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.

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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.

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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.

Mease P, *et al*. *Ann Rheum Dis* 2020; 79:1400–1413. doi: 10.1136/annrheumdis-2019-216761

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.

Mease P, *et al. Ann Rheum Dis* 2020; 79:1400–1413. doi: 10.1136/annrheumdis-2019-216761

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

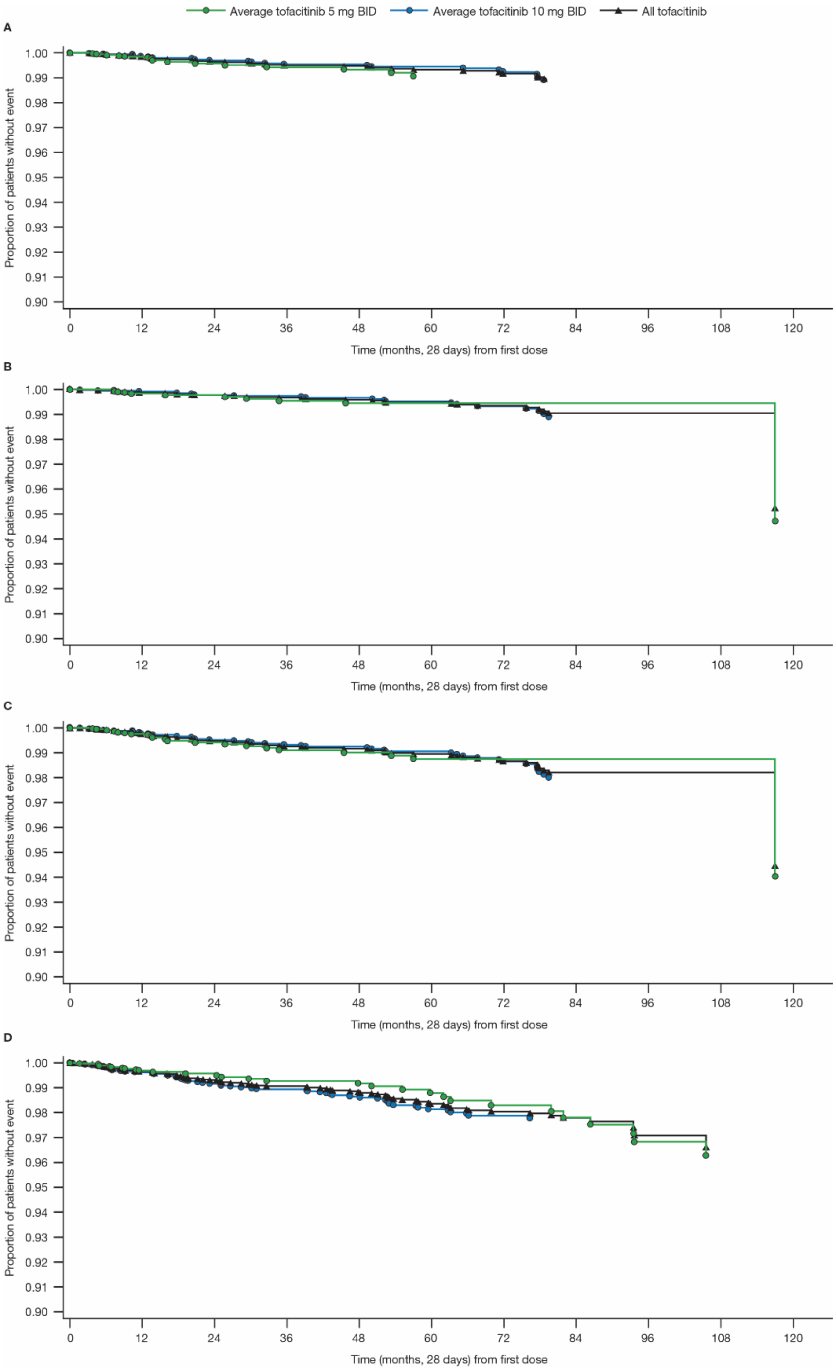
PT/SMQ	N	EBGM (EB_{05}–EB_{95})	ROR (ROR_{05}–ROR_{95})
Cavernous sinus thrombosis	1	0.84 (0.18-2.76)	1.65 (0.31-8.81)
Deep vein thrombosis	94	0.64 (0.54-0.76)	0.64 (0.54-0.76)
Embolism venous	2	0.36 (0.11-0.93)	0.36 (0.11-1.16)
Hepatic vein thrombosis	1	0.74 (0.16-2.42)	1.19 (0.23-6.19)
Jugular vein 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.

REFERENCES

1. European Medicines Agency. XELJANZ (tofacitinib): summary of product characteristics. 2019. https://www.ema.europa.eu/en/documents/referral/xeljanz-article-20-procedure-annex-iii_en.pdf (accessed November 15, 2019).

2. ClinicalTrials.gov. Safety study of tofacitinib versus tumor necrosis factor (TNF) inhibitor in subjects with rheumatoid arthritis. 2017. https://clinicaltrials.gov/ct2/show/NCT02092467 (accessed March 20, 2020).

3. Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum* 2009;60:1895-905.

4. Tanaka Y, Takeuchi T, Yamanaka H, et al. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. *Mod Rheumatol* 2015;25:514-21.

5. Fleischmann R, Cutolo M, Genovese MC, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum* 2012;64:617-29.

6. Kremer JM, Cohen S, Wilkinson BE, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination

with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis Rheum* 2012;64:970-81.

7. Tanaka Y, Suzuki M, Nakamura H, et al. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res (Hoboken)* 2011;63:1150-8.

8. Boyle DL, Soma K, Hodge J, et al. The JAK inhibitor tofacitinib suppresses synovial JAK1-STAT signalling in rheumatoid arthritis. *Ann Rheum Dis* 2015;74:1311-6.

9. Conaghan PG, Østergaard M, Bowes MA, et al. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naive, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. *Ann Rheum Dis* 2016;75:1024-33.

10. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis* 2016;75:687-95.

11. Winthrop KL, Wouters AG, Choy EH, et al. The safety and immunogenicity of live zoster vaccination in patients with rheumatoid arthritis before starting tofacitinib: a randomized Phase II trial. *Arthritis Rheumatol* 2017;69:1969-77.

12. van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum* 2013;65:559-70.

13. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367:508-19.

14. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012;367:495-507.

15. Kremer J, Li Z-G, Hall S, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2013;159:253-61.

16. Burmester GR, Blanco R, Charles-Schoeman C, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised Phase 3 trial. *Lancet* 2013;381:451-60.

17. Lee EB, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med* 2014;370:2377-86.

18. Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase

3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet* 2017;390:457-68.

19. Charles-Schoeman C, Fleischmann R, Davignon J, et al. Potential mechanisms leading to the abnormal lipid profile in patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. *Arthritis Rheumatol* 2015;67:616-25.

20. Kremer JM, Kivitz AJ, Simon-Campos JA, et al. Evaluation of the effect of tofacitinib on measured glomerular filtration rate in patients with active rheumatoid arthritis: results from a randomised controlled trial. *Arthritis Res Ther* 2015;17:95.

21. McInnes IB, Kim HY, Lee SH, et al. Open-label tofacitinib and double-blind atorvastatin in rheumatoid arthritis patients: a randomised study. *Ann Rheum Dis* 2014;73:124-31.

22. Tanaka Y, Sugiyama N, Toyoizumi S, et al. Modified- versus immediate-release tofacitinib in Japanese rheumatoid arthritis patients: a randomized, phase III, non-inferiority study. *Rheumatology (Oxford)* 2019;58:70-9.

23. Cohen SB, Pope J, Haraoui B, et al. Methotrexate withdrawal in patients with rheumatoid arthritis who achieve low disease activity with tofacitinib modified-release 11 mg once daily plus methotrexate (ORAL Shift): a randomised, phase 3b/4, non-inferiority trial. *Lancet Rheumatol* 2019;1:E23-34.

24. Fleischmann R, Wollenhaupt J, Takiya L, et al. Safety and maintenance of response for tofacitinib monotherapy and combination therapy in rheumatoid arthritis: an analysis of pooled data from open-label long-term extension studies. *RMD Open* 2017;3:e000491.

25. Papp KA, Menter A, Strober B, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol* 2012;167:668-77.

26. Papp KA, Menter MA, Abe M, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two, randomized, placebo-controlled, phase III trials. *Br J Dermatol* 2015;173:949-61.

27. Bachelez H, van de Kerkhof PC, Strohal R, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet* 2015;386:552-61.

28. Bissonnette R, Iversen L, Sofen H, et al. Tofacitinib withdrawal and retreatment in moderate-to-severe chronic plaque psoriasis: a randomized controlled trial. *Br J Dermatol* 2015;172:1395-406.

29. Krueger J, Clark JD, Suárez-Fariñas M, et al. Tofacitinib attenuates pathologic immune pathways in patients with psoriasis: a randomized phase 2 study. *J Allergy Clin Immunol* 2016;137:1079-90.

30. Papp KA, Krueger JG, Feldman SR, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: long-term efficacy and

safety results from 2 randomized phase-III studies and 1 open-label long-term extension study. *J Am Acad Dermatol* 2016;74:841-50.

31. Valenzuela F, Korman NJ, Bissonnette R, et al. Tofacitinib in patients with moderate to severe chronic plaque psoriasis: long-term safety and efficacy in an open-label extension study. *Br J Dermatol* 2018;179:853-62.

32. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. *N Engl J Med* 2017;377:1537-50.

33. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. *N Engl J Med* 2017;377:1525-36.