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Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data

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ABSTRACT

Objectives Tofacitinib is a Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ulcerative colitis, and has been investigated in psoriasis (PsO). Routine pharmacovigilance of an ongoing, open-label, blinded-endpoint, tofacitinib RA trial (Study A3921133; NCT02092467) in patients aged ≥50 years and with ≥1 cardiovascular risk factor identified a higher frequency of pulmonary embolism (PE) and all-cause mortality for patients receiving tofacitinib 10 mg twice daily versus those receiving tumour necrosis factor inhibitors and resulted in identification of a safety signal for tofacitinib. Here, we report the incidence of deep vein thrombosis (DVT), PE, venous thromboembolism (VTE; DVT or PE) and arterial thromboembolism (ATE) from the tofacitinib RA (excluding Study A3921133), PsA and PsO development programmes and observational studies. Data from an ad hoc safety analysis of Study A3921133 are reported separately within.

Methods This post-hoc analysis used data from separate tofacitinib RA, PsO and PsA programmes. Incidence rates (IRs; patients with events per 100 patient-years' exposure) were calculated for DVT, PE, VTE and ATE, including for populations stratified by defined baseline cardiovascular or VTE risk factors. Observational data from the US Corrona registries (including cardiovascular risk factor stratification), IBM MarketScan research database and the US FDA Adverse Event Reporting System (FAERS) database were analysed.

Results 12 410 tofacitinib-treated patients from the development programmes (RA: n=7964; PsO: n=3663; PsA: n=783) were included. IRs (95% CI) of thromboembolic events among the *all tofacitinib cohorts'* average tofacitinib 5 mg and 10 mg twice daily treated patients for RA, respectively, were: DVT (0.17 (0.09–0.27) and 0.15 (0.09–0.22)); PE (0.12 (0.06–0.22) and 0.13 (0.08–0.21)); ATE (0.32 (0.22–0.46) and 0.38 (0.28–0.49)). Among PsO patients, IRs were: DVT (0.06 (0.00–0.36) and 0.06 (0.02–0.15)); PE (0.13 (0.02–0.47) and 0.09 (0.04–0.19)); ATE (0.52 (0.22–1.02) and 0.22 (0.13–0.35)). Among PsA patients, IRs were: DVT (0.00 (0.00–0.28) and 0.13 (0.00–0.70)); PE (0.08 (0.00–0.43) and 0.00 (0.00–0.46)); ATE (0.31 (0.08–0.79) and 0.38 (0.08–1.11)). IRs were similar between tofacitinib doses and generally higher in patients with baseline cardiovascular or VTE risk factors. IRs from the overall Corrona populations and in Corrona RA patients (including tofacitinib-naïve/biologic disease-modifying antirheumatic drug-treated and tofacitinib-treated) with baseline cardiovascular risk factors were similar to IRs observed among the corresponding patients in the tofacitinib development programme. No signals of disproportionate reporting of DVT, PE or ATE with tofacitinib were identified in the FAERS database.

Conclusions DVT, PE and ATE IRs in the tofacitinib RA, PsO and PsA programmes were similar across tofacitinib

Key messages

What is already known about this subject?

- The risk of venous thromboembolism (VTE) (including deep vein thrombosis (DVT) and pulmonary embolism (PE)) and arterial thromboembolism (ATE) is elevated in patients with immune-mediated inflammatory diseases such as rheumatoid arthritis (RA), psoriasis (PsO) and psoriatic arthritis (PsA). Labelling for the Janus kinase (JAK) inhibitors tofacitinib, baricitinib and upadacitinib now includes thrombosis as a warning and/or as an adverse drug reaction, with specific variations according to region, country and JAK inhibitor.
- In February 2019, a safety analysis of Study A3921133 (NCT02092467)—an ongoing, postauthorisation safety surveillance study in RA patients aged ≥50 years and with ≥1 cardiovascular risk factor—completed by the Data Safety Monitoring Board reported an increased incidence of PE events and all-cause mortality in patients treated with tofacitinib 10 mg twice daily versus tumour necrosis factor inhibitors.
- DVT and PE events have been observed in the tofacitinib ulcerative colitis programme (phase 2, 3 and open-label extension studies); incidence rates (IRs; patients with events per 100 patient-years' exposure) were 0.04 (95% CI 0–0.23) and 0.16 (0.04–0.41), respectively.

Key messages

What does this study add?

- Analysis of data from the tofacitinib RA (excluding Study A3921133), PsO and PsA programmes shows DVT, PE and ATE IRs to be higher in patients with defined baseline cardiovascular or VTE risk factors versus those without, and consistent with IRs in cardiovascular risk factor-enriched patients from observational data. IRs in patients with baseline cardiovascular risk factors in the RA programme were broadly comparable to those in the ad hoc safety analysis of Study A3921133, although the IR (95% CI) for PE was higher in patients treated with tofacitinib 10 mg twice daily in Study A3921133 (0.54 (0.32–0.87)), versus patients with baseline cardiovascular risk factors treated with tofacitinib 10 mg twice daily in the RA programme (0.24 (0.13–0.41)).

How might this impact on clinical practice or future developments?

- VTE has been determined to be an important identified risk of tofacitinib treatment, and local labelling has been updated regarding risk factors for thromboembolism to reflect the ad hoc safety analysis of Study A3921133 and knowledge of the JAK inhibitor safety profile. Further research is needed to better understand the relationship between thromboembolic events and JAK inhibitors, including tofacitinib.

doses, and generally consistent with observational data and published IRs of other treatments. As expected, IRs of thromboembolic events were elevated in patients with versus without baseline cardiovascular or VTE risk factors, and were broadly consistent with those observed in the Study A3921133 ad hoc safety analysis data, although the IR (95% CI) for PE was greater in patients treated with tofacitinib 10 mg twice daily in Study A3921133 (0.54 (0.32–0.87)), versus patients with baseline cardiovascular risk factors treated with tofacitinib 10 mg twice daily in the RA programme (0.24 (0.13–0.41)).

INTRODUCTION

Tofacitinib is a Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ulcerative colitis (UC), and has been investigated in psoriasis (PsO; approved for use in moderate to severe plaque PsO in Russia only). Labelling for the JAK inhibitors tofacitinib,[1 2] baricitinib[3 4] and upadacitinib[5 6] now includes thrombosis as a warning and/or as an adverse drug reaction, with specific labelling varying by region or country, and by individual JAK inhibitor.

Inflammation is a risk factor for venous thromboembolism (VTE)—including deep vein thrombosis (DVT) and pulmonary embolism (PE)—and arterial thromboembolism (ATE).[7–9] Several attributes (including inflammatory diseases), family history, older age, Black race, smoking, hypertension, diabetes, cancer, hormone therapy, major surgical procedures, obesity and immobilisation are risk factors for VTE.[7 9–17] Increased incidence of VTE and ATE relative to the general population has been reported in patients with immune-mediated inflammatory diseases, including RA,[18–30] PsO[22 24 25 31–37] and PsA.[22 38 39]

An ongoing, randomised, open-label, blinded-endpoint (major adverse cardiovascular events (MACE) and malignancies excluding non-melanoma skin cancers), postauthorisation study in RA patients—Study A3921133 (ClinicalTrials.gov NCT02092467)—is evaluating the safety of tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily versus tumour necrosis factor inhibitors (TNFi) among patients with cardiovascular risk factors.[40] In February 2019, during routine analysis of all safety events, the external, independent tofacitinib Rheumatology Data Safety Monitoring Board reported that, in the ongoing Study A3921133, among other findings, the frequency of PE and all-cause mortality in patients receiving tofacitinib 10 mg twice daily was higher than in patients treated with a TNFi (full data set is not yet available).[1 41]

In order to better understand VTE and ATE in RA, PsO and PsA patients receiving tofacitinib, we present data from the overall RA, PsO and PsA development programmes; this analysis also includes patients in the development programmes randomised to adalimumab and methotrexate. The incidence rates (IRs; 95% CI) of DVT and PE in the tofacitinib UC programme have been previously reported (0.04 (0–0.23) and 0.16 (0.04–0.41), respectively).[42] We also report thrombotic events stratified by the presence or absence of elevated baseline cardiovascular risk (aligned as closely as possible with the inclusion criteria of Study A3921133, listed in the online supplementary text) and elevated VTE risk, measured at baseline (cardiovascular and VTE risk factors are listed in the methods), as well as the results of an ad hoc safety analysis of Study A3921133. Additional context for the observed IRs is provided through the reporting of observational data in RA, PsO and PsA patients from the US Corrona registries, IBM MarketScan research database and the US FDA Adverse Event Reporting System (FAERS) database.

METHODS

Clinical data

This was a posthoc analysis of safety data from phase 1 to 3, 3b/4 and long-term extension (LTE) clinical studies of tofacitinib in RA patients, from phase 2 to 3 and LTE studies of tofacitinib in PsO patients, and from phase 3 and LTE studies of tofacitinib in PsA patients. As Study A3921133 remains ongoing, its data were not included in these pooled analyses for any RA cohort; however, data from an ad hoc safety analysis are reported separately here (data have not yet been source-verified or subjected to standard quality-check procedures that would occur at the time of database lock, and may therefore be subject to change).[1]

Full details of study designs and inclusion/exclusion criteria for each completed study have previously been published (online supplementary table S1). The ongoing Study A3921133 (NCT02092467; data cut-off February 2019; database not locked; data have not yet been source-verified or subjected to standard quality-check procedures that would occur at the time of database lock, and may therefore be subject to change) has enrolled patients aged ≥50 years and with ≥1 cardiovascular risk factor, receiving a stable dose of methotrexate (cardiovascular risk factors and inclusion/exclusion criteria are reported in the online supplementary material). Studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and local regulations.

RA patients received tofacitinib immediate-release twice daily or in a modified-release formulation (once daily) either as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs); all PsA patients received tofacitinib immediate-release twice daily in combination with one csDMARD; all PsO patients received tofacitinib immediate-release twice daily as monotherapy.

Three posthoc analysis cohorts were defined for each of the three separate programmes (RA, PsO and PsA): *placebo-controlled cohort*, *dose-comparison and active-control cohort* and *all*

tofacitinib cohort; further details on each cohort are given in the online supplementary material. The *placebo-controlled cohort* included patients randomised to tofacitinib 5 or 10 mg twice daily or placebo up to month 3 (before any placebo-treated patients advanced to tofacitinib). The *dose-comparison and active-control cohort* included data from patients treated for ≤24 months for RA and ≤12 months for PsO and PsA, randomised to tofacitinib 5 or 10 mg twice daily (including those who advanced from placebo in the PsO and PsA programmes), adalimumab 40 mg subcutaneous once every 2 weeks (active control in one phase 2 RA study, one phase 3 RA study and one phase 3 PsA study; active comparator in one phase 3/4b RA study), or methotrexate ≤20 mg once weekly (comparator in one phase 2 and one phase 3 RA study). The *all tofacitinib cohort* encompassed all patients in each disease programme who received ≥1 dose of tofacitinib (primarily 5 or 10 mg twice daily or 11 mg once daily) in RA (≤114 months' tofacitinib exposure; final data as of 18 January 2019), PsO (≤66 months' tofacitinib exposure; final data as of 18 August 2016) and PsA (≤62 months' tofacitinib exposure; final data as of 31 July 2019) studies.

For the RA, PsO and PsA *all tofacitinib cohort*, dose group was categorised using two methods, as patients could change doses between the index and LTE studies, and within the LTE studies. For the average-dosing algorithm, patients were assigned to average tofacitinib 5 or 10 mg twice daily if the average total daily dose over the course of observation was <15 or ≥15 mg, respectively. For the constant-dosing algorithm, only patients exposed to a constant tofacitinib dose of 5 or 10 mg twice daily without prior exposure to a different tofacitinib dose or adalimumab were included in the algorithm; exposure and events captured after a dose switch were excluded from the constant-dose analysis.

Data were not pooled across RA, PsO and PsA. In the described posthoc analysis of the three cohorts, all available patient-level data was used, with no exclusion criteria applied specifically related to VTE or ATE.

Additional analyses within the pooled RA, PsO and PsA clinical trial data sets were conducted. Patients were stratified by the presence or absence of defined baseline cardiovascular or VTE risk factors. Patients were identified as having cardiovascular risk factors at baseline if they were aged ≥50 years and met ≥1 of the following criteria: current smoker, high-density lipoprotein (HDL) <40 mg/dL, history of hypertension diagnosis, history of diabetes diagnosis, history of myocardial infarction or history of coronary heart disease diagnosis; this definition of cardiovascular risk factors is similar to that used in the inclusion criteria of Study A3921133[1 40] and a recently completed trial of a TNFi (etanercept) versus an interleukin-6 inhibitor (tocilizumab) in RA patients with cardiovascular risk factors (ENTRACTE).[43] For the purposes of this analysis, patients were identified as having VTE risk factors if they met any of the following criteria at baseline: aged ≥60 years, current smoker, previous heart failure, previous VTE (DVT or PE), body mass index (BMI) ≥30 kg/m^2, Day 1 use of oral contraceptives or hormone replacement therapy, Day 1 use of antidepressants or Day 1 use of aspirin. Please note that this definition of VTE risk factors is specific to this analysis and reflects available data from the clinical trials; for this reason, it may differ to definitions used elsewhere.

DVT, PE and ATE events were identified using the Medical Dictionary for Regulatory Activities (MedDRA) selected (clinically relevant) Preferred Terms (PTs) from the Standardised MedDRA Queries (SMQs) *Embolic and thrombotic events, venous* and *Embolic and thrombotic events, arterial* (including PT for cases of myocardial infarction and ischaemic stroke). Given the potential that some PTs, consistent with DVT and ATE, are not included in the above SMQs, the database was also examined for clinically relevant terms for the SMQ *Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous*. Details are given in the online supplementary material. PTs were based on spontaneous reporting of adverse events by investigators and were not corroborated or confirmed by any protocol-mandated assessment or activity.

IRs were calculated as the number of patients with an event per 100 patient-years (PY) of exposure, defined as time to first event occurring during the risk period (minimum of a patient's last treatment dose date plus 28 days, date of death or up to the last observation date). Poisson 95% CIs for the IRs were calculated.

Separate IRs were calculated for DVT, PE and ATE events (including both outpatient and inpatient events), and for VTE (a composite of the first DVT or PE event). Patients who experienced more than one event were censored at the time of first event. For patients who experienced multiple events at the same time, each event was included in the DVT, PE and ATE IR estimates, respectively. For VTE event (DVT or PE) IR estimates, the patient was only included once, even if there was simultaneous reporting of DVT and PE in the same patient.

Kaplan-Meier analysis was performed for time to DVT, PE or ATE; total follow-up time was calculated up to the day of the first event (subject to the above risk period).

Observational/postmarketing data

For all observational data from the relevant US Corrona registries and MarketScan database, the IRs were calculated as patients with events per 100 PY of exposure (Corrona) or as events per 100 PY of exposure (MarketScan). Rates were standardised by age and sex distribution for each disease in the tofacitinib programme, unless otherwise stated (details given in the online supplementary material).

Data were obtained from the US Corrona registries[44] for RA, PsO or PsA patients who received non-biologic or biologic treatments (online supplementary table S2) from 6 November 2012 for RA, 1 April 2015 for PsO or 1 March 2013 for PsA, up to 31 December 2017. Exposure time was defined as the time in years from the index date (first date of prescription or administration of approved treatment after diagnosis) to the first VTE event (DVT or PE), last follow-up visit, or switch to tofacitinib, whichever came first.

An additional subanalysis within the RA Corrona-based post-authorisation safety study of tofacitinib[45] investigated the incidence of DVT and PE events in cohorts of patients with moderate to severe RA (Clinical Disease Activity Index (CDAI)>10 at initiation) initiating a biologic disease-modifying antirheumatic drug (bDMARD) or tofacitinib, who were aged ≥50 years and had ≥1 cardiovascular risk factor (details in the online supplementary material). Non-standardised/unadjusted (crude) IRs were calculated. The time to first DVT or PE event was also calculated.

Data were also obtained and analysed from the IBM MarketScan research database (hereafter MarketScan database)[46] for RA, PsO or PsA patients treated between 1 January 2010 and 31 December 2017 (online supplementary material). Exposure time was defined as the time in years from the index date to the first DVT or PE event, identified using ICD9/10 diagnosis codes and patient medication use.

Using the FAERS database, disproportionality analyses were performed on spontaneous reports to assess if there was a signal of disproportionate reporting (SDR) through analysis of observed-to-expected (O/E) reporting frequencies. Analyses were completed for the identified events of *Embolic and thrombotic events, venous, Embolic and thrombotic events, arterial* and *Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous*

SMQs reported in association with tofacitinib. For the shrinkage-adjusted O/E, an SDR was defined as a lower 5% bound of the 90% interval of the shrinkage-adjusted O/E ratio (EB_{05}) >2.[47] For the unadjusted metric, an SDR was defined as the lower 5% bound of the 90% interval of the reporting odds ratio (ROR_{05}) >2 and a minimum case count >2.

Patient and public involvement

Patients and the public were not involved in the design, analysis or results interpretation of this study. Patient-level data from the relevant data sets were used to complete the analysis.

RESULTS

Tofacitinib clinical trials

Patients

Overall, 12 410 tofacitinib-exposed patients from completed studies in the development programmes were included in this analysis: 7964 with RA, 3663 with PsO and 783 with PsA. Table 1 summarises demographics and baseline characteristics for all patients who received ≥1 dose of tofacitinib. Online supplementary tables S3–5 summarise the demographics and baseline characteristics data, stratified by the presence or absence of baseline cardiovascular or VTE risk factors.

Incidence of VTE and ATE: *placebo-controlled cohort*

During the first 90 days of tofacitinib treatment (up to month 3 in the *placebo-controlled cohorts*), the IRs of DVT, PE, VTE (DVT or PE) and ATE events were similar between tofacitinib doses and placebo across each of the RA (figure 1), PsO (figure 2) and PsA (figure 3) development programmes.

One patient with RA receiving placebo experienced both a DVT and a PE event; this patient was aged >50 years and had multiple risk factors, including current smoker, medical history of thrombosis and Day 1 use of hormone replacement therapy and antidepressants.

Incidence of VTE and ATE: *dose-comparison and active-control cohort*

In RA up to month 24, and in PsO and PsA up to month 12, IRs of DVT, PE, VTE (DVT or PE) and ATE events were similar between tofacitinib (both doses), adalimumab and methotrexate (figures 1–3).

Incidence of VTE and ATE: *all tofacitinib cohort*—all patients

Among RA (figure 1), PsO (figure 2) and PsA (figure 3) patients, the IRs of all events were similar for average tofacitinib 5 and 10 mg twice daily. Among RA patients, IRs for constant tofacitinib 10 mg twice daily were similar to those for constant tofacitinib 5 mg twice daily.

Analysis of Kaplan-Meier curves, showing proportions of RA patients in the tofacitinib development programme without a thromboembolic event, did not reveal any separation between dose groups, and most events occurred during the LTE. More events occurring during the LTE can be attributed to the longer observation time in the LTE versus the index studies. Further, the curves indicated a consistent rate of event occurrence over time (online supplementary figure S1). Thromboembolic events among PsO and PsA patients were too few to be represented in Kaplan-Meier curves.

Analysis of the SMQ *Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous*—to identify additional PTs consistent with VTE/ATE—revealed one patient each with cerebral thrombosis (RA programme; average 5 mg twice daily), intracardiac thrombus (RA programme; average 10 mg twice daily) and thrombotic stroke (PsO programme; average 10 mg twice daily). These events were not included in the IR calculations.

Incidence of VTE and ATE: *all tofacitinib cohort*—stratified by baseline cardiovascular or VTE risk factors

The IRs of DVT, PE, VTE (DVT or PE) and ATE were generally higher in patients with a baseline cardiovascular or VTE risk factor versus patients without (figures 1–3). IRs were lower in RA patients without risk factors (61% with no cardiovascular risk factors; 34% with no VTE risk factors) versus those with risk factors. Among PsA patients, all DVT and PE events were experienced by patients who had baseline cardiovascular or VTE risk factors. However, across all diseases, comparison of thromboembolic event IRs in patients with baseline cardiovascular or VTE risk was limited by the low number of events and did not illustrate meaningful differences across groups.

IRs were similar between average tofacitinib 5 and 10 mg twice daily among patients with cardiovascular or VTE risk factors (figures 1–3). For RA patients without cardiovascular or VTE risk factors, IRs of DVT, PE and VTE (but not ATE) were modestly numerically higher for average tofacitinib 10 mg twice daily relative to average tofacitinib 5 mg twice daily, but the number of events across all diseases in patients without risk factors was too low to draw firm conclusions.

Incidence of DVT and PE: *Study A3921133 (ad hoc safety analysis)*

The ongoing Study A3921133 includes 4362 randomised patients, and is accruing safety and efficacy data as specified per study protocol.[40] Patient demographics and baseline characteristics were balanced across treatment arms, and the patient population in Study A3921133 is generally consistent with the cardiovascular risk factor-enriched patient population from the RA programme (Pfizer data on file).

IRs (95% CI) in an ad hoc safety analysis of the ongoing Study A3921133 (NCT02092467; data cut-off February 2019; database not locked; data have not yet been source-verified or subjected to standard quality-check procedures that would occur at the time of database lock, and may therefore be subject to change) for DVT and PE with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and TNFi are reported in figure 4.[1] Compared with TNFi, the hazard ratios (HRs) (95% CI) for DVT/PE with tofacitinib 5 mg twice daily were 1.66 (0.60–4.57)/2.99 (0.81–11.06), and 2.13 (0.80–5.69)/5.96 (1.75–20.33) with tofacitinib 10 mg twice daily.[1]

Baseline risk factor analysis

When the individual baseline risk factors for each patient who experienced DVT, PE or ATE in completed studies of the tofacitinib development programmes were evaluated, the most common baseline risk factors in RA patients were C-reactive protein level (CRP) >2.87 mg/L, hypertension, aged ≥60 years and Day 1 use of corticosteroids; in PsO patients, CRP >2.87 mg/L, male sex and BMI ≥30 kg/m^2 appeared to be the most common baseline risk factors; events among PsA patients were too low to draw conclusions (online supplementary table S6). It should be noted that active disease was an inclusion criteria for the RA studies, with patients requiring either an erythrocyte sedimentation rate >28 mm/hour or CRP >7 mg/L. The vast majority of patients who experienced a thromboembolic event had multiple baseline risk factors (figure 5).

Table 1 Patient demographics and baseline characteristics for all tofacitinib-treated patients (*all tofacitinib cohort*) in completed studies in the RA, PsO and PsA development programmes, stratified by average tofacitinib dose*

	RA		PsO		PsA	
	Average tofacitinib 5 mg twice daily (N=3969)	Average tofacitinib 10 mg twice daily (N=3995)	Average tofacitinib 5 mg twice daily (N=920)	Average tofacitinib 10 mg twice daily (N=2743)	Average tofacitinib 5 mg twice daily (N=458)	Average tofacitinib 10 mg twice daily (N=325)
Age (years), mean (SD)	53.3 (12.4)	52.0 (11.6)	45.5 (13.3)	44.5 (12.7)	49.2 (11.9)	48.0 (12.2)
≥65 years of age, n (%)	722 (18.2)	548 (13.7)	71 (7.7)	149 (5.4)	42 (9.2)	30 (9.2)
≥50 years of age, n (%)	2606 (65.7)	2481 (62.1)	386 (42.0)	1015 (37.0)	238 (52.0)	160 (49.2)
Female, n (%)	3236 (81.5)	3286 (82.3)	323 (35.1)	794 (28.9)	258 (56.3)	170 (52.3)
Race, n (%)						
White	2417 (60.9)	2753 (68.9)	794 (86.3)	2341 (85.3)	434 (94.8)	305 (93.8)
Black	121 (3.0)	131 (3.3)	27 (2.9)	51 (1.9)	0 (0)	3 (0.9)
Asian	1126 (28.4)	686 (17.2)	42 (4.6)	207 (7.5)	11 (2.4)	12 (3.7)
Other/unknown	305 (7.7)	425 (10.6)	57 (6.2)	144 (5.2)	13 (2.8)	5 (1.5)
BMI (kg/m^2), mean (SD) (N1)	26.7 (6.2) (3961)	27.5 (6.5) (3993)	29.7 (6.5) (919)	29.9 (6.8) (2740)	29.5 (5.9) (458)	29.8 (6.2) (325)
BMI ≥30 kg/m^2, n (%) (N1)	982 (24.8) (3961)	1156 (29.0) (3993)	384 (41.8) (919)	1160 (42.3) (2740)	196 (42.8) (458)	137 (42.2) (325)
Smoking status, n (%)						
Never smoked	2522 (63.5)	2474 (61.9)	353 (38.4)	1059 (38.6)	289 (63.1)	196 (60.3)
Smoker	648 (16.3)	718 (18.0)	365 (39.7)	1015 (37.0)	92 (20.1)	48 (14.8)
Ex-smoker	689 (17.4)	699 (17.5)	202 (22.0)	669 (24.4)	77 (16.8)	81 (24.9)
Unknown	110 (2.8)	104 (2.6)	0	0	0	0
Comorbidities, n (%)						
Diabetes	365 (9.2)	286 (7.2)	128 (13.9)	371 (13.5)	61 (13.3)	46 (14.2)
Hypertension	1405 (35.4)	1413 (35.4)	219 (23.8)	595 (21.7)	180 (39.3)	119 (36.6)
Coronary heart disease	13 (0.3)	17 (0.4)	24 (2.6)	66 (2.4)	23 (5.0)	16 (4.9)
Myocardial infarction	50 (1.3)	50 (1.3)	8 (0.9)	24 (0.9)	6 (1.3)	9 (2.8)
History of hyperlipidemia, n (%)	740 (18.6)	794 (19.9)	220 (23.9)	641 (23.4)	94 (20.5)	73 (22.5)
Previous heart failure, n (%)	28 (0.7)	14 (0.4)	0	7 (0.3)	0	3 (0.9)
Previous VTE (DVT or PE), n (%)	40 (1.0)	48 (1.2)	2 (0.2)	9 (0.3)	3 (0.7)	7 (2.2)
CRP >2.87 mg/L, n (%) (N1)	3158 (80.2) (3939)	3188 (80.5) (3958)	378 (47.0) (804)	1119 (48.7) (2297)	288 (62.9) (458)	198 (60.9) (325)
Concomitant medication, n (%)						
Steroids	2070 (52.2)	2184 (54.7)	0†	0†	109 (23.8)	62 (19.1)
Anticoagulants	316 (8.0)	344 (8.6)	75 (8.2)	188 (6.9)	34 (7.4)‡	34 (10.5)‡
Antiplatelet agents	280 (7.1)	339 (8.5)	78 (8.5)	194 (7.1)	31 (6.8)‡	23 (7.1)‡
OCT or HRT‡	347 (8.7)	334 (8.4)	75 (0.2)	186 (6.8)	40 (8.7)	37 (11.4)
Antidepressants‡	278 (7.0)	367 (9.2)	54 (5.9)	132 (4.8)	56 (12.2)	37 (11.4)
Statins‡	182 (4.6)	438 (11.0)	127 (13.8)	360 (13.1)	58 (12.7)	42 (12.9)
Aspirin	246 (6.2)	305 (7.6)	70 (7.6)	172 (6.3)	28 (6.1)‡	22 (6.8)‡
Prior MTX use, n (%)	3610 (91.0)	3047 (76.3)	276 (30.0)	881 (32.1)	432 (94.3)	293 (90.2)
Prior csDMARD use (other than MTX), n (%)	1655 (41.7)	2084 (52.2)	83 (9.0)	307 (11.2)	205 (44.8)	165 (50.8)
Prior TNFi use, n (%)	463 (11.7)	782 (19.6)	140 (15.2)	440 (16.0)	190 (41.5)	187 (57.5)
Prior non-TNFi bDMARD use, n (%)	177 (4.5)	237 (5.9)	53 (5.8)	161 (5.9)	24 (5.2)	22 (6.8)

*Patients were assigned to average tofacitinib 5 or 10 mg twice daily if the average total daily dose over the course of observation was <15 or ≥15 mg, respectively.
†Concomitant steroids were not allowed in PsO trials.
‡Day 1 use.
bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DVT, deep vein thrombosis; HRT, hormone replacement therapy; MTX, methotrexate; n, number of patients with characteristic; N1, total number of patients for that characteristic; N, total number of patients; OCT, oral contraceptives; PE, pulmonary embolism; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SD, standard deviation; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism (DVT or PE).

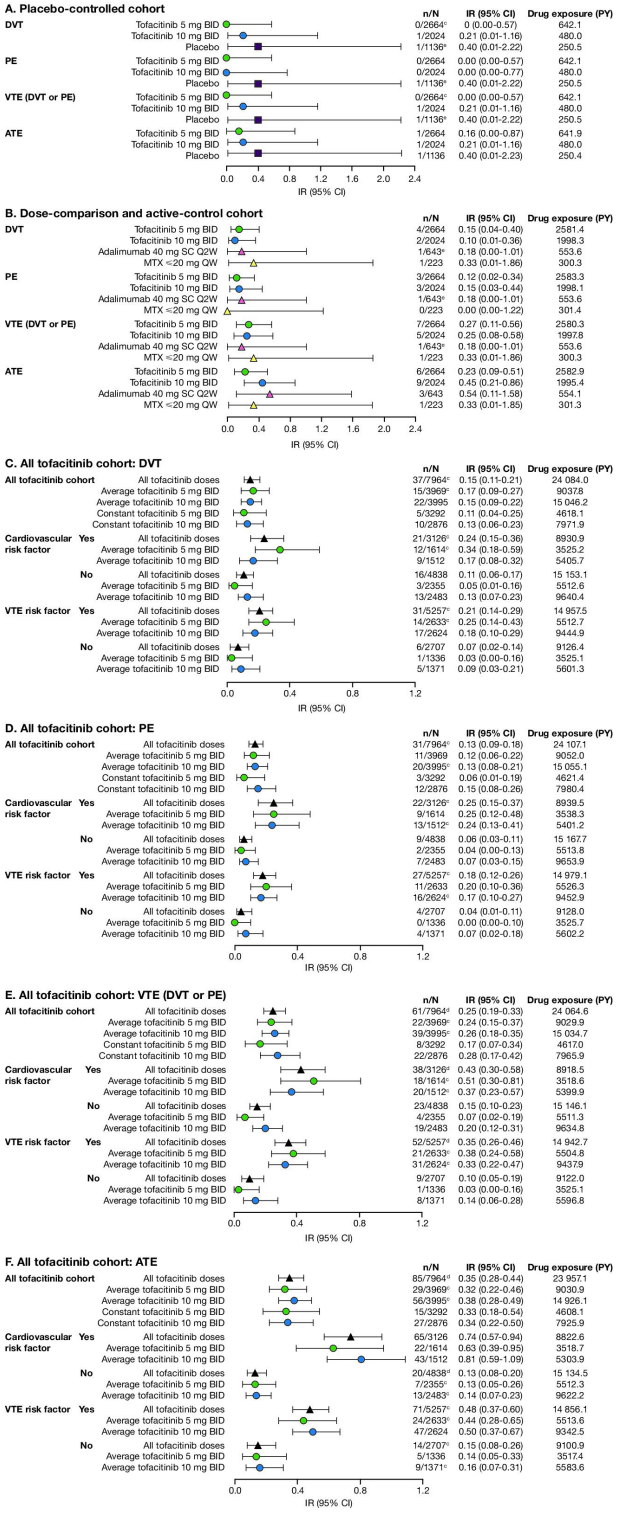

Figure 1 Drug exposure and incidence rates (95% CI) among RA patients in completed studies in the tofacitinib development programme for (A) the *placebo-controlled cohort*, (B) the *dose-comparison and active-control cohort*, and the *all tofacitinib cohort* for (C) DVT,(D) PE, (E) VTE (DVT or PE) and (F) ATE, including patients stratified by baseline cardiovascular[a] or VTE[b] risk factors; final data as of 18 January 2019. [a]Baseline cardiovascular risk factors were defined as any patient aged ≥50 years and meeting ≥1 of the following criteria at baseline: current smoker, HDL <40 mg/dL, history of hypertension diagnosis, history of diabetes diagnosis, history of myocardial infarction or history of coronary heart disease diagnosis. [b]Baseline VTE risk factors were defined as any patient meeting any of the following criteria at baseline: aged ≥60 years, current smoker, previous heart failure, previous VTE (DVT or PE), BMI ≥30 kg/m^2, Day 1 use of oral contraceptives or hormone replacement therapy, Day 1 use of antidepressants or Day 1 use of aspirin. [c]One or [d]two patients were not counted in the numerator of the IR calculations because the events occurred outside the defined risk period. [e]One patient experienced both DVT and PE. ATE, arterial thromboembolism; BID, twice daily; BMI, body mass index; DVT, deep vein thrombosis; HDL, high-density lipoprotein; IR, incidence rate (number of patients with an event per 100 PY of exposure); MTX, methotrexate; N, total number of patients; n, number of patients with an event; PE, pulmonary embolism; PY, patient-years; QW, once a week; Q2W, once every 2 weeks; RA, rheumatoid arthritis; SC, subcutaneous; VTE, venous thromboembolism.

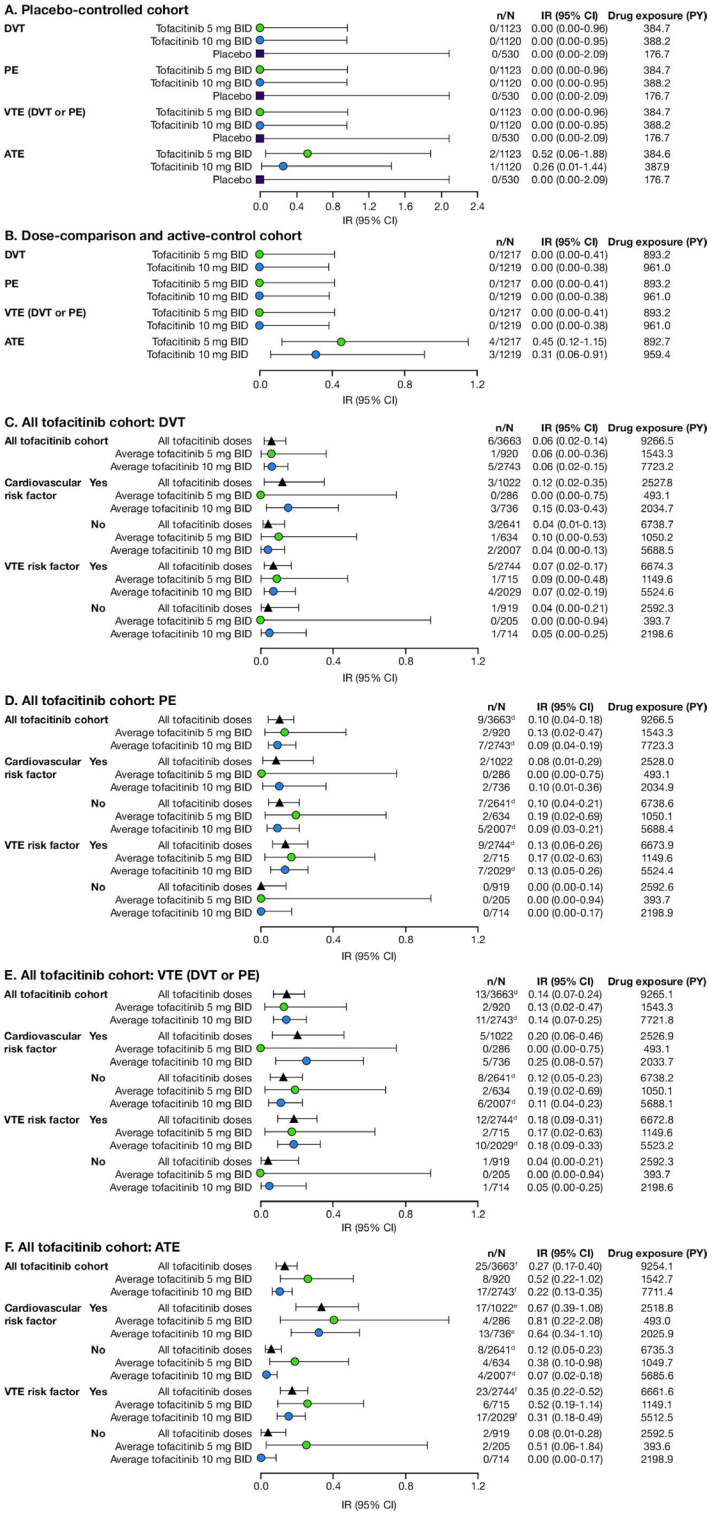

Figure 2 Drug exposure and incidence rates (95% CI) among PsO patients in completed studies in the tofacitinib development programme for (A) the *placebo-controlled cohort*, (B) the *dose-comparison and active-control cohort,*[a] and the *all tofacitinib cohort* for (C) DVT, (D) PE, (E) VTE (DVT or PE) and (F) ATE, including patients stratified by baseline cardiovascular[b] or VTE[c] risk factors; final data as of 18 August 2016. [a]The *dose-comparison and active-control* cohort includes patients receiving tofacitinib after switching from placebo. [b]Baseline cardiovascular risk factors were defined as any patient aged ≥50 years and meeting ≥1 of the following criteria at baseline: current smoker, HDL <40 mg/dL, history of hypertension diagnosis, history of diabetes diagnosis, history of myocardial infarction or history of coronary heart disease diagnosis. [c]Baseline VTE risk factors were defined as any patient meeting any of the following criteria at baseline: aged ≥60 years, current smoker, previous heart failure, previous VTE (DVT or PE), BMI ≥30 kg/m^2, Day 1 use of oral contraceptives or hormone replacement therapy, Day 1 use of antidepressants or Day 1 use of aspirin. [d]One, [e]three or [f]four patients were not counted in the numerators of the IR calculations because the events occurred outside the defined risk period.
ATE, arterial thromboembolism; BID, twice daily; BMI, body mass index; DVT, deep vein thrombosis; HDL, high-density lipoprotein; IR, incidence rate (number of patients with an event per 100 PY of exposure); N, total number of patients; n, number of patients with an event; PE, pulmonary embolism; PsO, psoriasis; PY, patient-years; VTE, venous thromboembolism.

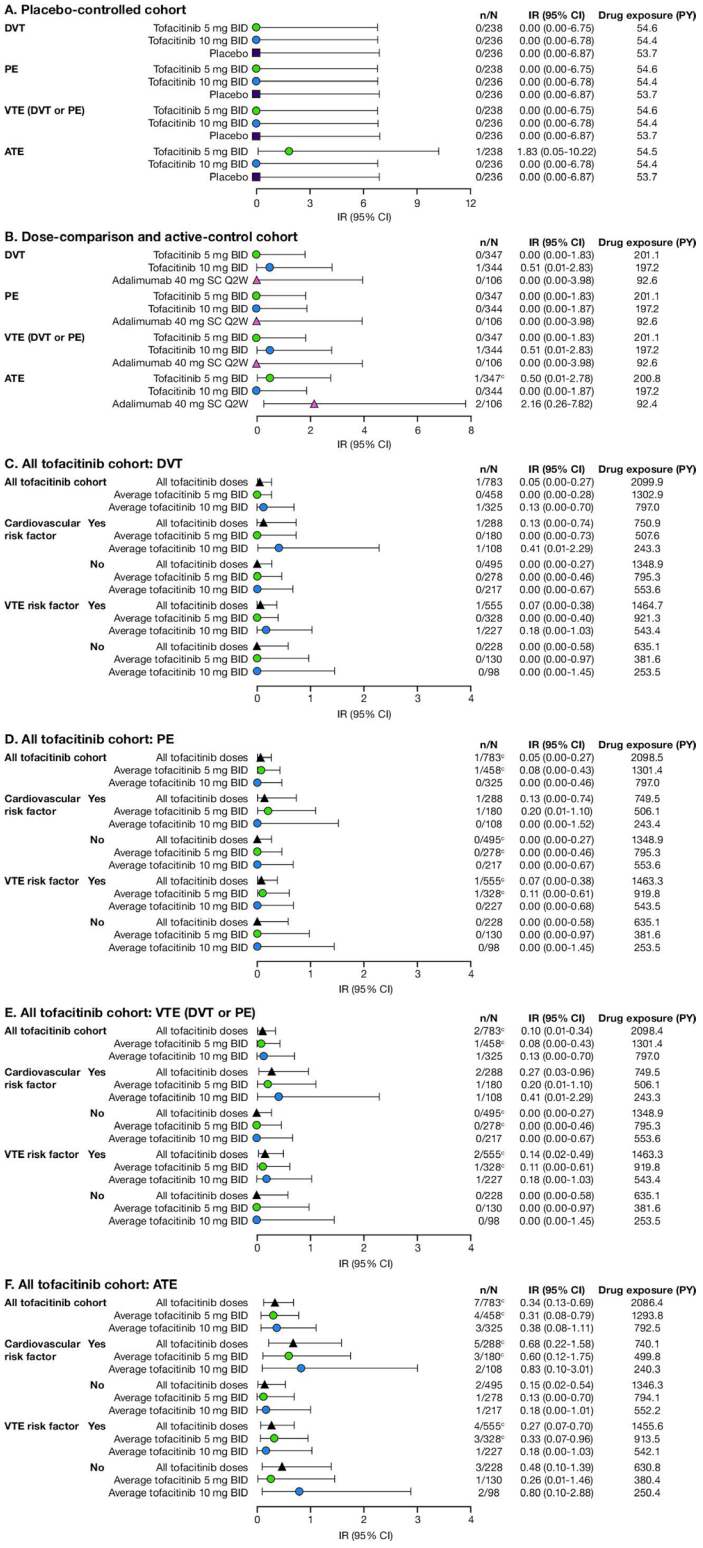

Figure 3 Drug exposure and incidence rates (95% CI) among PsA patients in completed studies in the tofacitinib development programme for (A) the *placebo-controlled cohort*, (B) the *dose-comparison and active-control cohort*, and the *all tofacitinib cohort* for (C) DVT, (D) PE, (E) VTE (DVT or PE) and (F) ATE, including patients stratified by baseline cardiovascular[a] or VTE[b] risk factors; final data as of 31 July 2019. [a]Baseline cardiovascular risk factors were defined as any patient aged ≥50 years and meeting ≥1 of the following criteria at baseline: current smoker, HDL <40 mg/dL, history of hypertension diagnosis, history of diabetes diagnosis, history of myocardial infarction or history of coronary heart disease diagnosis. [b]Baseline VTE risk factors were defined as any patient meeting any of the following criteria at baseline: aged ≥60 years, current smoker, previous heart failure, previous VTE (DVT or PE), BMI ≥30 kg/m^2, Day 1 use of oral contraceptives or hormone replacement therapy, Day 1 use of antidepressants or Day 1 use of aspirin. [c]One patient was not counted in the numerators of the IR calculations because the event occurred outside the defined risk period. ATE, arterial thromboembolism; BID, twice daily; BMI, body mass index; DVT, deep vein thrombosis; HDL, high-density lipoprotein; IR, incidence rate (number of patients with an event per 100 PY of exposure); N, total number of patients; n, number of patients with an event; PE, pulmonary embolism; PsA, psoriatic arthritis; PY, patient-years; Q2W, once every 2 weeks; SC, subcutaneous; VTE, venous thromboembolism.

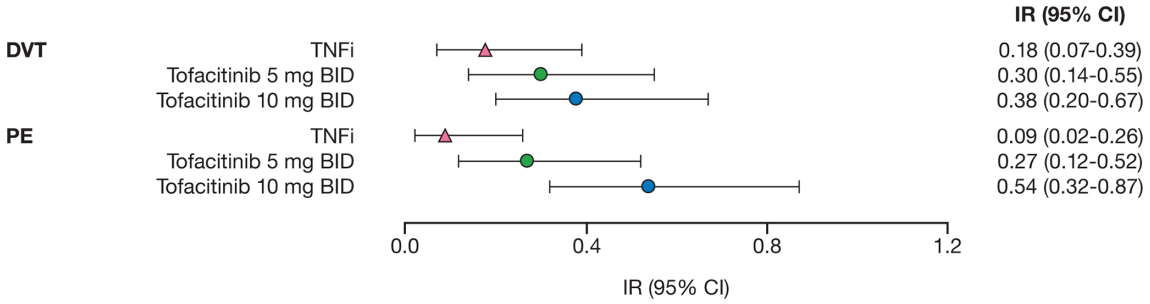

Figure 4 Incidence rates (95% CI) for DVT and PE among patients in Study A3921133 (ad hoc safety analysis).[a1] [a]Data cut-off February 2019; database not locked. Data have not yet been source-verified or subjected to standard quality-check procedures that would occur at the time of database lock, and may therefore be subject to change. BID, twice daily; DVT, deep vein thrombosis; IR, incidence rate (number of patients with an event per 100 PY of exposure); PE, pulmonary embolism; PY, patient-years; TNFi, tumour necrosis factor inhibitor.

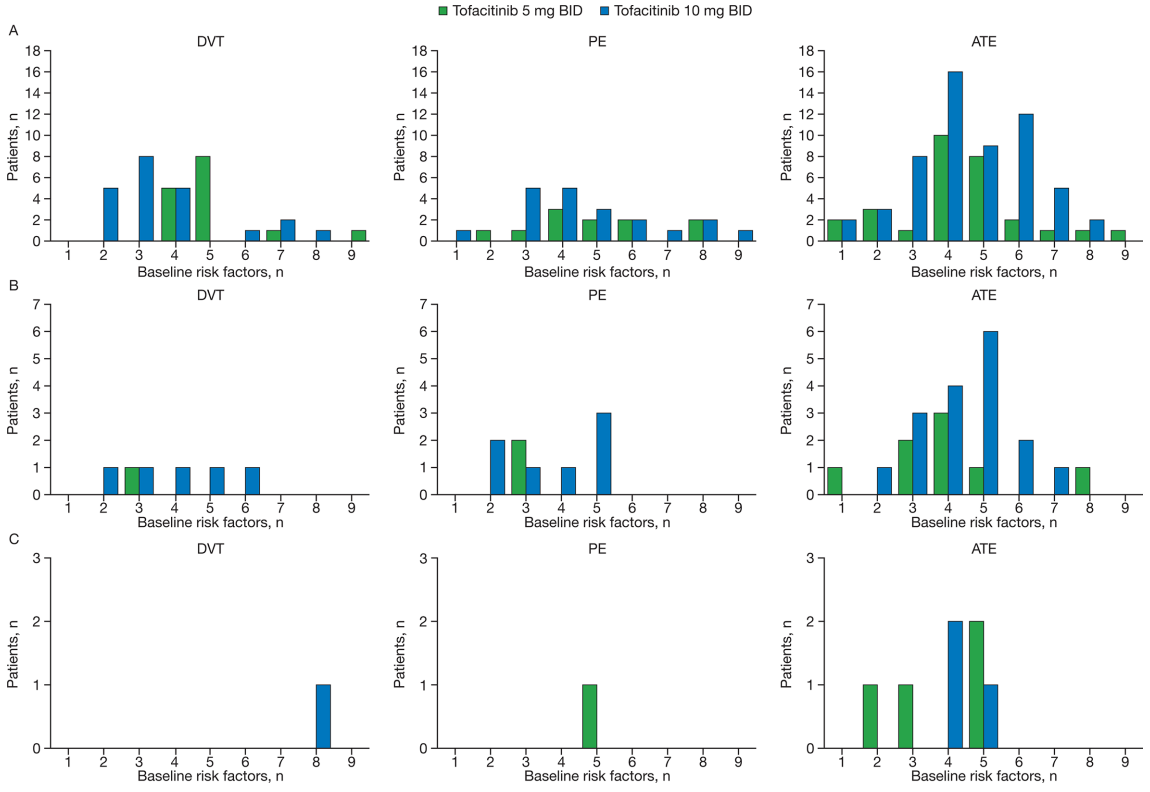

Figure 5 Number of baseline risk factors for patients who experienced a DVT, PE or ATE in completed studies in the (A) RA, (B) PsO and (C) PsA tofacitinib development programmes, stratified by tofacitinib dose. Those patients who had an event within the predefined risk period (minimum of a patient's last treatment dose date plus 28 days, date of death or up to the last observation date) are included. Details on the individual risk factors, and the number of patients who experienced each risk factor, are summarised in online supplementary table S6. ATE, arterial thromboembolism; BID, twice daily; DVT, deep vein thrombosis; n, number of patients with a given number of baseline risk factors; PE, pulmonary embolism; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis.

Comparison of clinical data and observational data

Patient demographics and baseline characteristics were generally similar between the tofacitinib programmes (table 1) and cohorts within the respective US Corrona registries (online supplementary table S7) and MarketScan database (online supplementary table S8).

Standardised IRs of VTE from the RA, PsA and PsO US Corrona registries were broadly comparable with those in the tofacitinib development programmes (online supplementary table S9). For RA patients in the MarketScan database, IRs were higher than those observed in the tofacitinib programme, but similar between those receiving tofacitinib and bDMARDs within the MarketScan database cohorts (online supplementary table S10).

Baseline demographics and disease characteristics for the subgroup analysis of the Corrona RA registry data of patients with moderate to severe disease activity (CDAI >10) and who were aged ≥50 years with ≥1 cardiovascular risk factor are given in online supplementary table S11. Unadjusted IRs for DVT, PE and VTE (DVT or PE) for bDMARD-initiating (tofacitinib-naïve) patients were higher in those with cardiovascular risk factors than in the overall subgroup population (figure 6); the frequency of VTE events in patients initiating tofacitinib with cardiovascular risk factors versus the overall subgroup population was too low to draw firm conclusions (figure 6).

Among RA patients in the US Corrona registry with moderate to severe disease activity (CDAI >10) who experienced a VTE (figure 5), the median (interquartile range (IQR)) time to first

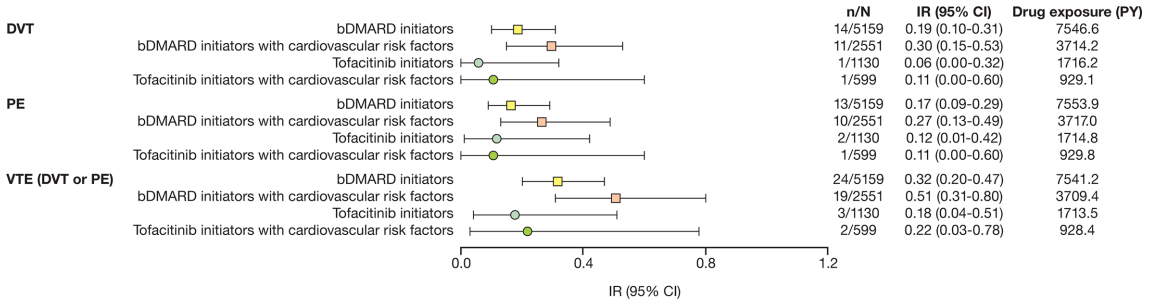

Figure 6 Drug exposure and unadjusted incidence rates (95% CI) for DVT, PE and VTE (DVT or PE) for RA patients with moderate to severe disease activity (CDAI >10) in the US Corrona RA registry subanalysis who were bDMARD[a] or tofacitinib[b] initiators; all patients, stratified by cardiovascular risk factors.[c] [a]Included patients with moderate to severe RA (CDAI >10 at time of initiation) in the Corrona RA registry initiating a first or subsequent bDMARD (each initiation was considered separately, such that there were multiple initiations per patient) and who were tofacitinib-naïve. [b]RA patients in the US Corrona registry initiating tofacitinib for the first time. [c]Defined as patients aged ≥50 years and with ≥1 of the following cardiovascular risk factors: current smoker, diagnosis of hypertension, diagnosis of diabetes mellitus, history of coronary artery disease (eg, cardiac arrest, heart attack, unstable angina, revascularisation procedures), family history of premature coronary heart disease or current extra-articular RA disease. bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; DVT, deep vein thrombosis; IR, incidence rate (number of patients with an event per 100 PY of exposure); N, number of RA patients; n, number of RA patients with events; PE, pulmonary embolism; PY, patient-years; RA, rheumatoid arthritis; VTE, venous thromboembolism.

event in patients initiating bDMARDs was 213.1 (91.3–334.8) days for DVT, and 395.7 (213.1–760.9) days for PE. Out of a total of 14 DVT events in patients initiating bDMARDs, four and seven events were reported within 3 and 6 months of bDMARD initiation, respectively; out of 13 PE events, none and three events were reported within 3 and 6 months of bDMARD initiation, respectively.

In patients in the Corrona RA registry with moderate to severe disease activity who were initiating tofacitinib, the time to the only reported DVT event was 608.8 days; and median (IQR) time to PE was 608.8 (91.3–1126.2) days. The DVT event did not occur within 6 months of tofacitinib initiation, and one each of the two reported PE events occurred within 3 and 6 months of initiation.

Postmarketing FAERS data

Based on 1210 unique reports (306 for embolic and thrombotic venous events, 422 for arterial events and 563 for unspecified/mixed vessel events) with tofacitinib FAERS data, this analysis did not identify any SDRs for tofacitinib events of interest at any time point (online supplementary table S12). Most O/E ratios for tofacitinib were <1; many events had an upper bound of <1 of the 90% interval of the O/E (56% of EB_{95}s and 40% of ROR_{95}s for PTs). Although O/E ratios for some events were >1, all were still below the SDR-defined threshold of 2 or were non-significant.

DISCUSSION

The objective of this analysis was to inform about thromboembolic events across large populations of RA, PsO and PsA patients treated with tofacitinib, including analyses of patients stratified by the presence or absence of baseline cardiovascular or VTE risk factors. Analysis of the RA (excluding the ongoing Study A3921133), PsO, and PsA tofacitinib development programmes revealed similar IRs of DVT, PE, VTE (DVT or PE) and ATE events for tofacitinib, placebo, adalimumab (an active control or comparator) and methotrexate in studies of ≤24 months' duration. There did not appear to be an elevated risk of thromboembolic events in the first 3 months of tofacitinib treatment, shown by the relative comparability of IR in the *placebo-controlled cohorts* with the other cohorts in the tofacitinib development programmes. This was reflected in data from the US Corrona RA registry, where the median time to DVT or PE was >200 days for bDMARDs and >600 days for tofacitinib. Furthermore, IRs were consistent across tofacitinib 5 and 10 mg twice-daily dose groups in the RA, PsO and PsA development programmes. The IRs of DVT and PE for RA, PsO and PsA were also similar to those reported in the tofacitinib UC programme,[42] indicating comparable incidences of thromboembolic events with tofacitinib across diseases.

Across the tofacitinib development programmes, the IRs of DVT or PE in tofacitinib-treated patients from the *all tofacitinib cohort* (ranges 0.00–0.17 and 0.00–0.15, respectively)—including data from LTE studies with longer cumulative tofacitinib exposure—were consistent with those previously reported for patients with RA (ranges 0.21–0.62 and 0.15–0.26, respectively)[19 20 22] and PsA (0.33–0.38 and 0.11–0.12, respectively),[22] who were untreated or receiving DMARDs, and for patients with severe PsO (0.36 and 0.11, respectively).[22] The IRs of ATE in the *all tofacitinib cohort* (range 0.22–0.52) were also similar to the IRs of ischaemic stroke (0.3 (95% CI 0.27–0.34))[37] and myocardial infarction (0.46 (95% CI 0.41–0.52))[48] reported in RA patients.

As expected, subanalyses of the RA, PsO and PsA clinical programmes, stratified by the presence or absence of baseline cardiovascular risk factors, showed that patients with risk factors were more likely to experience thromboembolic events than those without. IRs in patients without risk factors were very low. Most patients who experienced thromboembolic events also had multiple cardiovascular risk factors at baseline.

The IRs of DVT and PE among patients with a baseline cardiovascular risk factor in the RA programme were higher than those without baseline cardiovascular risk factors, and are broadly comparable to those from the ad hoc safety analysis data for Study A3921133 (NCT02092467; data cut-off February 2019; database not locked; data have not yet been source-verified or subjected to standard quality-check procedures that would occur at the time of database lock, and may therefore be subject to change) (figure 7).[1] The incidence of PE for tofacitinib 10 mg twice daily was higher in the ad hoc safety analysis of Study A3921133 (0.54 (0.32–0.87))[1] than that reported in the overall tofacitinib RA programme for patients with a baseline cardiovascular risk factor (0.24 (0.13–0.41)). In addition, IRs in RA patients with cardiovascular risk factors in the US Corrona RA registry initiating tofacitinib were not higher than in those initiating bDMARDs, and were comparable to those in the RA

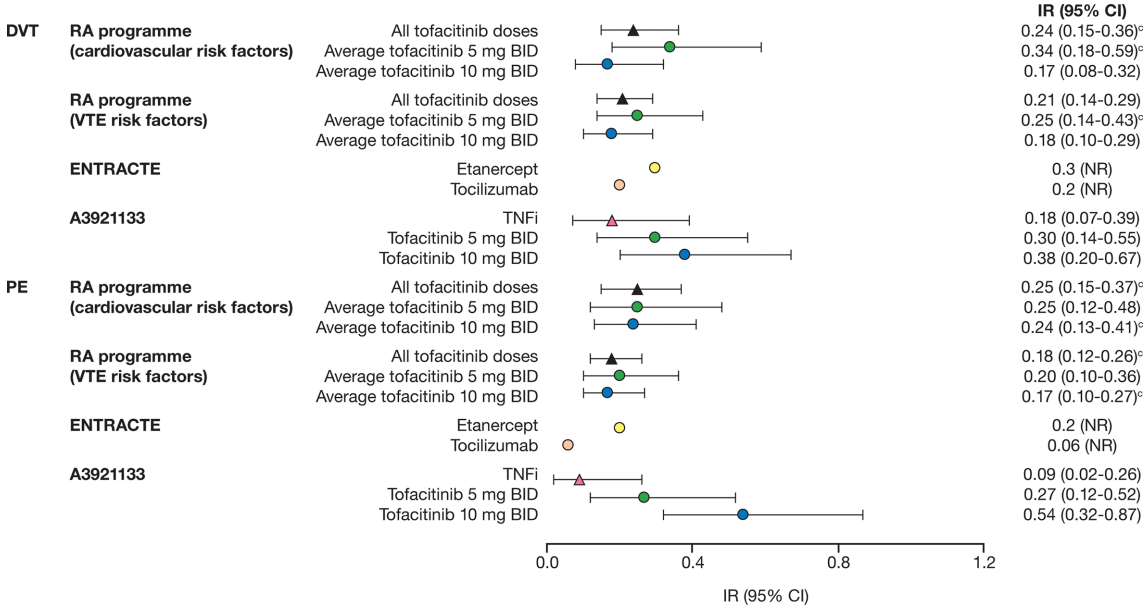

Figure 7 Incidence rates (95% CI) for DVT and PE among patients in the RA development programme, stratified by cardiovascular or VTE risk factors (*all tofacitinib cohort*),[a] the ENTRACTE trial[43] and Study A3921133.[b1] [a]Final data as of 18 January 2019. [b]Data cut-off February 2019; database not locked. Data have not yet been source-verified or subjected to standard quality-check procedures that would occur at the time of database lock, and may therefore be subject to change. [c]One patient was not counted in the numerators of the IR calculations because the event occurred outside the defined risk period. BID, twice daily; DVT, deep vein thrombosis; IR, incidence rate (number of patients with an event per 100 PY of exposure); NR, not reported; PE, pulmonary embolism; PY, patient-years; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

tofacitinib programme, although the frequency of events was low.

Study A3921133 is designed to assess differences between tofacitinib doses, maintain patients on the same dose throughout treatment (note patients randomised to tofacitinib 10 mg twice daily had their dose reduced to 5 mg twice daily as per protocol amendment in February 2019),[41] and encourage patients to remain in the study after treatment discontinuation. Given the observed incidence of MACE among RA patients using advanced therapies,[49–52] an endpoint-driven study such as Study A3921133 was projected to take >10 years if enrolling a non-enriched RA population. Therefore, the study was designed to enrich for cardiovascular risk, and enrolled patients aged ≥50 years and with ≥1 cardiovascular risk factor, with the goal of study completion in <8 years.

While the results of the tofacitinib development programme did not confirm an increased VTE/ATE risk or a dose relationship, it should be noted that although the phase 2 and 3 studies did examine tofacitinib dose differences, they were limited by patient number and observation time. In the LTE studies, patients could switch dose, and did not remain in the study after treatment discontinuation. The primary objective of the LTE studies was to examine long-term safety; they were not designed to formally assess dose differences. Furthermore, not all of the cardiovascular risk factors in the A3921133 eligibility criteria could be applied to the *all tofacitinib cohorts*, as some information was not collected as per study protocols. None of the studies (including Study A3921133) were specifically designed to assess VTE or ATE risk. A number of potential mechanisms have been investigated to understand the increased rate of PE in Study A3921133, but the exact mechanism remains unclear. Further analyses have been initiated, including biomarker analyses of Study A3921133.[41]

A recently published randomised, open-label trial (ENTRACTE) evaluated the risk of MACE with the interleukin-6 inhibitor tocilizumab versus the TNFi etanercept in RA patients with an inadequate response to csDMARDs or TNFi therapy, and ≥1 cardiovascular risk factor.[43] Similar to Study A3921133, ENTRACTE's primary endpoints included MACE. The reported IR point estimates for DVT and PE with etanercept are consistent with those reported in the US Corrona RA registry among patients initiating bDMARDs aged ≥50 years and with ≥1 cardiovascular risk factor (0.30 and 0.27 for DVT and PE, respectively), and are higher than those observed with TNFi-treated patients in the ad hoc safety analysis data for Study A3921133 (figure 7).[1]

RA, PsO and PsA patients with a baseline VTE risk factor were also more likely to experience thromboembolic events than those without. Further analysis of the patients who experienced PE in Study A3921133 is required to understand why IRs of PE were higher with tofacitinib 10 mg twice daily versus TNFi, and if drug class affects VTE risk in patients with pre-existing risk factors. Additional analyses of the different criteria used to define cardiovascular and VTE risk factors could further refine those particular risk factors associated with thromboembolic events.

IRs of DVT, PE or ATE events from the tofacitinib development programmes were similar to age- and sex-standardised IRs from the US Corrona registries. IRs of DVT or PE events were also comparable to those previously reported for RA patients from the US Corrona registry (including tofacitinib-treated patients) in a postapproval safety study.[45] The IRs from the MarketScan cohort were consistent with previously reported values,[53] and no differences were observed between the tofacitinib and bDMARD cohorts. The events included in the search terms for ATE in the tofacitinib development programme comprised a broad list of PTs for SMQs (including myocardial infarction and stroke), whereas myocardial infarction and stroke events were reported separately for the MarketScan database. Although direct comparisons are limited between the tofacitinib

development programme and the MarketScan database, the IRs of myocardial infarction and stroke in the MarketScan database suggest that overall rates of ATE were comparable between the two populations.

As patients with serious concomitant conditions are often excluded from randomised controlled trials (RCTs), real-world evidence would be expected to have higher rates of events of interest. Although data from the US Corrona registries and MarketScan database are not directly comparable with data from RCTs, these observational data were from patients selected on criteria reflecting participants in the tofacitinib development programmes; as such, we consider these appropriate for clinical context.

A published analysis of spontaneous reports in the FAERS database revealed disproportionate reporting frequencies for DVT and PE events with tofacitinib and ruxolitinib, concluding that JAK inhibitors might carry an increased risk of pulmonary thromboembolism.[54] Our analysis of FAERS data did not support a signal of increased risk of VTE or ATE with tofacitinib, that is, there were no SDRs for events of interest, although differences exist between study designs, including our choice of a commonly cited SDR-defining threshold of $EB_{05} > 2$[47] that was higher than that used in the published analysis. The disproportionality analysis used here provides O/E reporting for hypothesis generation or refinement, not for estimating IRs.

This posthoc analysis was limited by using non-adjudicated data from RA, PsO and PsA tofacitinib development programmes (plus the included RCTs not specifically designed to assess VTE or ATE risk), which limits comparisons between the tofacitinib development programmes and observational data (also not typically adjudicated), as well as precluding analyses on event severity, and event-related hospitalisations and deaths. Additionally, determining causality for hospitalisation and deaths following thromboembolic events is challenging, with unknown additional factors potentially playing a role. While the *all tofacitinib cohort* was not designed to examine differences between tofacitinib dose, as patients could switch tofacitinib dose in the LTE studies, most patients who entered the RA LTE study (part of the *all tofacitinib cohort* in the present analysis) received tofacitinib 10 mg twice daily, and the IRs of PE were similar to those in the tofacitinib 5 mg twice daily group, when using either the average- or constant-dose algorithm.[55] An important limitation of the average tofacitinib dosing method is that a patient is assigned to the same category throughout their experience in the programme, and thus events may be attributed to a dose category different from the actual dose received at the time of the event. This approach narrows the differences between point estimates for both doses, and confounds the ability to evaluate differences between them. While the constant-dosing method addresses some limitations of average dosing, exposure and events captured after a dose switch are censored from the analysis. This results in a shorter overall tofacitinib exposure, and the risk of confounding by the reasons for discontinuation or dose change. There is also a potential for under-reporting of VTE events, particularly DVTs; a DVT is identified in ≤50% of PE cases, but DVT could go undetected depending on the type of diagnostic testing, or if a DVT embolises before testing.[56–58] Moreover, timely access to diagnostic testing may vary by region or country, and may contribute to under-reporting of events. Data from the US Corrona registries provide real-world observational data from a wide variety of geographical sites in the USA; however, as in any observational registry, there is a possibility of channelling bias that is unmeasured with potential underascertainment. Under-reporting of VTE in the tofacitinib development programmes and observational data sources is thus problematic, which could be affected by the identification of VTE as a risk with tofacitinib treatment.

In conclusion, this analysis revealed that the incidence of DVT, PE and ATE in the tofacitinib development programmes (tofacitinib exposure of ≤23 497 PY in RA, ≤8955 PY in PsO and ≤2038 PY in PsA) was consistent with observational data in the US Corrona registries and MarketScan databases that include RA, PsO and PsA patients treated with non-biologic and biologic treatments. IRs of VTE and ATE in the RA, PsO and PsA tofacitinib development programmes were generally higher in patients with cardiovascular or VTE risk factors than in patients without. IRs of PE and DVT observed in patients with a baseline cardiovascular risk factor in the RA programme were similar to the Study A3921133 safety analysis, but with no evidence of differences across tofacitinib doses, which may reflect differences in study design. Future research on DVT, PE and ATE in the tofacitinib development programmes will focus on determining whether there are potential mechanistic explanations for thromboembolism related to tofacitinib use and JAK inhibition. Updates to local labelling of JAK inhibitors, such as tofacitinib, identify VTE as an important risk, and the results of this analysis highlight the importance of tailoring individual treatment while considering the risk factors for thromboembolism.

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Data availability statement Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the USA and/or EU, or (2) in programmes that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data

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ONLINE SUPPLEMENTARY MATERIAL

INTRODUCTION

Study A3921133 inclusion criteria and enrolment

Inclusion criteria included patients aged ≥50 years with moderate to severe rheumatoid arthritis (RA) and with ≥1 cardiovascular risk factor (defined as current cigarette smoker, diagnosis of hypertension, high-density lipoprotein (HDL) <40mg/dL, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease (including a history of revascularisation procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina or acute coronary syndrome) or presence of extra-articular disease associated with RA [eg, nodules, Sjögren's syndrome, anaemia of chronic disease, pulmonary manifestations]).[1] Patients were also required to be taking methotrexate without adequate control of symptoms.[2] Exclusion criteria included current or recent infection, clinically significant laboratory abnormalities and pregnancy.[2]

Co-primary endpoints are adjudicated malignancy (excluding non-melanoma skin cancer [NMSC]) and adjudicated major adverse cardiovascular events (MACE); cumulative incidence and statistical assessments are blinded. The study is an event-powered study that requires ≥1500 patients to be followed for 3 years; with a MACE target of 103 cases and a malignancy target of 138 cases.

METHODS

Dose changes in long-term extension (LTE) studies

RA: Patients from the qualifying index studies initiated tofacitinib 5 or 10 mg BID in the LTE studies (ORAL Sequel [NCT00413699] and NCT00661661). Tofacitinib dose could be reduced from 10 to 5 mg BID for safety reasons or could be increased from 5 to 10 mg BID for reasons of inadequate response.

PsO: All patients received tofacitinib 10 mg BID for 3 months in the LTE study, OPT Extend (NCT01163253). After 3 months, investigators could adjust the dose at each study visit (every 3 months) to tofacitinib 5 or 10 mg BID, based on safety or efficacy.

PsA: Patients who had participated in OPAL Broaden (NCT01877668) or OPAL Beyond (NCT01882439) could receive tofacitinib 5 mg BID in the LTE study, OPAL Balance (NCT01976364). Tofacitinib dose could be increased to 10 mg BID at the investigator's discretion after 1 month and decreased from 10 to 5 mg BID for safety reasons at any time.

Tofacitinib development programmes

Preferred Terms (Standardised Medical Dictionary for Regulatory Activities [MedDRA] Query)

The following Preferred Terms from the Standardised MedDRA Query (SMQ) were used to identify DVT from the SMQ '*Embolic and thrombotic events, venous*', PE

from the SMQ '*Embolic and thrombotic events, venous*' and ATE from the SMQ '*Embolic and thrombotic events, arterial*' (all system organ classes):

- **DVT:** axillary vein thrombosis, brachiocephalic vein occlusion, brachiocephalic vein thrombosis, Budd-Chiari syndrome, deep vein thrombosis, deep vein thrombosis postoperative, hepatic vein occlusion, hepatic vein thrombosis, iliac vein occlusion, inferior vena caval occlusion, mesenteric vein thrombosis, mesenteric venous occlusion, Paget-Schroetter syndrome, pelvic venous thrombosis, portal vein occlusion, portal vein thrombosis, portosplenomesenteric venous thrombosis, renal vein occlusion, renal vein thrombosis, splenic vein occlusion, splenic vein thrombosis, subclavian vein occlusion, subclavian vein thrombosis, superior vena cava occlusion, vena cava thrombosis, venous thrombosis limb, visceral venous thrombosis.

- **PE:** embolism venous, postprocedural pulmonary embolism, pulmonary embolism, pulmonary infarction, pulmonary thrombosis.

- **ATE:** acute myocardial infarction, amaurosis, amaurosis fugax, aortic embolus, aortic thrombosis, arterial occlusive disease, arterial thrombosis, basal ganglia infarction, basilar artery occlusion, basilar artery thrombosis, blindness transient, brachiocephalic artery occlusion, capsular warning syndrome, carotid arterial embolus, carotid artery occlusion, carotid artery thrombosis, cerebellar artery occlusion, cerebellar artery thrombosis, cerebral artery embolism, cerebral artery occlusion, cerebral artery thrombosis, cerebral hypoperfusion, cerebrovascular stenosis, coeliac artery occlusion, coronary

artery embolism, coronary artery occlusion, coronary artery thrombosis, embolism arterial, femoral artery embolism, hepatic artery embolism, hepatic artery occlusion, hepatic artery thrombosis, iliac artery embolism, iliac artery occlusion, ischaemic cerebral infarction, ischaemic stroke, lacunar infarction, Leriche syndrome, mesenteric arterial occlusion, mesenteric artery embolism, mesenteric artery stenosis, mesenteric artery thrombosis, myocardial infarction, myocardial necrosis, papillary muscle infarction, penile artery occlusion, peripheral arterial occlusive disease, peripheral artery occlusion, peripheral artery thrombosis, peripheral embolism, post procedural myocardial infarction, postinfarction angina, precerebral artery occlusion, precerebral artery thrombosis, pulmonary artery occlusion, pulmonary artery thrombosis, renal artery occlusion, renal artery thrombosis, renal embolism, retinal artery embolism, retinal artery occlusion, retinal artery thrombosis, silent myocardial infarction, spinal artery embolism, spinal artery thrombosis, splenic artery thrombosis, splenic embolism, subclavian artery embolism, subclavian artery occlusion, subclavian artery thrombosis, transient ischaemic attack, truncus coeliacus thrombosis, vertebral artery occlusion, vertebral artery thrombosis.

Preferred Terms included in the SMQ *Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous* (not included in the SMQs *Embolic and thrombotic events, arterial* and *Embolic and thrombotic events, venous*):

- Adrenal thrombosis, atrial thrombosis, brain stem embolism, cardiac ventricular thrombosis, cerebellar embolism, cerebral microembolism, cerebral

thrombosis, cerebral vascular occlusion, embolic stroke, intracardiac thrombus, thrombotic cerebral infarction, thrombotic stroke.

Observational data sources

US Corrona registries

Two patient populations were considered for the RA, PsO and PsA Corrona registries. The 'All registry' population included all patients enrolled in the Corrona registries irrespective of when they started a biologic or non-biologic therapy (excluding patients enrolled in the registry already taking tofacitinib); these patients may have been receiving biologic or non-biologic therapy at the time of enrolment, or they may have started biologic or non-biologic therapy at the time of enrolment. The 'Drug initiators' population included all patients in the Corrona registries who initiated a specific (non-tofacitinib) drug upon, or after, enrolment into the registry (excluding patients already on a drug at the time of enrolment who did not initiate a new therapy whilst in the registry). For conventional synthetic DMARDs, initiation was considered as the first drug initiation captured only if the patient was biologic DMARD (bDMARD)-naïve at the time of initiation. For bDMARD, initiation was considered as first drug initiation captured only if the patient was naïve to tofacitinib; patients could have been bDMARD-naïve or experienced at the time of initiation.

Data were included from the start of data collection for each indication to 31 December 2017. Thromboembolic events were VTE, defined as DVT or PE and ATE (defined as ≥1 of peripheral ATE event, urgent peripheral arterial revascularisation, myocardial infarction, transient ischaemic attack and stroke).

In a sub-analysis of data from the RA Corrona registry to investigate VTE risk, the patient populations were:

- Patients with active moderate to severe RA who were initiating a bDMARD (tofacitinib-naïve; could have previously received a different bDMARD), with moderate to severe disease activity (Clinical Disease Activity Index [CDAI] >10 at initiation)
- A subpopulation of these patients that were aged ≥50 years and with ≥1 cardiovascular risk factor
- Patients with moderate to severe RA (CDAI >10 at initiation) who were initiating tofacitinib for the first time
- A subpopulation of these patients that were aged ≥50 years and with ≥1 cardiovascular risk factor

Cardiovascular risk factors were defined as: RA patients that were aged ≥50 years and with ≥1 of the following cardiovascular risk factors: current smoker, diagnosis of hypertension, diagnosis of diabetes mellitus, history of coronary artery disease (eg, cardiac arrest, heart attack, unstable angina, revascularisation procedures), family history of premature coronary heart disease or current extra-articular RA disease.

Data for patients initiating a bDMARD were from the onset of targeted collection of pulmonary embolism outcomes (March 2012) to 31 July 2019; data for tofacitinib initiators were included from the approval of tofacitinib (November 2012) to 31 July 2018.

IBM® MarketScan® research database

Patients were included in the analysis if they were aged ≥18 years and initiated a non-biologic or biologic treatment (or tofacitinib for RA only) for treatment of the relevant indication between 1 January 2010 and 31 December 2017 (online supplementary table S2).

Outpatient and hospitalised DVT and ATE, and hospitalised PE events, included in the analysis were those with relevant diagnosis codes and where treatment was prescribed within 60 days of the DVT, PE or ATE diagnosis, or if the patient died in hospital. Myocardial infarction and stroke were assessed separately from ATE.

Cohorts were defined using exclusion criteria reflecting those in the tofacitinib clinical programme for each disease:

Rheumatoid arthritis:

- History of any other rheumatic autoimmune disease, other than Sjögren's syndrome (psoriatic arthritis, reactive arthritis, systemic lupus erythematosus, systemic sclerosis [scleroderma], idiopathic inflammatory myositis, systemic vasculitides [giant cell arteritis, polyarteritis nodosa, granulomatosis with polyangitis, eosinophilic granulomatosis with polyangitis, microscopic polyangitis, polymyalgia rheumatica]).

- History of any lymphoproliferative disorder, such as Epstein-Barr virus (EBV)-related lymphoproliferative disorder; history of lymphoma or leukaemia (included under previous malignancy).

- Current or previous malignancy, except for non-melanoma skin cancer (NMSC) or cervical carcinoma *in situ*.
- Infection with human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus.
- Pregnancy during baseline period.

Psoriasis:

- Solid organ or autologous bone marrow transplantation.
- Infection with HIV (HIV Disease Registry).
- Advanced kidney disease (defined as ICD-9 disease code corresponding to moderate or severe chronic kidney disease [chronic kidney disease, Stage III (moderate), chronic kidney disease, Stage IV (severe), chronic kidney disease, Stage V, end-stage renal disease]).
- Advanced liver disease (defined as history of ascites, hepatic encephalopathy or oesophageal varices).
- Cancer diagnoses (excluding NMSC).
- Pregnancy during baseline period.

The above exclusion criteria were also considered as censoring criteria (except for pregnancy during follow-up period instead of during baseline period), in addition to other exposure censoring criteria.

Psoriatic arthritis:

- Solid organ or bone marrow transplantation; infection with HIV, hepatitis B virus or hepatitis C virus.
- Advanced kidney disease.
- Advanced liver disease (defined as history of ascites, hepatic encephalopathy or oesophageal varices).
- Any malignancy other than NMSC.
- Prior diagnosis of rheumatic disease other than psoriatic arthritis (systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis, dermatomyositis, fibromyalgia, gout, reactive arthritis, chronic Lyme disease,non-specific inflammatory connective tissue).
- Prior history of any lymphoproliferative disorder, such as EBV-related lymphoproliferative disorder, history of lymphoma or leukaemia.
- Prior history of diverticulitis.
- Average daily prednisone >10 mg/day within 6 months prior to the index date.
- Intra-articular joint injection (eg, glucocorticoids) within 28 days prior to the index date.
- Baseline UVA/UVB treatment.
- Hospitalised infection within 6 months prior to the index date.

- Zoster vaccination within 6 weeks prior to the index date, and antimicrobial therapy within 2 weeks of index date.
- Pregnancy during 12-month baseline period.

The following exclusion criteria were also considered as censoring criteria:

- Solid organ or bone marrow transplantation; infection with HIV, hepatitis B virus or hepatitis C virus.
- Advanced kidney disease.
- Advanced liver disease (defined as history of ascites, hepatic encephalopathy or oesophageal varices).
- Any malignancy other than NMSC.
- Prior history of rheumatic disease other than psoriatic arthritis (systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis, dermatomyositis, fibromyalgia, gout, reactive arthritis, chronic Lyme disease, non-specific inflammatory connective tissue).
- Diagnosis of any lymphoproliferative disorder, such as EBV-related lymphoproliferative disorder, history of lymphoma or leukaemia.
- Pregnancy during follow-up period.

Table S1 RCTs, LTE studies and treatments included in each analysis cohort of RA, PsO or PsA patients in the tofacitinib development programme

		Placebo-controlled cohort	Dose-comparison and active-control cohort	All tofacitinib cohort
RA	**RCTs**	**Phase 2** DMARD-InR patients: NCT00147498[a];[3] NCT00687193[a];[4] NCT00550446[a][5] MTX-InR patients: NCT00413660[b];[6] NCT00603512[b];[7] NCT00976599[b][8] MTX-naïve patients: NCT01164579[a,b][9] Prior treatment not specified: NCT01359150[a,b];[10] NCT02147587[b][11] **Phase 3** MTX-InR patients: ORAL Scan (NCT00847613)[b];[12] ORAL Standard (NCT00853385)[b][13]	**Phase 2** DMARD-InR patients: NCT00147498[a];[3] NCT00687193[a];[4] NCT00550446[a][5] MTX-InR patients: NCT00413660[b];[6] NCT00603512[b];[7] NCT00976599[b][8] MTX-naïve patients: NCT01164579[a,b][9] Prior treatment not specified: NCT01359150[a,b];[10] NCT02147587[b][11] **Phase 3** MTX-InR patients: ORAL Scan (NCT00847613)[b];[12] ORAL Standard (NCT00853385)[b][13]	**Phase 1** NCT01262118[19] DMARD-InR patients: NCT01484561[c] (background DMARDs permitted, not required)[20] **Phase 2** DMARD-InR patients: NCT00147498[a];[3] NCT00687193[a];[4] NCT00550446[a][5] MTX-InR patients: NCT00413660[b];[6] NCT00603512[b];[7] NCT00976599[b][8] MTX-naïve patients: NCT01164579[a,b][9] Prior treatment not specified: NCT01359150[a,b;][10] NCT02147587[b;][11] NCT01059864[a][21]

DMARD-InR patients: ORAL Solo (NCT00814307)[a];[14] ORAL Sync (NCT00856544)[c][15] TNFi-InR patients: ORAL Step (NCT00960440)[b][16] MTX-naïve: ORAL Start (NCT01039688)[a][17] **Phase 3b/4** MTX-InR patients: ORAL Strategy (NCT02187055)[a,b][18]	DMARD-InR patients: ORAL Solo (NCT00814307)[a];[14] ORAL Sync (NCT00856544)[c][15] TNFi-InR patients: ORAL Step (NCT00960440)[b][16] MTX-naïve: ORAL Start (NCT01039688)[a][17] **Phase 3b/4** MTX-InR patients: ORAL Strategy (NCT02187055)[a,b][18]	**Phase 3** MTX-InR patients: ORAL Scan (NCT00847613)[b];[12] ORAL Standard (NCT00853385)[b][13] DMARD-InR patients: ORAL Solo (NCT00814307)[a];[14] ORAL Sync (NCT00856544)[c][15] TNFi-InR patients: ORAL Step (NCT00960440)[b][16] MTX-naïve: ORAL Start (NCT01039688)[a][17] MTX-InR patients: NCT02281552[b][22] **Phase 3b/4** MTX-InR patients: ORAL Strategy (NCT02187055)[a,b][18] MTX-InR patients: NCT02831855[b][23] **LTE** ORAL Sequel (NCT00413699);[24] NCT00661661[24]

	Treatment[d]	Patients randomised to tofacitinib 5 or 10 mg BID, or placebo up to month 3 Patients randomised to adalimumab 40 mg SC Q2W (active control in NCT00550446 and ORAL Standard; active comparator in ORAL Strategy) or MTX up to 20 mg QW (active control; NCT01164579 and ORAL Start only) up to month 3 (not included in analysis)	Patients randomised to tofacitinib 5 or 10 mg BID, adalimumab 40 mg SC Q2W (active control in NCT00550446 and ORAL Standard; active comparator in ORAL Strategy) or MTX up to 20 mg QW (NCT01164579 and ORAL Start only) up to 24 months	Patients who received ≥1 dose of tofacitinib
PsO	**RCTs**	**Phase 2** NCT00678210[a][25] **Phase 3** OPT Pivotal 1 (NCT01276639)[a];[26] OPT Pivotal 2 (NCT01309737)[a];[26] OPT Compare (NCT01241591)[a][27]	**Phase 3** OPT Pivotal 1 (NCT01276639)[a];[26] OPT Pivotal 2 (NCT01309737)[a];[26] OPT Re-treatment (NCT01186744)[a,e][28]	**Phase 2** NCT00678210[a][25] NCT01710046[29] **Phase 3** OPT Pivotal 1 (NCT01276639)[a];[26] OPT Pivotal 2 (NCT01309737)[a];[26] OPT Compare (NCT01241591)[a];[27] OPT Re-treatment (NCT01186744)[a][28] **LTE** OPT Extend (NCT01163253)[30,31]
	Treatment[d]	Patients randomised to tofacitinib 5 or 10 mg BID, or placebo up to month 3	Patients who received tofacitinib 5 or 10 mg BID (including those who advanced from placebo) up to 12 months	Patients who received ≥1 dose of tofacitinib

		Patients randomised to etanercept 50 mg BIW (OPT Compare only)		
PsA	**RCTs**	**Phase 3** csDMARD-InR patients: OPAL Broaden (NCT01877668)[c][32] TNFi-InR patients: OPAL Beyond (NCT01882439)[c][33]	**Phase 3** csDMARD-InR patients: OPAL Broaden (NCT01877668)[c][32] TNFi-InR patients: OPAL Beyond (NCT01882439)[c][33]	**Phase 3** csDMARD-InR patients: OPAL Broaden (NCT01877668)[c][32] TNFi-InR patients: OPAL Beyond (NCT01882439)[c][33] **LTE** OPAL Balance (NCT01976364)
	Treatment[d]	Patients randomised to tofacitinib 5 or 10 mg BID, or placebo up to month 3 Patients randomised to adalimumab 40 mg SC Q2W (active control; OPAL Broaden only) (not included in analysis)	Patients who received tofacitinib 5 or 10 mg BID (including those who advanced from placebo) or adalimumab 40 mg SC Q2W (active control; OPAL Broaden only) up to 12 months	Patients who received ≥1 dose of tofacitinib

[a]Monotherapy.

[b]Combination therapy with MTX.

[c]Combination therapy with csDMARD (mainly MTX).

[d]Only treatment doses included in this analysis are listed; patients may have received other doses in some studies.

[e]Study design included switches from active treatment to placebo and back to active treatment.

BID, twice daily; BIW, twice weekly; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; InR, inadequate response; LTE, long-term extension; MTX, methotrexate; PsA, psoriatic arthritis; PsO, psoriasis; QW, once a week; Q2W, once every 2 weeks; RA, rheumatoid arthritis; RCT, randomised controlled trial; SC, subcutaneous; TNFi, tumour necrosis factor inhibitor.

Table S2 Tofacitinib treatment comparators used in the US Corrona registries and MarketScan research database

	RA	PsO	PsA
US Corrona registry			
Non-biologic treatments	Hydroxychloroquine, leflunomide, MTX, sulfasalazine	Apremilast, cyclosporine, MTX, acitretin, hydroxyurea, mycophenolate mofetil, sulfasalazine, 6-thioguanine	Hydroxychloroquine, leflunomide, MTX, sulfasalazine, apremilast
Biologic treatments	Abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab	Alefacept, brodalumab, efalizumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, secukinumab, ustekinumab	Adalimumab, certolizumab pegol, etanercept, infliximab, secukinumab, ustekinumab
MarketScan research database			
Non-biologic treatments	MTX, leflunomide, sulfasalazine, hydroxychloroquine	MTX, leflunomide, cyclosporine, apremilast	MTX, leflunomide, sulfasalazine, apremilast
Biologic treatments	Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, tocilizumab	Etanercept, adalimumab, infliximab, certolizumab pegol, ustekinumab, secukinumab	Adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, ustekinumab, secukinumab

MTX, methotrexate; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis.

Table S3 Patient demographics and baseline characteristics for all tofacitinib-treated patients (*all tofacitinib cohort*), stratified by defined baseline cardiovascular[a] or VTE [b] risk factors in the RA development programme

	With baseline cardiovascular risk (N=3126)		**Without baseline cardiovascular risk (N=4838)**		**With baseline VTE risk (N=5257)**		**Without baseline VTE risk (N=2707)**	
	Average tofacitinib 5 mg BID (N=1614)	Average tofacitinib 10 mg BID (N=1512)	Average tofacitinib 5 mg BID (N=2355)	Average tofacitinib 10 mg BID (N=2483)	Average tofacitinib 5 mg BID (N=2633)	Average tofacitinib 10 mg BID (N=2624)	Average tofacitinib 5 mg BID (N=1336)	Average tofacitinib 10 mg BID (N=1371)
Age (years), mean (SD)	61.2 (7.4)	59.7 (6.9)	47.9 (12.2)	47.2 (11.4)	56.6 (12.2)	55.1 (11.4)	46.7 (9.8)	45.9 (9.6)
≥65 years of age, n (%)	497 (30.8)	376 (24.9)	225 (9.6)	172 (6.9)	722 (27.4)	548 (20.9)	0	0
≥50 years of age, n (%)	1614 (100)	1512 (100)	992 (42.1)	969 (39.0)	1944 (73.8)	1868 (71.2)	662 (49.6)	613 (44.7)
Female, n (%)	1227 (76.0)	1178 (77.9)	2009 (85.3)	2108 (84.9)	2085 (79.2)	2107 (80.3)	1151 (86.2)	1179 (86.0)
Race, n (%)								

White	1103 (68.3)	1176 (77.8)	1314 (55.8)	1577 (63.5)	1816 (69.0)	2046 (78.0)	601 (45.0)	707 (51.6)
Black	64 (4.0)	59 (3.9)	57 (2.4)	72 (2.9)	102 (3.9)	105 (4.0)	19 (1.4)	26 (1.9)
Asian	370 (22.9)	166 (11.0)	756 (32.1)	520 (20.9)	550 (20.9)	241 (9.2)	576 (43.1)	445 (32.5)
Other	77 (4.8)	111 (7.3)	228 (9.7)	314 (12.6)	165 (6.3)	232 (8.8)	140 (10.5)	193 (14.1)
BMI (kg/m^2), mean (SD)	28.1 (6.2)	29.0 (6.5)	25.8 (6.1)	26.6 (6.3)	28.3 (6.7)	29.4 (6.9)	23.6 (3.4)	23.8 (3.4)
[N1]	[1609]	[1511]	[2352]	[2482]	[2625]	[2623]	[1336]	[1370]
BMI ≥30 kg/m^2, n (%)	524 (32.6)	584 (38.6)	458 (19.5)	572 (23.0)	982 (37.4)	1156 (44.1)	0 [1336]	0 [1370]
[N1]	[1609]	[1511]	[2482]	[2482]	[2625]	[2623]		
Smoking status, n (%)								
Never smoked	839 (52.0)	735 (48.6)	1683 (71.5)	1739 (70.0)	1407 (53.4)	1307 (49.8)	1115 (83.5)	1167 (85.1)
Smoker	420 (26.0)	423 (28.0)	228 (9.7)	295 (11.9)	648 (24.6)	718 (27.4)	0	0
Ex-smoker	327 (20.3)	326 (21.6)	362 (15.4)	373 (15.0)	511 (19.4)	530 (20.2)	178 (13.3)	169 (12.3)
Unknown	28 (1.7)	28 (1.9)	82 (3.5)	76 (3.1)	67 (2.5)	69 (2.6)	43 (3.2)	35 (2.6)

Comorbidities, n (%)								
Diabetes	304 (18.8)	236 (15.6)	61 (2.6)	50 (2.0)	303 (11.5)	237 (9.0)	62 (4.6)	49 (3.6)
Hypertension	1187 (73.5)	1146 (75.8)	218 (9.3)	267 (10.8)	1148 (43.6)	1173 (44.7)	257 (19.2)	240 (17.5)
Coronary heart disease	13 (0.8)	17 (1.1)	0	0	12 (0.5)	17 (0.6)	1 (0.1)	0
Myocardial infarction	50 (3.1)	45 (3.0)	0	5 (0.2)	49 (1.9)	46 (1.8)	1 (0.1)	4 (0.3)
History of hyperlipidemia, n (%)	504 (31.2)	495 (32.7)	236 (10.0)	299 (12.0)	633 (24.0)	663 (25.3)	107 (8.0)	131 (9.6)
Previous heart failure, n (%)	24 (1.5)	12 (0.8)	4 (0.2)	2 (0.1)	28 (1.1)	14 (0.5)	0	0
Previous VTE (DVT or PE), n (%)	29 (1.8)	27 (1.8)	11 (0.5)	21 (0.8)	40 (1.5)	48 (1.8)	0	0
CRP ≥3.0 mg/L, n (%)	1274 (79.3)	1224 (81.7)	1855 (79.7)	1931 (78.6)	2095 (80.2)	2113 (81.3)	1034 (78.2)	1042 (76.8)
[N1]	[1607]	[1499]	[2328]	[2457]	[2612]	[2599]	[1323]	[1357]
Concomitant medication, n (%)								
Steroids	788 (48.8)	810 (53.6)	1282 (54.4)	1374 (55.3)	1331 (50.6)	1406 (53.6)	739 (55.3)	778 (56.7)
Anticoagulants	249 (15.4)	255 (16.9)	67 (2.8)	89 (3.6)	307 (11.7)	339 (12.9)	9 (<1.0)	5 (<1.0)
Antiplatelet agents	224 (13.9)	248 (16.4)	56 (2.4)	91 (3.7)	276 (10.5)	335 (12.8)	4 (<1.0)	4 (<1.0)
OCT or HRT[c]	35 (2.2)	56 (3.7)	312 (13.2)	278 (11.2)	347 (13.2)	334 (12.7)	0	0
Antidepressants[c]	150 (9.3)	174 (11.5)	128 (5.4)	193 (7.8)	278 (10.6)	367 (14.0)	0	0
Statins[c]	139 (8.6)	309 (20.4)	43 (1.8)	129 (5.2)	164 (6.2)	383 (14.6)	18 (1.3)	55 (4.0)

Aspirin	200 (12.4)	224 (14.8)	46 (2.0)	81 (3.3)	246 (9.3)	305 (11.6)	0	0
Prior MTX use, n (%)	1490 (92.3)	1168 (77.2)	2120 (90.0)	1879 (75.7)	2427 (92.2)	2019 (76.9)	1183 (88.5)	1028 (75.0)
Prior csDMARD use (other than MTX), n (%)	661 (41.0)	775 (51.3)	994 (42.2)	1309 (52.7)	1013 (38.5)	1307 (49.8)	642 (48.1)	777 (56.7)
Prior TNFi use, n (%)	207 (12.8)	328 (21.7)	256 (10.9)	454 (18.3)	344 (13.1)	605 (23.1)	119 (8.9)	177 (12.9)
Prior non-TNFi bDMARD use, n (%)	70 (4.3)	100 (6.6)	107 (4.5)	137 (5.5)	133 (5.1)	182 (6.9)	44 (3.3)	55 (4.0)

[a]Baseline cardiovascular risk factors were defined as a patient aged ≥50 years AND meeting one of the following criteria at baseline: current smoker, HDL<40 mg/dL, history of hypertension diagnosis, history of diabetes diagnosis, history of myocardial infarction or history of coronary heart disease diagnosis.

[b]Baseline VTE risk factors were defined as any patient meeting any of the following criteria at baseline: aged ≥60 years, current smoker, previous heart failure, previous VTE (DVT or PE), BMI ≥30 kg/m^2, Day 1 use of oral contraceptives or hormone replacement therapy, Day 1 antidepressant use or Day 1 aspirin use.

[c]Day 1 use.

bDMARD, biologic disease-modifying antirheumatic drug; BID, twice daily; BMI, body mass index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DVT, deep vein thrombosis; HDL, high-density lipoprotein; HRT, hormone replacement therapy; MTX, methotrexate; N, total number of patients; n, patient with characteristic; N1, total number of patients assessed in a specific category; OCT, oral contraceptives; PE, pulmonary embolism; RA, rheumatoid arthritis; SD, standard deviation; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism.

Table S4 Patient demographics and baseline characteristics for all tofacitinib-treated patients (*all tofacitinib cohort*), stratified by defined baseline cardiovascular[a] or VTE [b] risk factors in the PsO development programme

	With baseline cardiovascular risk (N=1022)		**Without baseline cardiovascular risk (N=2641)**		**With baseline VTE risk (N=2744)**		**Without baseline VTE risk (N=919)**	
	Average tofacitinib 5 mg BID (N=286)	Average tofacitinib 10 mg BID (N=736)	Average tofacitinib 5 mg BID (N=634)	Average tofacitinib 10 mg BID (N=2007)	Average tofacitinib 5 mg BID (N=715)	Average tofacitinib 10 mg BID (N=2029)	Average tofacitinib 5 mg BID (N=205)	Average tofacitinib 10 mg BID (N=714)
Age (years), mean (SD)	58.0 (6.6)	58.1 (6.3)	39.9 (11.5)	39.6 (10.7)	46.6 (13.6)	45.6 (13.1)	41.8 (11.1)	41.5 (11.2)
≥65 years of age, n (%)	53 (18.5)	113 (15.4)	18 (2.8)	36 (1.8)	71 (9.9)	149 (7.3)	0	0
≥50 years of age, n (%)	286 (100)	736 (100)	100 (15.8)	279 (13.9)	326 (45.6)	802 (39.5)	60 (29.3)	213 (29.8)
Female, n (%)	105 (36.7)	209 (28.4)	218 (34.4)	585 (29.1)	267 (37.3)	663 (32.7)	56 (27.3)	131 (18.3)
Race, n (%)								
White	252 (88.1)	625 (84.9)	542 (85.5)	1716 (85.5)	628 (87.8)	1767 (87.1)	166 (81.0)	574 (80.4)
Black	10 (3.5)	18 (2.4)	17 (2.7)	33 (1.6)	19 (2.7)	43 (2.1)	8 (3.9)	8 (1.1)
Asian	13 (4.5)	47 (6.4)	29 (4.6)	160 (8.0)	28 (3.9)	125 (6.2)	14 (6.8)	82 (11.5)

Other	11 (3.8)	46 (6.3)	46 (7.3)	98 (4.9)	40 (5.6)	94 (4.6)	17 (8.3)	50 (7.0)
BMI (kg/m^2), mean (SD)	30.7 (5.7)	31.2 (6.4)	29.3 (6.7)	29.4 (6.9)	30.8 (6.8)	31.4 (7.2)	25.9 (2.8)	25.8 (2.9)
[N1]	[285]	[735]	[615]	[2005]	[715]	[2028]	[204]	[712]
BMI ≥30 kg/m^2, n (%)	146 (51.2)	388 (52.8)	238 (37.5)	772 (38.5)	384 (53.7)	1160 (57.2)	0 [204]	0 [712]
[N1]	[285]	[735]	[634]	[2005]	[715]	[2028]		
Smoking status, n (%)								
Never smoked	81 (28.3)	206 (28.0)	272 (42.9)	853 (42.5)	209 (29.2)	592 (29.2)	144 (70.2)	467 (65.4)
Smoker	124 (43.4)	293 (39.8)	241 (38.0)	722 (36.0)	365 (51.0)	1015 (50.0)	0	0
Ex-smoker	81 (28.3)	237 (32.2)	121 (19.1)	432 (21.5)	141 (19.7)	422 (20.8)	61 (29.8)	247 (34.6)
Comorbidities, n (%)								
Diabetes	93 (32.5)	235 (31.9)	35 (5.5)	136 (6.8)	114 (15.9)	328 (16.2)	14 (6.8)	43 (6.0)
Hypertension	155 (54.2)	399 (54.2)	64 (10.1)	196 (9.8)	190 (26.6)	516 (25.4)	29 (14.1)	79 (11.1)
Coronary heart disease	21 (7.3)	46 (6.3)	3 (0.5)	20 (1.0)	22 (3.1)	61 (3.0)	2 (1.0)	5 (0.7)
Myocardial infarction	8 (2.8)	18 (2.4)	0	6 (0.3)	7 (1.0)	23 (1.1)	1 (0.5)	1 (0.1)
History of hyperlipidemia, n (%)	121 (42.3)	315 (42.8)	99 (15.6)	326 (16.2)	183 (25.6)	531 (26.2)	37 (18.0)	110 (15.4)
Previous heart failure, n (%)	0	2 (0.3)	0	5 (0.2)	0	7 (0.3)	0	0
Previous VTE (DVT or PE) , n (%)	1 (0.3)	3 (0.4)	1 (0.2)	6 (0.3)	2 (0.3)	9 (0.4)	0	0

CRP >2.87 mg/L, n (%)	146 (57.7)	361 (58.2)	232 (42.1)	758 (45.2)	319 (51.3)	896 (52.3)	59 (32.4)	223 (38.3)
[N1]	[253]	[620]	[551]	[1677]	[622]	[1714]	[182]	[583]
Concomitant medication, n (%)								
Anticoagulants[c]	59 (20.6)	127 (17.3)	16 (2.5)	61 (3.0)	75 (10.5)	187 (9.2)	0	1 (0.1)
Antiplatelet agents[c]	58 (20.3)	125 (17.0)	20 (3.2)	69 (3.4)	77 (10.8)	191 (9.4)	1 (0.5)	3 (0.4)
OCT or HRT[c]	10 (3.5)	8 (1.1)	65 (10.3)	178 (8.9)	75 (10.5)	186 (9.2)	0	0
Antidepressants[c]	23 (8.0)	51 (6.9)	31 (4.9)	81 (4.0)	54 (7.6)	132 (6.5)	0	0
Statins[c]	80 (28.0)	222 (30.2)	47 (7.4)	138 (6.9)	110 (15.4)	308 (15.2)	17 (8.3)	52 (7.3)
Aspirin[c]	55 (19.2)	117 (15.9)	15 (2.4)	55 (2.7)	70 (9.8)	172 (8.5)	0	0
Prior MTX use, n (%)	82 (28.7)	258 (35.1)	194 (30.6)	623 (31.0)	217 (30.3)	657 (32.4)	59 (28.8)	224 (31.4)
Prior csDMARD use (other than MTX), n (%)	25 (8.7)	85 (11.5)	58 (9.1)	222 (11.1)	60 (8.4)	225 (11.1)	23 (11.2)	82 (11.5)
Prior TNFi use, n (%)	45 (15.7)	143 (19.4)	95 (15.0)	297 (14.8)	112 (15.7)	341 (16.8)	28 (13.7)	99 (13.9)
Prior non-TNFi bDMARD use, n (%)	18 (6.3)	64 (8.7)	35 (5.5)	97 (4.8)	43 (6.0)	123 (6.1)	10 (4.9)	38 (5.3)

[a]Baseline cardiovascular risk factors were defined as a patient aged ≥50 years AND meeting one of the following criteria at baseline: current smoker, HDL<40 mg/dL, history of hypertension diagnosis, history of diabetes diagnosis, history of myocardial infarction, or history of coronary heart disease diagnosis.

[b]Baseline VTE risk factors were defined as any patient meeting any of the following criteria at baseline: aged ≥60 years, current smoker, previous heart failure, previous VTE (DVT or PE), BMI ≥30 kg/m^2, Day 1 use of oral contraceptives or hormone replacement therapy, Day 1 antidepressant use or Day 1 aspirin use.

[c]Day 1 use.

bDMARD, biologic disease-modifying antirheumatic drug; BID, twice daily; BMI, body mass index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DVT, deep vein thrombosis; HDL, high-density lipoprotein; HRT, hormone replacement therapy; MTX, methotrexate; N, total number of patients; n, patient with characteristic; N1, total number of patients assessed in a specific category; OCT, oral contraceptives; PE, pulmonary embolism; PsO, psoriasis; SD, standard deviation; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism.

Table S5 Patient demographics and baseline characteristics for all tofacitinib-treated patients (*all tofacitinib cohort*), stratified by defined baseline cardiovascular[a] or VTE[b] risk factors in the PsA development programme

	With baseline cardiovascular risk (N=288)		**Without baseline cardiovascular risk (N=495)**		**With baseline VTE risk (N=555)**		**Without baseline VTE risk (N=228)**	
	Average tofacitinib 5 mg BID (N=180)	Average tofacitinib 10 mg BID (N=108)	Average tofacitinib 5 mg BID (N=278)	Average tofacitinib 10 mg BID (N=217)	Average tofacitinib 5 mg BID (N=328)	Average tofacitinib 10 mg BID (N=227)	Average tofacitinib 5 mg BID (N=130)	Average tofacitinib 10 mg BID (N=98)
Age (years), mean (SD)	59.3 (6.2)	58.9 (6.0)	42.6 (9.9)	42.6 (10.8)	51.1 (11.9)	49.9 (12.4)	44.2 (10.2)	43.7 (10.5)
≥65 years of age, n (%)	36 (20.0)	24 (22.2)	6 (2.2)	6 (2.8)	42 (12.8)	30 (13.2)	0	0
≥50 years of age, n (%)	180 (100)	108 (100)	58 (20.9)	52 (24.0)	191 (58.2)	124 (54.6)	47 (36.2)	36 (36.7)
Female, n (%)	101 (56.1)	55 (50.9)	157 (56.5)	115 (53.0)	198 (60.4)	132 (58.1)	60 (46.2)	38 (38.8)
Race, n (%)								
White	177 (98.3)	103 (95.4)	257 (92.4)	202 (93.1)	316 (96.3)	215 (94.7)	118 (90.8)	90 (91.8)
Black	0	1 (0.9)	0	2 (0.9)	0	2 (0.9)	0	1 (1.0)

Asian	1 (0.6)	1 (0.9)	10 (3.6)	11 (5.1)	6 (1.8)	6 (2.6)	5 (3.8)	6 (6.1)
Other	2 (1.1)	3 (2.8)	11 (4.0)	2 (0.9)	6 (1.8)	4 (1.8)	7 (5.4)	1 (1.0)
BMI (kg/m^2), mean (SD)	31.2 (6.0)	31.2 (6.0)	28.5 (5.6)	29.1 (6.2)	31.0 (6.2)	31.5 (6.4)	25.8 (3.0)	25.7 (2.9)
BMI ≥30 kg/m^2, n (%)	97 (53.9)	53 (49.1)	99 (35.6)	84 (38.7)	196 (59.8)	137 (60.4)	0	0
Smoking status, n (%)								
Never smoked	102 (56.7)	58 (53.7)	187 (67.3)	138 (63.6)	174 (53.0)	121 (53.3)	115 (88.5)	75 (76.5)
Smoker	38 (21.1)	21 (19.4)	54 (19.4)	27 (12.4)	92 (28.0)	48 (21.1)	0	0
Ex-smoker	40 (22.2)	29 (26.9)	37 (13.3)	52 (24.0)	62 (18.9)	58 (25.6)	15 (11.5)	23 (23.5)
Unknown	0	0	0	0	0	0	0	0
Comorbidities, n (%)								
Diabetes	46 (25.6)	28 (25.9)	15 (5.4)	18 (8.3)	52 (15.9)	43 (18.9)	9 (6.9)	3 (3.1)
Hypertension	137 (76.1)	85 (78.7)	43 (15.5)	34 (15.7)	147 (44.8)	97 (42.7)	33 (25.4)	22 (22.4)
Coronary heart disease	18 (10.0)	13 (12.0)	5 (1.8)	3 (1.4)	20 (6.1)	14 (6.2)	3 (2.3)	2 (2.0)
Myocardial infarction	4 (2.2)	7 (6.5)	2 (0.7)	2 (0.9)	6 (1.8)	8 (3.5)	0	1 (1.0)
History of hyperlipidemia, n (%)	64 (35.6)	42 (38.9)	30 (10.8)	31 (14.3)	77 (23.5)	59 (26.0)	17 (13.1)	14 (14.3)
Previous heart failure, n (%)	0	3 (2.8)	0	0	0	3 (1.3)	0	0
Previous VTE (DVT or PE), n (%)	3 (1.7)	3 (2.8)	0	4 (1.8)	3 (0.9)	7 (3.1)	0	0

CRP >2.87 mg/L, n (%)	114 (63.3)	65 (60.2)	174 (62.6)	133 (61.3)	210 (64.0)	136 (59.9)	78 (60.0)	62 (63.3)
Concomitant medication, n (%)								
Steroids	46 (25.6)	22 (20.4)	63 (22.7)	40 (18.4)	75 (22.9)	41 (18.1)	34 (26.2)	21 (21.4)
Anticoagulants[c]	31 (17.2)	26 (24.1)	3 (1.1)	8 (3.7)	34 (10.4)	31 (13.7)	0	3 (3.1)
Antiplatelet agents[c]	27 (15.0)	19 (17.6)	4 (1.4)	4 (1.8)	31 (9.5)	23 (10.1)	0	0
OCT or HRT[c]	4 (2.2)	5 (4.6)	36 (12.9)	32 (14.7)	40 (12.2)	37 (16.3)	0	0
Antidepressants[c]	25 (13.9)	18 (16.7)	31 (11.2)	19 (8.8)	56 (17.1)	37 (16.3)	0	0
Statins[c]	47 (26.1)	32 (29.6)	11 (4.0)	10 (4.6)	50 (15.2)	38 (16.7)	8 (6.2)	4 (4.1)
Aspirin[c]	25 (13.9)	19 (17.6)	3 (1.1)	3 (1.4)	28 (8.5)	22 (9.7)	0	0
Prior MTX use, n (%)	170 (94.4)	95 (88.0)	262 (94.2)	198 (91.2)	311 (94.8)	206 (90.7)	121 (93.1)	87 (88.8)
Prior csDMARD use (other than MTX), n (%)	84 (46.7)	58 (53.7)	121 (43.5)	107 (49.3)	149 (45.4)	114 (50.2)	56 (43.1)	51 (52.0)
Prior TNFi use, n (%)	86 (47.8)	72 (66.7)	104 (37.4)	115 (53.0)	144 (43.9)	143 (63.0)	46 (35.4)	44 (44.9)
Prior non-TNFi bDMARD use, n (%)	13 (7.2)	11 (10.2)	11 (4.0)	11 (5.1)	22 (6.7)	16 (7.0)	2 (1.5)	6 (6.1)

[a]Baseline cardiovascular risk factors were defined as a patient aged ≥50 years AND meeting one of the following criteria at baseline: current smoker, HDL<40 mg/dL, history of hypertension diagnosis, history of diabetes diagnosis, history of myocardial infarction, or history of coronary heart disease diagnosis.

[b]Baseline VTE risk factors were defined as any patient meeting any of the following criteria at baseline: aged ≥60 years, current smoker, previous heart failure, previous VTE (DVT or PE), BMI ≥30 kg/m^2, Day 1 use of oral contraceptives or hormone replacement therapy, Day 1 antidepressant use or Day 1 aspirin use.

[c]Day 1 use.

bDMARD, biologic disease-modifying antirheumatic drug; BID, twice daily; BMI, body mass index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DVT, deep vein thrombosis; HDL, high-density lipoprotein; HRT, hormone replacement therapy; MTX, methotrexate; N, total number of patients; n, patient with characteristic; OCT, oral contraceptives; PE, pulmonary embolism; PsA, psoriatic arthritis; SD, standard deviation; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism.

Table S6. Summary of RA, PsO and PsA patients (*all tofacitinib cohort*) who experienced a DVT, PE or ATE, stratified by selected baseline risk factors reported for those patients[a]

		Baseline risk factor, n																
Event	**Total patients with event**	≥50 to <60 years of age	≥60 years of age	Male	BMI ≥30 kg/m^2	Smoker	Baseline CRP >2.87 mg/L	Diabetes	Hypertension	Previous VTE	Previous heart failure	History of coronary heart disease	History of myocardial infarction	Day 1 aspirin use	Day 1 anticoagulant use	Day 1 antidepressant use	Day 1 oral corticosteroid use	Day 1 OCP or HRT use
RA																		
Average tofacitinib 5 mg BID																		
DVT	**15**	6	7	4	8	4	15	3	10	0	1	0	0	2	2	1	11	2
PE	**11**	3	7	2	5	4	10	0	7	2	0	0	0	2	3	1	8	1
ATE	**29**	12	16	4	13	6	23	8	18	1	1	0	2	2	3	3	14	1
Average tofacitinib 10 mg BID																		
DVT	**22**	3	11	6	4	4	13	3	10	1	0	0	1	5	5	1	11	4
PE	**20**	5	13	4	8	2	18	1	12	1	1	0	2	6	6	4	9	3
ATE	**57**	24	31	20	19	13	46	8	37	2	0	1	1	15	17	3	24	3
PsO																		
Average tofacitinib 5 mg BID																		
DVT	**1**	0	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0
PE	**2**[b]	0	0	1	1	1	1	0	1	0	0	0	0	0	0	1	0	0
ATE	**8**	5	1	6	2	4	5	2	3	0	0	1	0	1	1	1	0	0

		Baseline risk factor, n																
Event	**Total patients with event**	≥50 to <60 years of age	≥60 years of age	Male	BMI ≥30 kg/m^2	Smoker	Baseline CRP >2.87 mg/L	Diabetes	Hypertension	Previous VTE	Previous heart failure	History of coronary heart disease	History of myocardial infarction	Day 1 aspirin use	Day 1 anticoagulant use	Day 1 antidepressant use	Day 1 oral corticosteriod use	Day 1 OCP or HRT use
Average tofacitinib 10 mg BID																		
DVT	**5**	3	2	3	4	2	1	2	2	0	0	0	1	0	0	0	0	0
PE	**7**	1	2	3	5	2	4	1	3	1	0	0	0	1	1	0	0	2
ATE	**17**	9	6	14	8	9	8	6	7	0	0	1	0	3	4	1	0	0
PsA																		
Average tofacitinib 5 mg BID																		
DVT	**0**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PE	**1**	0	1	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0
ATE	**4**	2	2	2	2	0	3	0	3	0	0	0	0	0	0	0	1	0
Average tofacitinib 10 mg BID																		
DVT	**1**	0	1	1	1	0	1	1	1	0	1	0	0	0	0	0	1	0
PE	**0**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ATE	**3**	2	1	3	1	0	2	0	2	0	0	1	1	0	0	0	0	0

[a]The number in each risk factor cell represents how many patients in that row had that baseline risk factor. Patients who experienced an event outside the defined risk period were not included.

[b]One patient had both a DVT and PE.

ATE, arterial thromboembolism; BID, twice daily; BMI, body mass index; CRP, C-reactive protein; DVT, deep vein thrombosis; HRT, hormone replacement therapy; n, number of patients with event; OCP, oral contraceptive pill; PE, pulmonary embolism; VTE, venous thromboembolism.

Table S7 Patient demographics and baseline characteristics for RA, PsO and PsA patients in the US Corrona registries (all excluding tofacitinib)[a]

	RA		PsO		PsA	
	All registry (N=11 985)	**Drug initiators (N=5190)**	**All registry (N=3879)**	**Drug initiators (N=1945)**	**All registry (N=1926)**	**Drug initiators (N=855)**
Age (years), mean (SD)	58.6 (13.5)	57.5 (13.6)	49.9 (14.5)	50.1 (14.7)	53.7 (13.1)	53.8 (13.0)
≥65 years of age, n (%)	4336 (36.2)	1717 (33.1)	641 (16.5)	323 (16.6)	420 (21.8)	185 (21.6)
Female, n (%)	9243 (77.1)	4035 (77.8)	1854 (47.8)	964 (49.6)	998 (51.8)	460 (53.8)
Race, n (%)						
White	10 608 (88.5)	4578 (88.2)	3027 (78.0)	1549 (79.6)	1754 (91.1)	770 (90.1)
Black	744 (6.2)	330 (6.4)	140 (3.6)	77 (4.0)	7 (0.4)	5 (0.6)
Asian	171 (1.4)	57 (1.1)	411 (10.6)	179 (9.2)	37 (1.9)	20 (2.3)
Indigenous American	79 (0.7)	40 (0.8)	13 (0.3)	4 (0.2)	4 (0.2)	3 (0.4)
Other/unknown	383 (3.2)	185 (3.6)	288 (7.4)	136 (7.0)	124 (6.4)	57 (6.7)
BMI (kg/m^2), mean (SD)	29.9 (7.2)	30.3 (7.3)	30.8 (7.4)	31.2 (7.6)	31.6 (7.3)	32.2 (7.7)
BMI >30 kg/m^2, n (%)	5059 (42.6)	2318 (45.1)	1818 (46.9)	969 (49.8)	987 (51.2)	463 (54.2)
Smoking status, n (%)						
Never smoked	6034 (51.0)	2499 (48.8)	1961 (50.6)	932 (47.9)	992 (51.5)	427 (49.9)
Smoker	1634 (13.8)	873 (17.0)	653 (16.8)	350 (18.0)	210 (10.9)	105 (12.3)
Ex-smoker	4174 (35.3)	1750 (34.2)	1236 (31.9)	646 (33.2)	678 (35.2)	305 (35.6)

Comorbidities, n (%)						
0	5886 (49.1)	2711 (52.2)	2826 (72.9)	1587 (81.6)	1394 (72.4)	784 (91.7)
1	2913 (24.3)	1206 (23.2)	793 (20.4)	274 (14.1)	379 (19.7)	54 (6.3)
2 or more	3186 (26.6)	1273 (24.5)	260 (6.7)	84 (4.3)	153 (7.9)	17 (2.0)
Prior thromboembolism history, n (%)						
Any VTE	195 (1.6)	85 (1.6)	31 (0.8)	8 (0.4)	25 (1.3)	15 (1.8)
PE	79 (0.7)	39 (0.8)	12 (0.3)	4 (0.2)	11 (0.6)	5 (0.6)
DVT	137 (1.1)	58 (1.1)	20 (0.5)	5 (0.3)	19 (1.0)	14 (1.6)
ATE	567 (4.7)	217 (4.2)	142 (3.7)	71 (3.7)	66 (3.4)	34 (4.0)
Concomitant NSAIDs, n (%)	6148 (51.3)	2479 (47.8)	882 (22.7)	431 (22.2)	813 (42.2)	320 (37.4)
Prednisone use, n (%)	3526 (29.4)	1700 (32.8)	4 (0.1)	0	258 (13.4)	72 (8.4)
Anti-platelet agent use, n (%)	180 (1.5)	91 (1.8)	81 (2.1)	43 (2.2)	N/A	N/A

[a]The 'All registry' population included all patients enrolled in the Corrona registries irrespective of when they started a biologic or non-biologic therapy (excluding patients enrolled in the registry already taking tofacitinib). The 'Drug initiator' population included all patients in the Corrona registries who initiated a specific (non-tofacitinib) drug upon, or after, enrolment in the registry (excluding patients already on a drug at the time of enrolment who did not initiate a new therapy while in the registry); further details are in the online supplementary materials.

ATE, arterial thromboembolism; BMI, body mass index; DVT, deep vein thrombosis; N, number of treatment courses; n, number of treatment courses for which patient characteristics are indicated; N/A, not available; NSAID, non-steroidal anti-inflammatory drug; PE, pulmonary embolism; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SD, standard deviation; VTE, venous thromboembolism.

Table S8 Patient demographics and baseline characteristics for RA, PsO and PsA patients in the MarketScan research databases

	RA (N=65 550)	**PsO (N=47 474)**	**PsA (N=12 959)**
Age (years), mean (SD)	53.1 (12.1)	47.9 (12.8)	49.1 (11.3)
≥65 years of age, n (%)	8364 (12.8)	2979 (6.3)	686 (5.3)
Female, n (%)	52 017 (79.4)	24 950 (52.6)	7105 (54.8)
Smoking status, n (%)			
Smoker	8123 (12.4)	5913 (12.5)	1149 (8.9)
Prior thromboembolism history, n (%)			
Any VTE	4021 (6.1)	1763 (3.7)	443 (3.4)
PE	944 (1.4)	290 (0.6)	65 (0.5)
DVT	3558 (5.4)	1639 (3.5)	407 (3.1)
ATE	212 (0.3)	66 (0.1)	258 (2.0)
Acute myocardial infarction	2204 (3.4)	1052 (2.2)	124 (1.0)
Stroke	1186 (1.8)	505 (1.1)	10 (0.1)
Comorbidities, n (%)			
Diabetes	10 656 (16.3)	7665 (16.1)	2092 (16.1)
Hypertension	31 708 (48.4)	19 591 (41.3)	5469 (42.2)

Baseline treatment [a], n (%)			
csDMARDs	44 562 (68.0)	13 554 (28.6)	8386 (64.7)
bDMARDs	31 034 (47.3)	18 235 (38.4)	5056 (39.0)
Tofacitinib	2195 (3.3)	-	-
Apremilast	-	2537 (5.3)	856 (6.6)
Glucocorticoid use in prior 3 months	33 277 (50.8)	6927 (14.6)	3074 (23.7)
Treatment initiated at index date, n (%)			
Abatacept	7439 (11.3)	-	-
Adalimumab	12 580 (19.2)	12 864 (27.1)	3427 (26.4)
Certolizumab pegol	2903 (4.4)	592 (1.2)	553 (4.3)
Etanercept	10 867 (16.6)	5490 (11.6)	2305 (17.8)
Golimumab	3156 (4.8)	-	557 (4.3)
Infliximab	3477 (5.3)	1199 (2.5)	888 (6.9)
Rituximab	2557 (3.9)	-	-
Secukinumab	-	3061 (6.4)	802 (6.2)
Tocilizumab	4517 (6.9)	-	-
Tofacitinib	5521 (8.4)	-	-
Ustekinumab	-	7901 (16.6)	980 (7.6)
cDMARDs	12 533 (19.1)	8538 (18.0)	1638 (12.6)

Concomitant medication, n (%)			
Antibiotics	59 514 (90.8)	41 282 (87.0)	11 200 (86.4)
Anticoagulants	8582 (13.1)	3410 (7.2)	972 (7.5)
Beta blockers	15 183 (23.2)	8750 (18.4)	2380 (18.4)
Hormonal therapy[b]	17 284 (33.2)	9237 (37.0)	2487 (35.0)
NSAIDs	53 668 (81.9)	27 633 (58.2)	10 474 (80.8)
Statins	19 397 (29.6)	13 538 (28.5)	3547 (27.4)

[a]Based on use within 1 year prior to index date, unless otherwise stated.

[b]Female patients only, based on patients with available data (RA: n=52 017; PsO: n=24 950; PsA: n=7105).

ATE, arterial thromboembolism; bDMARD, biologic disease-modifying antirheumatic drug; cDMARD, conventional disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DVT, deep vein thrombosis; N, number of treatment courses; n, number of treatment courses for which patient characteristics are indicated; NSAID, non-steroidal anti-inflammatory drug; PE, pulmonary embolism; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SD, standard deviation; VTE, venous thromboembolism.

Table S9 Drug exposure, incidence proportions and standardised[a] incidence rates (95% CI) for DVT, PE, VTE (DVT or PE) and ATE for RA, PsO and PsA patients in the US Corrona registries (excluding tofacitinib), stratified by medication status[b]

n (%) **IR [95% CI]** **Exposure, PY**	**DVT**	**PE**	**VTE** **(DVT or PE)**	**ATE**
RA				
All registry	45 (0.4)	45 (0.4)	78 (0.7)	169 (1.4)
(N=11 985)	0.13 [0.07-0.27]	0.14 [0.06-0.29]	0.23 [0.14-0.41]	0.46 [0.33-0.67]
	26 633	26 617	26 573	26 443
Drug initiators	9 (0.2)	9 (0.2)	16 (0.3)	37 (0.7)
(N=5190)	0.13 [0.03-0.54]	0.15 [0.04-0.57]	0.24 [0.09-0.70]	0.50 [0.25-1.06]
	6435	6435	6428	6408
PsO				
All registry	4 (0.1)	2 (0.1)	5 (0.1)	18 (0.5)
(N=3879)	0.13 [0.03-0.34]	0.06 [0.01-0.23]	0.14 [0.04-0.35]	0.27 [0.14-0.46]
	2924	2927	2924	2912
Drug initiators	1 (0.1)	1 (0.1)	1 (0.1)	7 (0.4)
(N=1945)	0.13 [0.00-0.67]	0.13 [0.00-0.67]	0.13 [0.00-0.67]	0.33 [0.10-0.82]
	930	930	930	926
PsA				
All registry	4 (0.2)	3 (0.2)	6 (0.3)	18 (0.9)
(N=1926)	0.09 [0.02-0.25]	0.03 [0.01-0.13]	0.12 [0.04-0.27]	0.34 [0.19-0.58]
	4479	4485	4479	4461
Drug initiators	1 (0.1)	1 (0.1)	1 (0.1)	7 (0.8)
(N=855)	0.03 [0.00-0.33]	0.03 [0.00-0.33]	0.03 [0.00-0.33]	0.41 [0.14-0.99]
	1472	1472	1472	1470

[a]Standardised against age-sex distribution for the tofacitinib (5 and 10 mg BID) clinical trial population for each development programme.

[b]The 'All registry' population included all patients enrolled in the Corrona registries irrespective of when they started a biologic or non-biologic therapy (excluding patients enrolled in the registry already taking tofacitinib). The 'Drug initiator' population included all patients in the Corrona registries who initiated a specific (non-tofacitinib) drug upon, or after, enrolment in the registry (excluding patients already on a drug at the time of enrolment who did not initiate a new therapy while in the registry); further details are in the online supplementary materials.

In general, exposure time was defined as time in years from the index date to first event (VTE [DVT or PE] or ATE [defined as peripheral ATE event, urgent peripheral arterial revascularisation, myocardial infarction, transient ischaemic attack or stroke]), last follow-up visit, discontinuation + 90 days, or switch to tofacitinib, whichever came first. For enrolment, index date was defined as enrolment date into the Corrona Registry. For first drug exposure, index date was defined as the first non-tofacitinib biologic or non-biologic initiation (drug start date for first time use of drug therapy). Drug initiation for the first drug exposure approach could occur at, or after, enrolment.

ATE, arterial thromboembolism; BID, twice daily; CI, confidence interval; DVT, deep vein thrombosis; IR, incidence rate (number of patients with an event per 100 PY of exposure); N, total number of patients; n, number of patients with events; PE, pulmonary embolism; PsA, psoriatic arthritis; PsO, psoriasis; PY, patient-years; RA, rheumatoid arthritis; VTE, venous thromboembolism.

Table S10 Drug exposure, incidence proportions, and standardised[a] incidence rates (95% CI) for DVT, PE, VTE (DVT or PE), ATE, acute myocardial infarction and stroke for RA, PsO and PsA patients in the MarketScan research databases[b], stratified by medication status[c]

n (%) **IR [95% CI]** **Exposure, PY**	**DVT**	**PE**	**VTE (DVT or PE)**	**ATE**	**Acute myocardial infarction**	**Stroke**
RA						
All DMARD	511 (0.8)	157 (0.2)	589 (0.9)	29 (0.04)	235 (0.4)	216 (0.3)
initiators[d]	0.80 [0.73-0.88]	0.25 [0.21-0.29]	0.93 [0.85-1.01]	0.05 [0.03-0.07]	0.36 [0.31-0.41]	0.34 [0.29-0.39]
(N=65 550)	60 665	60 965	60 611	61 037	60 890	60 928
bDMARD	376 (0.8)	117 (0.2)	433 (0.9)	20 (0.04)	163 (0.3)	143 (0.3)
initiators[d]	0.81 [0.73-0.90]	0.25 [0.21-0.30]	0.94 [0.85-1.03]	0.04 [0.03-0.07]	0.35 [0.30-0.41]	0.31 [0.26-0.37]
(N=47 496)	45 044	45 258	45 006	45 310	45 206	45 234
Tofacitinib	47 (0.9)	10 (0.2)	53 (1.0)	2 (0.04)	17 (0.3)	13 (0.2)
(N=5521)	0.93 [0.68-1.26]	0.19 [0.09-0.37]	1.05 [0.78-1.39]	0.04 [0.00-0.17]	0.32 [0.18-0.53]	0.27 [0.14-0.48]
	4801	4835	4799	4837	4825	4830
PsO						
All treatment	147 (0.3)	47 (0.1)	172 (0.4)	11 (0.02)	92 (0.2)	61 (0.1)
initiators[e]	0.32 [0.27-0.39]	0.10 [0.07-0.14]	0.37 [0.31-0.44]	0.02 [0.01-0.05]	0.21 [0.17-0.27]	0.12 [0.09-0.17]
(N=47 474)	41 637	41 721	41 619	41 748	41 695	41 711

Biologic treatment	103 (0.3)	39 (0.1)	124 (0.4)	5 (0.02)	64 (0.2)	38 (0.1)
initiators[e]	0.31 [0.25-0.39]	0.12 [0.08-0.17]	0.37 [0.30-0.45]	0.02 [0.00-0.04]	0.22 [0.17-0.28]	0.11 [0.08-0.16]
(N=31 107)	29 948	30 008	29 932	30 036	29 999	30 007
PsA						
All DMARD	34 (0.3)	10 (0.1)	41 (0.3)	3 (0.02)	28 (0.2)	13 (0.1)
initiators[f]	0.33 [0.22-0.48]	0.09 [0.04-0.18]	0.39 [0.28-0.55]	0.03 [0.01-0.11]	0.25 [0.16-0.38]	0.12 [0.06-0.22]
(N=12 959)	11 632	11 667	11 628	11 671	11 643	11 661
bDMARD	31 (0.3)	10 (0.1)	38 (0.4)	2 (0.02)	26 (0.3)	12 (0.1)
initiators[f]	0.39 [0.26-0.58]	0.11 [0.05-0.23]	0.47 [0.32-0.67]	0.02 [0.00-0.11]	0.31 [0.19-0.48]	0.13 [0.06-0.25]
(N=9615)	9340	9370	9335	9376	9347	9364

[a]Standardised against age-sex distribution for the tofacitinib (5 and 10 mg BID) clinical trial population for each development programme.

[b]Exclusion criteria were applied (details in online supplementary material).

[c]Details of treatments are in online supplementary table S2.

[d]Includes: MTX, leflunomide, sulfasalazine, hydroxychloroquine, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, tocilizumab; bDMARD initiators: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, tocilizumab.

[e]Includes: MTX, leflunomide, cyclosporine, apremilast, etanercept, adalimumab, infliximab, certolizumab pegol, ustekinumab, secukinumab; Biologic treatment initiators: etanercept, adalimumab, infliximab, certolizumab pegol, ustekinumab, secukinumab.

[f]Includes: MTX, leflunomide, sulfasalazine, apremilast, adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, ustekinumab, secukinumab; bDMARD initiators: adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, ustekinumab, secukinumab.

ATE, arterial thromboembolism; bDMARD, biologic DMARD; BID, twice daily; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; DVT, deep vein thrombosis; IR, incidence rate (number of events per 100 PY of exposure); MTX, methotrexate; N, total number of patients; n, number of events; PE, pulmonary embolism; PsA, psoriatic arthritis; PsO, psoriasis; PY, patient-years; RA, rheumatoid arthritis; VTE, venous thromboembolism.

Table S11 Patient demographics and baseline characteristics for patients (CDAI >10) in the US Corrona RA registry sub-analysis that were bDMARD or tofacitinib initiators; all patients, stratified by cardiovascular risk factors

	bDMARD initiators[a] (N=5159)	**bDMARD initiators[a] with cardiovascular risk factors[b] (N=2551)**	**Tofacitinib initiators[c] (N=1130)**	**Tofacitinib initiators[c] with cardiovascular risk factors[b] (N=599)**
Age (years), mean (SD)	57.9 (12.9)	63.9 (8.8)	59.5 (12.3)	64.2 (8.7)
≥65 years of age, n (%)	1698 (32.9)	1142 (44.8)	403 (35.7)	274 (45.7)
Female, n (%)	4188 (81.2)	2010 (78.8)	913 (80.8)	465 (77.6)
BMI ≥30 kg/m^2, n (%)	2454 (47.8)	1259 (49.7)	536 (47.9)	311 (52.3)
Smoking status, n (%)				
Never smoked	2475 (48.6)	985 (38.8)	525 (46.8)	235 (39.4)
Smoker	966 (19.0)	696 (27.4)	232 (20.7)	170 (28.5)
Ex-smoker	1657 (32.5)	856 (33.7)	364 (32.5)	192 (32.2)

Comorbidities, n (%)				
Diabetes	572 (11.1)	502 (19.7)	145 (12.8)	135 (22.5)
Hypertension	1717 (33.3)	1543 (60.5)	428 (37.9)	386 (64.4)

[a]Included patients with moderate to severe RA (CDAI >10 at initiation) in the Corrona RA registry initiating a first or subsequent bDMARD (each initiation was considered separately such that there were multiple initiations per patient) and were tofacitinib-naïve.

[b]Defined as patients aged ≥50 years AND with ≥1 of the following cardiovascular risk factors: current smoker, diagnosis of hypertension, diagnosis of diabetes mellitus, history of coronary artery disease (eg, cardiac arrest, heart attack, unstable angina, revascularisation procedures), family history of premature coronary heart disease or current extra-articular RA disease.

[c]RA patients in the US Corrona registry initiating tofacitinib for the first time.

BMI, body mass index; bDMARD, biologic disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; N, total number of RA patients; n, number of RA patients with events; RA, rheumatoid arthritis; SD, standard deviation.

Table S12 FAERS data disproportionality analysis for tofacitinib

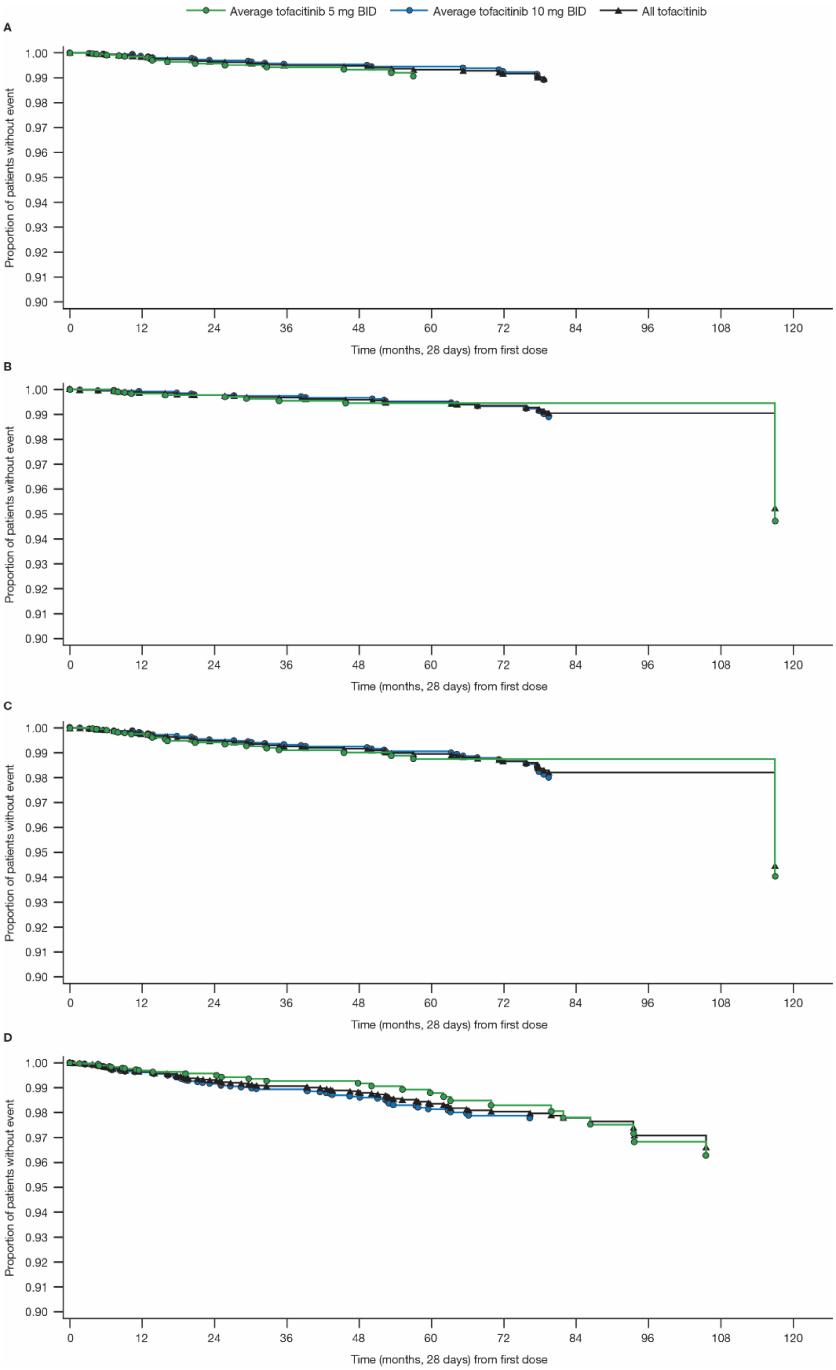
PT/SMQ	N	EBGM (EB_{05}–EB_{95})	ROR (ROR_{05}–ROR_{95})
Cavernous sinus thrombosis	1	0.84 (0.18-2.76)	1.65 (0.31-8.81)
Deep vein thrombosis	94	0.64 (0.54-0.76)	0.64 (0.54-0.76)
Embolism venous	2	0.36 (0.11-0.93)	0.36 (0.11-1.16)
Hepatic vein thrombosis	1	0.74 (0.16-2.42)	1.19 (0.23-6.19)
Jugular vein thrombosis	1	0.25 (0.05-0.82)	0.23 (0.04-1.17)
Pelvic venous thrombosis	1	0.27 (0.06-0.90)	0.25 (0.05-1.29)
Portal vein thrombosis	2	0.29 (0.09-0.74)	0.28 (0.09-0.89)
Post procedural pulmonary embolism	1	0.77 (0.16-2.53)	1.32 (0.25-7.06)
Postoperative thrombosis	1	0.50 (0.11-1.66)	0.59 (0.11-3.10)
Pulmonary embolism	169	0.76 (0.67-0.86)	0.76 (0.67-0.86)
Pulmonary thrombosis	53	1.76 (1.40-2.19)	1.83 (1.45-2.30)
Retinal vein occlusion	2	0.30 (0.09-0.77)	0.29 (0.09-0.93)
Thrombophlebitis	9	0.92 (0.52-1.52)	0.98 (0.57-1.70)
Thrombophlebitis superficial	4	0.43 (0.18-0.87)	0.43 (0.19-0.98)
Vena cava thrombosis	1	0.31 (0.07-1.02)	0.29 (0.06-1.53)
Venous occlusion	2	0.39 (0.12-1.01)	0.40 (0.12-1.29)
Venous thrombosis	5	0.50 (0.23-0.96)	0.51 (0.24-1.07)
Venous thrombosis limb	1	0.20 (0.04-0.65)	0.17 (0.03-0.88)
'*Embolic and thrombotic events, venous*' SMQ, narrow	306	0.66 (0.60-0.73)	0.66 (0.60-0.72)
Acute myocardial infarction	26	0.39 (0.28-0.53)	0.39 (0.28-0.53)
Amaurosis	1	0.52 (0.11-1.72)	0.63 (0.12-3.25)
Aortic thrombosis	1	0.41 (0.09-1.36)	0.43 (0.08-2.27)
Arterial occlusive disease	12	0.64 (0.39-1.00)	0.65 (0.41-1.05)
Arterial stent insertion	1	0.85 (0.18-2.80)	1.69 (0.32-8.83)
Arterial thrombosis	1	0.27 (0.06-0.89)	0.25 (0.05-1.28)
Basal ganglia infarction	1	0.69 (0.15-2.26)	1.03 (0.20-5.35)
Blindness transient	4	0.25 (0.11-0.51)	0.24 (0.10-0.54)
Carotid artery occlusion	5	0.55 (0.26-1.05)	0.57 (0.27-1.19)
Cerebral artery occlusion	2	0.6 (0.19-1.54)	0.68 (0.21-2.19)
Cerebral artery thrombosis	1	0.6 (0.13-1.96)	0.78 (0.15-4.13)
Coronary arterial stent insertion	4	0.34 (0.15-0.70)	0.34 (0.15-0.77)
Coronary artery bypass	3	0.3 (0.11-0.66)	0.29 (0.11-0.75)
Coronary artery occlusion	16	0.53 (0.35-0.78)	0.53 (0.35-0.81)

Coronary artery thrombosis	2	0.51 (0.16-1.32)	0.56 (0.17-1.79)
Hepatic artery thrombosis	1	0.84 (0.18-2.78)	1.67 (0.31-8.85)
Ischaemic stroke	9	0.16 (0.09-0.26)	0.15 (0.09-0.26)
Lacunar infarction	2	0.41 (0.13-1.04)	0.41 (0.13-1.33)
Myocardial infarction	269	0.83 (0.75-0.92)	0.83 (0.75-0.92)
Peripheral arterial occlusive disease	5	0.49 (0.23-0.95)	0.51 (0.24-1.06)
Peripheral artery occlusion	1	0.2 (0.04-0.66)	0.17 (0.03-0.9)
Peripheral artery thrombosis	1	0.26 (0.06-0.86)	0.24 (0.05-1.23)
Peripheral embolism	1	0.33 (0.07-1.08)	0.32 (0.06-1.66)
Renal artery occlusion	1	0.84 (0.18-2.77)	1.67 (0.31-8.93)
Renal artery thrombosis	1	0.77 (0.16-2.55)	1.33 (0.26-6.93)
Stress cardiomyopathy	7	0.36 (0.19-0.64)	0.36 (0.19-0.67)
Thrombotic thrombocytopenic purpura	7	0.81 (0.43-1.43)	0.87 (0.47-1.63)
Transient ischaemic attack	51	0.64 (0.50-0.79)	0.64 (0.50-0.80)
'*Embolic and thrombotic events, arterial*' SMQ, narrow	422	0.58 (0.54-0.63)	0.57 (0.53-0.62)
Antiphospholipid syndrome	1	0.27 (0.06-0.90)	0.25 (0.05-1.30)
Brain stem infarction	1	0.38 (0.08-1.26)	0.39 (0.08-2.02)
Cardiac ventricular thrombosis	2	0.76 (0.24-1.97)	0.97 (0.30-3.14)
Cerebellar infarction	1	0.26 (0.06-0.86)	0.24 (0.05-1.23)
Cerebral infarction	14	0.21 (0.14-0.32)	0.21 (0.14-0.33)
Cerebral ischaemia	3	0.26 (0.10-0.59)	0.25 (0.10-0.65)
Cerebral thrombosis	6	0.81 (0.40-1.48)	0.88 (0.45-1.72)
Cerebrovascular accident	303	0.83 (0.75-0.91)	0.83 (0.75-0.91)
Diplegia	4	0.69 (0.30-1.41)	0.75 (0.33-1.72)
Disseminated intravascular coagulation	15	0.5 (0.32-0.74)	0.5 (0.33-0.77)
Embolic stroke	3	0.27 (0.10-0.61)	0.26 (0.10-0.68)
Embolism	10	0.53 (0.31-0.85)	0.53 (0.32-0.90)
Haemorrhagic stroke	7	0.26 (0.13-0.45)	0.25 (0.13-0.47)
Hemiparesis	5	0.11 (0.05-0.21)	0.1 (0.05-0.22)
Hemiplegia	7	0.32 (0.17-0.56)	0.31 (0.17-0.59)
Infarction	9	0.48 (0.27-0.80)	0.48 (0.28-0.84)
Intestinal infarction	1	0.48 (0.10-1.58)	0.54 (0.10-2.84)
Intracardiac mass	1	0.8 (0.17-2.62)	1.45 (0.27-7.8)
Intracardiac thrombus	2	0.28 (0.09-0.73)	0.27 (0.09-0.88)
Monoplegia	5	0.43 (0.20-0.83)	0.43 (0.21-0.91)
Paraplegia	3	0.42 (0.16-0.95)	0.43 (0.17-1.12)
Paresis	1	0.21 (0.05-0.70)	0.19 (0.04-0.96)

Prosthetic cardiac valve thrombosis	1	1.03 (0.22-3.40)	3.43 (0.61-19.15)
Renal vascular thrombosis	1	0.91 (0.19-2.99)	2.06 (0.39-10.91)
Splenic infarction	1	0.27 (0.06-0.89)	0.25 (0.05-1.29)
Thrombosis	173	0.94 (0.82-1.06)	0.94 (0.83-1.06)
Vascular stent insertion	1	0.98 (0.21-3.22)	2.68 (0.50-14.47)
'*Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous*' SMQ, narrow	563	0.6 (0.56-0.64)	0.59 (0.55-0.64)

EB_{05}, lower 5% bound of the 90% interval of the shrinkage-adjusted O/E ratio; EB_{95}, upper 5% bound of the 90% interval of the shrinkage-adjusted O/E ratio; EBGM, empirical Bayesian geometric mean (shrinkage-adjusted O/E ratio); FAERS, US FDA Adverse Events Reporting System; N, case count or observed count of event; O/E, observed-to-expected; PT, Preferred Term; ROR, reporting odds ratio; ROR_{05}, lower 5% bound of the 90% interval of the ROR; ROR_{95}, upper 5% bound of the 90% interval of the ROR; SMQ, Standardised Medical Dictionary for Regulatory Activities query.

Figure S1 Kaplan-Meier plots showing proportions of RA patients in the tofacitinib development programme without (A) DVT, (B) PE, (C) VTE (DVT or PE) or (D) ATE



Total follow-up time calculated up to the day of the first event (subject to a risk period of 28 days beyond the last dose or to the data cut-off date).

ATE, arterial thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; RA, rheumatoid arthritis; VTE, venous thromboembolism.

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