 10.93 (42/384)	
Fleischmann 2012	51.43	86.55 (528/610)	67.05 (409/610)	Steroids: 59.83 (365/610)	22.95 (140/610)
	50.44	00.00 (400/507)	00 10 (407 (507)	Anti-Malarial agents: 16.55 (101/610)	
Kremer 2012	53.14	80.08 (406/507)	86.19 (437/507)	Steroids: 58.18 (295/507) 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) MTX: 100 (399/399) 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) MTX: 79.04 (626/792)	9.47 (75/792)
McIness 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) 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)	0 (0/301)
	0.110			Hydroxychloroquine: 17.27 (52/301) MTX: 99.66 (300/301)	0 (0,001)
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) Steroids: 65.2 (1647/2526)	85 (2147/2526)
Eleischmann 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) MTX: 100 (299/299)	0 (0/004)
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)	6.71 (19/283)
Kremer 2016	57 4	80.07 (221/276)	Not reported	MTX: 100 (276/276)	100 (276/276)
Mohamed 2016	40 Q	18 / 2 (21/11/)	7/ 56 (85/11/)	MTX: 100 (BA subjects)	100 (210/210)
Tanaka 2016	40.9 54.2	91 29 (119/145)	0 (0/145)	Storoide: 58.62 ( $85/145$ )	
	54.2	01.30 (110/143)	0 (0/143)	MTX: 100 (145/145)	
Westhovens 2016	53.28	80.97 (481/594)	Not reported	Steroids: 59.26 (352/594) MTX: 100 (594/594)	8.41 (50/594)
Yamanaka 2016	52.6	83.12 (404/486)	0 (0/486)	Steroids: 69.13 (336/486) 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) MTX: 68.57 (48/70)	68.57 (48/70)
Keystone 2017	53	83 (110/133)	Not reported	Steroids: 46 (61/133) MTX: 75 (100/133) 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) 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)	0 (0/127)
Avila Machado 2018	58	77 (16810/21832)	Not reported	Steroids: 67.69 (14780/21832)	

## Supplementary Table 1. Continued

	Mean	Female	White	Concomitant	Prior
Study	age (y)	(%, n/N)	(%, n/N)	treatments	biologic use
Burmester 2018	55.7	78.66 (520/661)	Not reported	Steroids: 46.14 (305/661) MTX: 60.36 (399/661) 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) MTX: 72.94 (364/499) 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) MTX: 82.11 (459/559)	87.45 (489/559)
Tanaka 2018	58	77.03 (161/209)	0 (0/209)	Steroids: 49.28 (103/209) MTX: 100(209/209)	22.9 (48/209)
Yun 2018	Not reporte	d 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) Prior MTX: 100 (648/648)	
Takeuchi 2019	54.05	75.67 (423/559)	Not reported	Steroids: 43.29 (242/559) 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) 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 Psoriasis	53.3	81.92 (3671/4481)	70.85 (3175/4481)	Not reported	
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	40	31.23 (208/000)	92.19 (014/000)	Not reported	28.07 (187/000)
Asabina 2016	43.5	17 17 (17/99)	02.40 (1333/1839) 0 (0/99)	Steroids: 6.06 (6/99)	15 15 (15/00)
Papp 2016	45.5	29 55 (523/1770)	82 15 (1454/1770)	Not reported	13.13 (13/33)
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) MTX: 54.19 (71/131) DMARD: 74.04 (97/131)	15.26 (20/131)
Valenzuela 2018 Inflammatory bowel d	46 isease	29.40 (843/2867)	86.53 (2480/2867)	Not reported	
Sandborn 2012	42.64	42.36 (88/194)	90.72 (176/194)	Steroids: 34.02 (66/194) 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 (101/1/4)
Lichtenstein 2018	41.2	41.21 (389/944)	Not reported	Not reported	AE AE (10/00)
Rubin 2016	30.4	45.45 (10/22)	Not reported	Not reported	43.43 (10/22) 77 60 (10//250)
Panes 2018	42.3 ⊿∩ 7	Not reported	Not reported	Not reported	11.00 (194/200)
Deepak 2019	-10.7	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) Immunomodulators: 8.62 (5/58) Vedolizumab: 5.17 (3/58)	Anti TNF: 93.1 (54/58) Vedolizumab: 81.03 (47/58) 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) DMARD: 33.33 (69/207)	
van der Heijde 2018	41.5	25.86 (30/116)	Not reported	Steroids: 14.65 (17/116) MTX: 11.20 (13/116) 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

	AE (%, n/N) JAK	AE (%, n/N)	SAE (%, n/N) JAK	SAE (%, n/N)
Study	inhibitors patients	comparator patients	inhibitors patients	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)	0–3 months: 54.91	0–3 months: 1.23 (6/488)	0-3 months: 4.92 (6/122)
	3–6 months: 40 (244/610)	(67/122)	3–6 months: 1.96 (12/610)	
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)	0-3 months: 50 (156/	0-3 months: 5.43 (22/405)	0-3 months: 2.24 (7/312)
	3–6 months: 31.93 (145/454)	312)	3-6 months: 3.74 (17/454)	3–6 months: 3.04 (8/263)
	6-12 months: 41.32 (212/513)	3-6 months: 31.94 (84/263)	6-12 months: 4.09 (21/513)	6-12 months: 3.43 (7/204)
		6-12 months: 40.68		
		(83/204)		
Burmester 2013	0-3 months: 55.05 (147/267)	0–3 months: 56.81 (75/	0-3 months: 1.49 (4/267)	0-3 months: 4.54 (6/132)
	3-6 months: 41.85 (167/399)	132)	3-6 months: 4.01 (16/399)	
Kremer 2013	68.42 (533/779)	62.26 (99/159)	5.77 (45/779)	3.77 (6/159)
McIness 2013	46.84 (52/111)		1.80 (2/111)	
van der Heiide 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)	11.02 (22, 100)
Tanaka 2014	50 19 (133/265)	44 23 (23/52)	3 01 (8/265)	1 92 (1/52)
Wollenhaunt 2014	76.84 (3152/4102)	44.20 (20/02)	15 35 (630///102)	1.62 (1762)
Kevetone 2015	$n_{12}$ weeks: $15.32$ (92/203)	45 91 (45/98)	$n_{-12}$ weeks: 1.97 (4/203)	3 06 (3/98)
	12-24 weeks: 45.90 (56/122)	43.31 (43/30)	$12_24$ weeks: $3.27(4/122)$	0.00 (0/00)
Kremer 2015	A3 29 (A2/97)	50.98 (26/51)	2 06 (2/97)	0 (0/51)
Curtic 2015	2 03 (74/2526)	30.30 (20/31)	2.00 (2/97)	0 (0/31)
Eloisobmann 2016	2.33 (74/2320)	70 02 (1/7/186)	10.30 (80/770)	11 82 (22/186)
Fleischmann 2016	74 86 (280/274)	79.03 (147/160)	7 75 (20/274)	0.52 (20/210)
	74.80 (280/374)	62 62 (112/176)	7.10 (14/251)	3.32 (20/210) 7.29 (12/176)
Genovese 2016	74.07 (200/331) 45.78 (114/240)	03.03 (112/170)	2.01 (8/040)	0 (0/50)
Genovese 2010	45.78 (114/249)	20 (13/30)	3.21 (0/249)	0 (0/30)
Kavanaugn 2016	39.85 (110/278) 60.45 (122/220)	44.26 (25/56)	2.09 (0/270)	1 79 (1/56)
Mehamad 2016	14.09 (6(40)	44.30 (23/30)	2.27 (3/220)	1.78 (1/50)
	14.26 (6/42)	21.42 (3/14)		0.04 (1 (40)
Tanaka 2016	56.25 (54/96)	53.06 (26/49)	2.08 (2/96)	2.04 (1/49)
Westnovens 2016	52.60 (283/538)	57.14 (32/56)	2.04 (11/538)	7.14 (4/56)
Yamanaka 2016	97.94 (476/486)	70.01 (1.01 (0.00)	28.60 (139/486)	4.00 (11 (000)
Dougados 2017	69.29 (316/456)	70.61 (161/228)	3.94 (18/456)	4.82 (11/228)
Fleischmann 2017	60.13 (4577760)	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)	56.21 (95/169)	0–12 weeks: 6.08 (20/329)	0 (0/169)
	12-24 weeks: 54.32 (245/451)		12–24 weeks: 4.43 (20/451)	
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 dis	sease			
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)	Induction: 61.11 (55/90)	Induction: 7.60 (13/171)	Induction: 3.33 (3/90)
	Maintenance: 57.31 (98/171)	Maintenance: 48.89 (44/90)	Maintenance: 8.18 (14/171)	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)					
Purmostor 2012	1.75 (9/513)					0.25 (1/200)
Kremer 2013	1.25 (5/399)	0 13 (1/779)			0 38 (3/779)	0.25 (1/399)
McIness 2013	1.10 (0/110)	0.10 (1/1/0)			0.00 (0/110)	
van der Heiide 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)	0110 (0,101)	
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 (1/3/4)	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)	0.00 (1 (051)
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)
Kromor 2016	0 (0/220)	1.31 (1/270)	0 45 (1/220)		0 45 (1/220)	0.01 (2/220)
Westhovens 2016	0.93 (5/538)	0.74 (4/538)	0.43 (1/220)		0.43 (1/220)	0.31 (2/220)
Yamanaka 2016	0.00 (0,000)	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	х <i>у</i>	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)	0 4 0 (4 5 (0 0 0 4)
Conen 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)
Genovese 2018	0-12 weeks	0-12 weeks:		0-12 weeks	0 -12 weeks	0.51 (15/2905)
Genovese 2010	1 52 (5/329)	1 52 (5/329)		0-12 WEEKS.	012 Weeks.	0-12 weeks.
	12-24 weeks:	12-24 weeks:		12-24 weeks:	12-24 weeks:	12-24 weeks:
	1.33 (6/451)	1.1 (5/451)		0.22 (1/451)	0.22 (1/451)	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)	1 70 (10 (00 4)				
Tanaka 2019	1.73 (12/694)	1.73 (12/694)	1 05 (10/707)		0.01 (16/707)	
Wollenhaunt 2019	5.52 (44/797) (395/4/81)	7.9 (03/797) (526/4481)	1.25 (10/797)	2.31 (20/797) (138/4/81)	2.01 (10/797)	0.98 (11/1181)
Peoriasis	(000/4401)	(520/4401)	(110/4401)	(130/4401)	(02/4401)	0.30 (44/4401)
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 Dis	sease					
Sandborn 2012	1.37 (2/146)					
Sandborn 2014	0.95 (1/105)					

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%Cl)]	SAEs [RR (95%Cl)	
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 Ta	able 6. Pooled Risk	of AE According to T	pe of JAK Inhibitor	(Controlled Studies)
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	Tofacitinib, RR (95% Cl)	Baricitinib, RR (95% Cl)	Upadacitinib, RR (95% CI)	Filgotinib, RR (95% Cl)
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.