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

Philip Mease,1 Christina Charles-Schoeman,2 Stanley Cohen,3 Lara Fallon,4 John Woolcott,5 Huifeng Yun,6 Joel Kremer,7 Jeffrey Greenberg,8 Wendi Malley,8 Alina Onofrei,8 Keith S Kanik,9 Daniela Graham,9 Cunshan Wang,9 Carol Connell,9 Hernan Valdez,10 Manfred Hauben,10,11 Eric Hung,10 Ann Madsen,10 Thomas V Jones,5 Jeffrey R Curtis6

1Swedish Medical Center, Providence St. Joseph Health and University of Washington, Seattle, WA, USA
2University of California, Los Angeles, CA, USA
3Metroplex Research Center, Dallas, TX, USA
4Pfizer Inc, Kirkland, QC, Canada
5Pfizer Inc, Collegeville, PA, USA
6University of Alabama at Birmingham, Birmingham, AL, USA
7Albany Medical College and The Center for Rheumatology, Albany, NY, USA
8Corrona LLC, Waltham, MA, USA
9Pfizer Inc, Groton, CT, USA
10Pfizer Inc, New York, NY, USA
11NYU Langone Health, New York, NY, USA
ONLINE SUPPLEMENTARY MATERIAL

INTRODUCTION

Study A3921133 inclusion criteria and enrolment

METHODS

Dose changes in long-term extension (LTE) studies

Tofacitinib development programmes

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

Observational data sources

US Corrona registries

IBM® MarketScan® research database

TABLES AND FIGURES

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

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

Table S3 Patient demographics and baseline characteristics for all tofacitinib-treated patients (all tofacitinib cohort), stratified by baseline cardiovasculara or VTEb risk factors in the RA development programme
Table S4 Patient demographics and baseline characteristics for all tofacitinib-treated patients (all tofacitinib cohort), stratified by defined baseline cardiovascular or VTE risk factors in the PsO development programme

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

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

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

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

Table S9 Drug exposure, incidence proportions and standardised IRs (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

Table S10 Drug exposure, incidence proportions and standardised IRs (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, stratified by medication status

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

Table S12 FAERS data disproportionality analysis for tofacitinib
**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) and (D) ATE

**REFERENCES**
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 (e.g., 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                                  | Phase 1                |
| DMARD-InR patients:       | DMARD-InR patients:                      |                        |
| NCT00147498;[3] NCT00687193;[4] | NCT00147498;[3] NCT00687193;[4]          |                        |
| NCT00550446;[5]           | NCT00550446;[5]                          |                        |
| MTX-InR patients:         | MTX-InR patients:                        |                        |
| NCT00413660;[6] NCT00603512;[7] | NCT00413660;[6] NCT00603512;[7]          |                        |
| NCT00976599;[8]           | NCT00976599;[8]                          |                        |
| MTX-naïve patients:       | MTX-naïve patients:                      |                        |
| NCT01164579;[9]           | NCT01164579;[9]                          |                        |
| Prior treatment not specified: | Prior treatment not specified: |                        |
| NCT01359150;[10]         | NCT01359150;[10]                         |                        |
| NCT02147587;[11]         | NCT02147587;[11]                         |                        |
| **Phase 3**               | Phase 2                                  | Phase 3                |
| MTX-InR patients:         | MTX-InR patients:                        |                        |
| ORAL Scan (NCT00847613);[12]| ORAL Scan (NCT00847613);[12]          |                        |
| ORAL Standard (NCT00853385);[13] | ORAL Standard (NCT00853385);[13]          |                        |
| MTX-naïve patients:       | MTX-naïve patients:                      |                        |
| NCT01164579;[9]           | NCT01164579;[9]                          |                        |
| Prior treatment not specified: | Prior treatment not specified: |                        |
| NCT01359150;[10]         | NCT02147587;[11]                         |                        |
| NCT01059864;[21]          | NCT01059864;[21]                         |                        |
| DMARD-InR patients:          | DMARD-InR patients:          | Phase 3                      |
|------------------------------|------------------------------|-----------------------------|
| ORAL Solo (NCT00814307)\sup{a}\sup{[14]} | ORAL Solo (NCT00814307)\sup{a}\sup{[14]} | MTX-InR patients:           |
| ORAL Sync (NCT00856544)\sup{c}\sup{[15]} | ORAL Sync (NCT00856544)\sup{c}\sup{[15]} | ORAL Scan (NCT00847613)\sup{b}\sup{[12]} |
| TNFi-InR patients:           | TNFi-InR patients:           | ORAL Standard (NCT00853385)\sup{b}\sup{[13]} |
| ORAL Step (NCT00960440)\sup{b}\sup{[16]} | ORAL Step (NCT00960440)\sup{b}\sup{[16]} | DMARD-InR patients:         |
| MTX-naïve:                   | MTX-naïve:                   | ORAL Solo (NCT00814307)\sup{c}\sup{[14]} |
| ORAL Start (NCT01039688)\sup{a}\sup{[17]} | ORAL Start (NCT01039688)\sup{a}\sup{[17]} | ORAL Sync (NCT00856544)\sup{c}\sup{[15]} |
| Phase 3b/4                   | Phase 3b/4                   | TNFi-InR patients:          |
| MTX-InR patients:            | MTX-InR patients:            | ORAL Step (NCT00960440)\sup{b}\sup{[16]} |
| ORAL Strategy (NCT02187055)\sup{a}\sup{b}\sup{[18]} | ORAL Strategy (NCT02187055)\sup{a}\sup{b}\sup{[18]} | MTX-naïve:                   |
|                              |                              | ORAL Start (NCT01039688)\sup{a}\sup{[17]} |
|                              |                              | MTX-InR patients:           |
|                              |                              | NCT02281552\sup{b}\sup{[22]}           |
| Phase 3b/4                   |                              |                              |
| MTX-InR patients:            |                              |                              |
| ORAL Strategy (NCT02187055)\sup{a}\sup{b}\sup{[18]} |                              |                              |
| MTX-InR patients:            |                              |                              |
| NCT02831855\sup{b}\sup{[23]} |                              |                              |

**LTE**

ORAL Sequel (NCT00413699)\sup{24}  
NCT00661661\sup{24}
| PsO RCTs | Phase 2 | Phase 3 | Phase 2 |
|----------|---------|---------|---------|
|          | NCT00678210[^25] | OPT Pivotal 1 (NCT01276639)[^26] | NCT00678210[^25] |
|          | OPT Pivotal 2 (NCT01309737)[^26] | OPT Re-treatment (NCT01186744)[^28] | NCT01710046[^29] |
|          | OPT Compare (NCT01241591)[^27] |          |         |
| Treatmentd | Patients randomised to tofacitinib 5 or 10 mg BID, or placebo up to month 3 | Patients who received ≥1 dose of tofacitinib | Patients who received ≥1 dose of tofacitinib |
|          | Patients randomised to tofacitinib 5 or 10 mg BID, or placebo up to month 3 | Patients who received ≥1 dose of tofacitinib | }
Patients randomised to etanercept 50 mg BIW (OPT Compare only)

| PsA RCTs | Phase 3 | Phase 3 | Phase 3 |
|----------|---------|---------|---------|
| csDMARD-InR patients: | csDMARD-InR patients: | csDMARD-InR patients: |
| OPAL Broaden (NCT01877668)\(^{[32]}\) | OPAL Broaden (NCT01877668)\(^{[32]}\) | OPAL Broaden (NCT01877668)\(^{[32]}\) |
| TNFi-InR patients: | TNFi-InR patients: | TNFi-InR patients: |
| OPAL Beyond (NCT01882439)\(^{[33]}\) | OPAL Beyond (NCT01882439)\(^{[33]}\) | OPAL Beyond (NCT01882439)\(^{[33]}\) |
| LTE | | |
| OPAL Balance (NCT01976364) | | |

| 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) or adalimumab 40 mg SC Q2W (active control; OPAL Broaden only) up to 12 months | Patients who received ≥1 dose of tofacitinib |
|------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------|
| Monotherapy. | Combination therapy with MTX. | Combination therapy with csDMARD (mainly MTX). | Only treatment doses included in this analysis are listed; patients may have received other doses in some studies. |
| 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. |
|                              | RA                                      | PsO                                      | PsA                                      |
|------------------------------|-----------------------------------------|------------------------------------------|------------------------------------------|
| US Corrona registry          | Hydroxychloroquine, leflunomide, MTX,  | Apremilast, cyclosporine, MTX,           | Hydroxychloroquine, leflunomide,         |
| Non-biologic treatments      | sulfasalazine                           | acitretin, hydroxyurea, mycophenolate    | MTX, sulfasalazine, apremilast           |
|                              | MTX, leflunomide, sulfasalazine          | mofetil, sulfasalazine, 6-thioguanine    |                                          |
| Biologic treatments          | Abatacept, adalimumab, anakinra,         | Alefacept, brodalumab, efalizumab,       | Adalimumab, certolizumab pegol,          |
|                              | certolizumab pegol, etanercept,          | etanercept, golimumab, guselkumab,       | etanercept, infliximab, secukinumab,     |
|                              | golimumab, infliximab, rituximab,        | infliximab, ixekizumab, secukinumab,     | ustekinumab                              |
|                              | tocilizumab                              |                                          |                                          |
| MarketScan research database | MTX, leflunomide, sulfasalazine,         | MTX, leflunomide, cyclosporine,          | MTX, leflunomide, sulfasalazine,         |
| Non-biologic treatments      | hydroxychloroquine                       | apremilast                               | apremilast                               |
| Biologic treatments          | Adalimumab, certolizumab pegol,          | Etanercept, adalimumab, infliximab,      | Adalimumab, etanercept, infliximab,      |
|                              | etanercept, golimumab, infliximab,       | certolizumab pegol, ustekinumab,         | golimumab, certolizumab pegol,           |
|                              | abatacept, rituximab, tocilizumab        | secukinumab                              | 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) |
|------------------------------|------------------------------------------|---------------------------------------------|--------------------------------|---------------------------------|
| 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 (%)                  |                                          |                                             |                                |                                |
|       | [N1]       | [1609]       | [1511]       | [2482]       | [2352]       | [2625]       | [2623]       | [1336]       | [1370]       |
|-------|------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| White | 1113 (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/m²), 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)   |
| BMI ≥30 kg/m², n (%) | 524 (32.6) | 584 (38.6)   | 458 (19.5)   | 572 (23.0)   | 982 (37.4)   | 1156 (44.1)  | 0 [1336]     | 0 [1370]     |
| 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)     |

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### Comorbidities, n (%)

| Condition                        | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 | Group 6 | Group 7 | Group 8 |
|----------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|
| 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       | 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          | 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)        | 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) |
| CRP ≥3.0 mg/L, n (%) [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<sup>a</sup>           | 35 (2.2) | 56 (3.7) | 312 (13.2) | 278 (11.2) | 347 (13.2) | 334 (12.7) | 0 | 0 |
| Antidepressants<sup>c</sup>      | 150 (9.3) | 174 (11.5) | 128 (5.4) | 193 (7.8) | 278 (10.6) | 367 (14.0) | 0 | 0 |
| Statins<sup>c</sup>              | 139 (8.6) | 309 (20.4) | 43 (1.8) | 129 (5.2) | 164 (6.2) | 383 (14.6) | 18 (1.3) | 55 (4.0) |
|                     | 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)     |

*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.

*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/m², Day 1 use of oral contraceptives or hormone replacement therapy, Day 1 antidepressant use or Day 1 aspirin use.

*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 | Without baseline cardiovascular risk | With baseline VTE risk | Without baseline VTE risk |
|-------------------|----------------------------------|-------------------------------------|------------------------|--------------------------|
|                   | (N=1022)                         | (N=2641)                            | (N=2744)               | (N=919)                  |
| Average tofacitinib | 5 mg BID (N=286)                 | 10 mg BID (N=736)                  | 5 mg BID (N=634)      | 10 mg BID (N=2007)      |
| Age (years), mean (SD) | 58.0 (6.6)                      | 58.1 (6.3)                          | 39.9 (11.5)            | 39.6 (10.7)              |
| ≥65 years of age, n (%) | 53 (18.5)                        | 113 (15.4)                          | 18 (2.8)               | 36 (1.8)                 |
| ≥50 years of age, n (%) | 286 (100)                        | 736 (100)                           | 100 (15.8)             | 279 (13.9)               |
| Female, n (%)       | 105 (36.7)                       | 209 (28.4)                          | 218 (34.4)             | 585 (29.1)               |
| Race, n (%)         |                                  |                                    |                        |                          |
| White              | 252 (88.1)                       | 625 (84.9)                          | 542 (85.5)             | 1716 (85.5)              |
| Black              | 10 (3.5)                         | 18 (2.4)                            | 17 (2.7)               | 33 (1.6)                 |
| Asian              | 13 (4.5)                         | 47 (6.4)                            | 29 (4.6)               | 160 (8.0)                |

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|                | [N1]  | [N1]  | [N1]  | [2005] | [2005] | [2028] | [2028] |
|----------------|-------|-------|-------|--------|--------|--------|--------|
| 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) |
| 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] |
| 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 |
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.

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/m², Day 1 use of oral contraceptives or hormone replacement therapy, Day 1 antidepressant use or Day 1 aspirin use.

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 | Without baseline cardiovascular risk | With baseline VTE risk | Without baseline VTE risk |
|--------------------------|-----------------------------------|--------------------------------------|------------------------|--------------------------|
|                          | (N=288)                           | (N=495)                              | (N=555)                | (N=228)                  |
| Average tofacitinib      |                                   |                                     |                        |                          |
| 5 mg BID                 | Average tofacitinib 10 mg BID     | 5 mg BID                             | 10 mg BID              |
| (N=180)                  | (N=108)                           | (N=278)                              | (N=217)                |
| Age (years), mean (SD)   | 59.3 (6.2)                        | 58.9 (6.0)                           | 42.6 (9.9)             | 42.6 (10.8)              |
| ≥65 years of age, n (%)  | 36 (20.0)                         | 24 (22.2)                            | 6 (2.2)                | 6 (2.8)                  |
| ≥50 years of age, n (%)  | 180 (100)                         | 108 (100)                            | 58 (20.9)              | 52 (24.0)                |
| Female, n (%)            | 101 (56.1)                        | 55 (50.9)                            | 157 (56.5)             | 115 (53.0)               |
| Race, n (%)              | White 177 (98.3)                  | 103 (95.4)                           | 257 (92.4)             | 202 (93.1)               |
|                          | Black 0                          | 1 (0.9)                              | 0                      | 2 (0.9)                  |
|                          |                                   |                                     |                        |                          |
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| Category                                      | BMI (kg/m²), mean (SD) | BMI ≥30 kg/m², n (%) | Smoking status, n (%) | Comorbidities, n (%) |
|----------------------------------------------|-------------------------|----------------------|-----------------------|----------------------|
| Asian                                        | 1 (0.6)                 | 10 (3.6)             | 102 (56.7)           | 46 (25.6)           |
| Other                                        | 2 (1.1)                 | 11 (4.0)             | 38 (21.1)            | 137 (76.1)          |
| BMI (kg/m²), mean (SD)                       | 31.2 (6.0)              | 31.0 (6.2)           | 137 (60.4)           | 59 (32.2)           |
| BMI ≥30 kg/m², n (%)                         | 97 (53.9)               | 99 (35.6)            | 102 (56.7)           | 46 (25.6)           |
| Smoking status, n (%)                        |                         |                      |                      |                     |
| Never smoked                                 | 102 (56.7)              | 138 (63.6)           | 187 (67.3)           | 137 (76.1)          |
| Smoker                                       | 38 (21.1)               | 27 (12.4)            | 54 (19.4)            | 85 (78.7)           |
| Ex-smoker                                    | 40 (22.2)               | 52 (24.0)            | 37 (13.3)            | 43 (15.5)           |
| Unknown                                      | 0                       | 0                    | 0                    | 0                    |
| Comorbidities, n (%)                         |                         |                      |                      |                     |
| Diabetes                                     | 46 (25.6)               | 52 (15.9)            | 18 (8.3)             | 15 (5.4)            |
| Hypertension                                 | 137 (76.1)              | 147 (44.8)           | 85 (78.7)            | 43 (15.5)           |
| Coronary heart disease                       | 18 (10.0)               | 20 (6.1)             | 13 (12.0)            | 34 (15.5)           |
| Myocardial infarction                        | 4 (2.2)                 | 6 (1.8)              | 2 (0.7)              | 5 (1.8)             |
| History of hyperlipidemia, n (%)             | 64 (35.6)               | 59 (26.0)            | 42 (38.9)            | 31 (14.3)           |
| Previous heart failure, n (%)                | 0                       | 0                    | 0                    | 0                    |
| Previous VTE (DVT or PE), n (%)              | 3 (1.7)                 | 3 (0.9)              | 3 (2.8)              | 4 (1.8)             |
| 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* | 31 (17.2) | 26 (24.1) | 3 (1.1) | 8 (3.7) | 34 (10.4) | 31 (13.7) | 0 | 3 (3.1) |
| Antiplatelet agents* | 27 (15.0) | 19 (17.6) | 4 (1.4) | 4 (1.8) | 31 (9.5) | 23 (10.1) | 0 | 0 |
| OCT or HRT* | 4 (2.2) | 5 (4.6) | 36 (12.9) | 32 (14.7) | 40 (12.2) | 37 (16.3) | 0 | 0 |
| Antidepressants* | 25 (13.9) | 18 (16.7) | 31 (11.2) | 19 (8.8) | 56 (17.1) | 37 (16.3) | 0 | 0 |
| Statins* | 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* | 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) |

*aBaseline cardiovascular risk factors were defined as a patient aged $\geq50$ 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.

*bBaseline VTE risk factors were defined as any patient meeting any of the following criteria at baseline: aged $\geq60$ years, current smoker, previous heart failure, previous VTE (DVT or PE), BMI $\geq30$ kg/m², Day 1 use of oral contraceptives or hormone replacement therapy, Day 1 antidepressant use or Day 1 aspirin use.

*cDay 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.

| Event  | RA total patients with event | RA tofacitinib 5 mg BID | RA tofacitinib 10 mg BID | PsO total patients with event | PsO tofacitinib 5 mg BID | PsO tofacitinib 10 mg BID |
|--------|-----------------------------|--------------------------|--------------------------|-------------------------------|--------------------------|--------------------------|
|        | 250–<60 years of age        | 250–<60 years of age     | Male                      | BMI<30 kg/m²                  | Skeletal                  | Baseline CRP >2.5 mg/L   | Diabetics                | Hypertension              | Previous VTE              | Previous heart failure    | History of coronary heart disease | History of peptic ulcer infection | Day 1 aspirin use | Day 1 antiplatelet use | Day 1 anticoagulant use | Day 1 oral corticosteroid use | Day 1 OCP or HRT use |
| DVT    | 15                          | 6                        | 7                        | 4                             | 8                        | 4                        | 15                       | 3                          | 10                         | 0                        | 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 5 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                         |
|        | Average tofacitinib 10 mg BID|                          |                          |                               |                           |                           |                           |                             |                             |                           |                           |                           |                           |                           |                           |                             |                             |                           |                           |                           |
|        | DVT                         | 1                        | 0                        | 0                            | 0                          | 1                        | 0                        | 0                          | 0                          | 0                        | 0                        | 0                        | 0                        | 0                        | 0                        | 0                        | 0                        | 0                        | 0                         |
|        | PE                          | 2                        | 0                        | 0                            | 1                          | 1                        | 1                        | 1                          | 0                          | 0                        | 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                         |
| Event    | Total patients with event | ≤50 to ≤60 years of age (%) | >60 years of age (%) | Male (%) | BMI <25 kg/m² (%) | Smoker (%) | Baseline CRP ≥1.5 mg/L (%) | Diabetic (%) | 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 antiplatelet 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                      |
| PE       | 7                          | 1                            | 2                    | 3        | 5                 | 2          | 4                          | 1            | 3                 | 1               | 0                          | 0                        | 0                          | 1                | 1                      | 0                      | 2                      |
| ATE      | 17                         | 9                            | 6                    | 14       | 8                 | 9          | 8                          | 6            | 7                 | 0               | 0                          | 1                        | 0                          | 3                | 4                      | 1                      | 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                      |
| PE       | 1                          | 0                            | 1                    | 1        | 1                 | 0          | 1                          | 0            | 1                 | 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                      |
| **Average tofacitinib 10 mg BID** | | | | | | | | | | | | | | | | | | |
| DVT      | 1                          | 0                            | 1                    | 1        | 1                 | 0          | 1                          | 1            | 1                 | 0               | 1                          | 0                        | 0                          | 0                | 0                      | 0                      | 1                      |
| PE       | 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               | 1                          | 1                        | 0                          | 0                | 0                      | 0                      | 0                      |

*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.

*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 All registry (N=11,985) | RA Drug initiators (N=5,190) | PsO All registry (N=3,879) | PsO Drug initiators (N=1,945) | PsA All registry (N=1,926) | PsA 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 (%) | 4,336 (36.2)               | 1,717 (33.1)                 | 641 (16.5)                 | 323 (16.6)                    | 420 (21.8)                | 185 (21.6)                |
| Female, n (%)         | 9,243 (77.1)               | 4,035 (77.8)                 | 1,854 (47.8)               | 964 (49.6)                    | 998 (51.8)                | 460 (53.8)                |
| Race, n (%)           |                            |                              |                            |                               |                           |                           |
| White                | 10,608 (88.5)              | 4,578 (88.2)                 | 3,027 (78.0)               | 1,549 (79.6)                  | 1,754 (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 (%) | 5,059 (42.6)          | 2,318 (45.1)                 | 1,818 (46.9)               | 969 (49.8)                    | 987 (51.2)                | 463 (54.2)                |
| Smoking status, n (%) |                            |                              |                            |                               |                           |                           |
| Never smoked         | 6,034 (51.0)               | 2,499 (48.8)                 | 1,961 (50.6)               | 932 (47.9)                    | 992 (51.5)                | 427 (49.9)                |
| Smoker               | 1,634 (13.8)               | 873 (17.0)                   | 653 (16.8)                 | 350 (18.0)                    | 210 (10.9)                | 105 (12.3)                |
| Ex-smoker            | 4,174 (35.3)               | 1,750 (34.2)                 | 1,236 (31.9)               | 646 (33.2)                    | 678 (35.2)                | 305 (35.6)                |
### Comorbidities, n (%)

| Comorbidities | 0 | 1 | 2 or more |
|---------------|---|---|-----------|
|               | 5886 (49.1) | 2711 (22.2) | 2826 (22.9) |
|               | 1587 (81.6) | 274 (14.1) | 379 (19.7) |
|               | 1394 (72.4) | 153 (7.9) | 784 (91.7) |

### Prior thromboembolism history, n (%)

| Prior thromboembolism | Any VTE | PE | DVT | ATE | Concomitant NSAIDs, n (%) | Prednisone use, n (%) | Anti-platelet agent use, n (%) |
|------------------------|---------|----|-----|-----|---------------------------|----------------------|-------------------------------|
|                        | 195 (1.6) | 79 (0.8) | 137 (1.1) | 567 (4.7) | 6148 (51.3) | 3526 (29.4) | 180 (1.5) |
|                        | 85 (1.6) | 39 (0.8) | 58 (1.1) | 217 (4.2) | 2479 (47.8) | 1700 (32.8) | 91 (1.8) |
|                        | 31 (0.8) | 12 (0.3) | 20 (0.5) | 142 (3.7) | 882 (22.7) | 4 (0.1) | 81 (2.1) |
|                        | 8 (0.4)  | 4 (0.2)  | 5 (0.3)  | 71 (3.7)  | 431 (22.2) | 0 | 43 (2.2) |
|                        | 25 (1.3) | 11 (0.6) | 19 (1.0) | 66 (3.4)  | 813 (42.2) | 258 (13.4) | N/A |
|                        | 15 (1.8) | 5 (0.6)  | 14 (1.6) | 34 (4.0)  | 320 (37.4) | 72 (8.4)  | N/A |

### 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

*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 |         |                |               |
| 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*, n (%)

| Treatment                | csDMARDs | bDMARDs | Tofacitinib | Apremilast | Glucocorticoid use in prior 3 months |
|--------------------------|----------|---------|-------------|------------|-------------------------------------|
| 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 (%)

| Treatment            | Abatacept | Adalimumab | Certolizumab pegol | Etanercept | Golimumab | Infliximab | Rituximab | Secukinumab | Tocilizumab | Tofacitinib | Ustekinumab | cDMARDs |
|----------------------|-----------|------------|--------------------|------------|-----------|-----------|-----------|------------|-------------|-------------|-------------|----------|---------|
| 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 (%)

| Medication       | RA     | PsO    | PsA    |
|------------------|--------|--------|--------|
| 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| 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)  |

*aBased on use within 1 year prior to index date, unless otherwise stated.

*bFemale 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\textsuperscript{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\textsuperscript{b}

|       | n (%) | IR [95% CI] | DVT | PE | VTE (DVT or PE) | ATE |
|-------|-------|-------------|-----|----|----------------|-----|
|       | Exposure, PY |       |     |    |                |     |
| 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] |
| 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] |
| 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] |
| 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] |
| 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] |
| 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] |

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

\textsuperscript{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 Corona 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] | DVT | PE | VTE (DVT or PE) | ATE | Acute myocardial infarction | Stroke |
|-------|-------------|-----|----|-----------------|-----|-----------------------------|--------|
| **Exposure, PY** | | | | | | | |
| **RA** | | | | | | | |
| All DMARD initiators\(^d\) | (N=65 550) | 511 (0.8) | 157 (0.2) | 589 (0.9) | 29 (0.04) | 235 (0.4) | 216 (0.3) |
| bDMARD initiators\(^d\) | (N=47 496) | 376 (0.8) | 117 (0.2) | 433 (0.9) | 20 (0.04) | 163 (0.3) | 143 (0.3) |
| Tofacitinib | (N=5521) | 47 (0.9) | 10 (0.2) | 53 (1.0) | 2 (0.04) | 17 (0.3) | 13 (0.2) |
| **PsO** | | | | | | | |
| All treatment initiators\(^c\) | (N=47 474) | 147 (0.3) | 47 (0.1) | 172 (0.4) | 11 (0.02) | 92 (0.2) | 61 (0.1) |

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Biologic treatment initiators<sup>c</sup>

|                      | N=31 107 |   |   |   |   |   |
|----------------------|----------|----------|----------|----------|----------|----------|
|                      |          |          |          |          |          |          |
| All DMARD initiators |          |          |          |          |          |          |
|                      | 29 948   | 30 008   | 29 932   | 30 036   | 29 999   | 30 007   |
| bDMARD initiators    |          |          |          |          |          |          |
|                      | 11 632   | 11 667   | 11 628   | 11 671   | 11 643   | 11 661   |
|                      | 10 011   | 10 011   | 10 011   | 10 011   | 10 011   | 10 011   |
|                      | 30 959   | 31 018   | 30 969   | 31 031   | 30 999   | 31 007   |

PsA

<sup>d</sup>Exclusion criteria were applied (details in online supplementary material).

<sup>e</sup>Details of treatments are in online supplementary table S2.

<sup>f</sup>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.

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.

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

<sup>b</sup>Exclusion criteria were applied (details in online supplementary material).

<sup>c</sup>Details of treatments are in online supplementary table S2.

<sup>d</sup>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.

<sup>e</sup>Includes: MTX, leflunomide, cyclosporine, apremilast, etanercept, adalimumab, infliximab, certolizumab pegol, ustekinumab, secukinumab; Biologic treatment initiators: etanercept, adalimumab, infliximab, certolizumab pegol, ustekinumab, secukinumab.

<sup>f</sup>Includes: MTX, leflunomide, sulfasalazine, apremilast, adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, ustekinumab, secukinumab; bDMARD initiators: adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, ustekinumab, secukinumab.
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<sup>a</sup> (N=5159) | bDMARD initiators<sup>a</sup> with cardiovascular risk factors<sup>b</sup> (N=2551) | Tofacitinib initiators<sup>c</sup> (N=1130) | Tofacitinib initiators<sup>c</sup> with cardiovascular risk factors<sup>b</sup> (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<sup>2</sup>, 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 (%) | n (%) | n (%) | n (%) | 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) |

aIncluded 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.

bDefined 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.

cRA 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 (EB05–EB95) | ROR (ROR05–ROR95) |
|----------------------------------------|---|-----------------|-----------------|
| 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) |
| Condition                                      | SMQ, narrow | OR (95% CI)   |
|------------------------------------------------|-------------|---------------|
| Coronary artery thrombosis                    | 2           | 0.51 (0.16-1.32) |
| Hepatic artery thrombosis                     | 1           | 0.84 (0.18-2.78) |
| Ischaemic stroke                              | 9           | 0.16 (0.09-0.26) |
| Lacunar infarction                            | 2           | 0.41 (0.13-1.04) |
| Myocardial infarction                         | 269         | 0.83 (0.75-0.92) |
| Peripheral arterial occlusive disease         | 5           | 0.49 (0.23-0.95) |
| Peripheral artery occlusion                   | 1           | 0.2 (0.04-0.66)  |
| Peripheral artery thrombosis                  | 1           | 0.26 (0.06-0.86) |
| Peripheral embolism                           | 1           | 0.33 (0.07-1.08) |
| Renal artery occlusion                        | 1           | 0.84 (0.18-2.77) |
| Renal artery thrombosis                       | 1           | 0.77 (0.16-2.55) |
| Stress cardiomyopathy                         | 7           | 0.36 (0.19-0.64) |
| Thrombotic thrombocytopenic purpura           | 7           | 0.81 (0.43-1.43) |
| Transient ischaemic attack                    | 51          | 0.64 (0.50-0.79) |
| “Embolic and thrombotic events, arterial”     | 422         | 0.58 (0.54-0.63) |
| Antiphospholipid syndrome                     | 1           | 0.27 (0.06-0.90) |
| Brain stem infarction                         | 1           | 0.38 (0.08-1.26) |
| Cardiac ventricular thrombosis                | 2           | 0.76 (0.24-1.97) |
| Cerebellar infarction                         | 1           | 0.26 (0.06-0.86) |
| Cerebellar infarction                         | 14          | 0.21 (0.14-0.32) |
| Cerebral ischaemia                            | 3           | 0.26 (0.10-0.59) |
| Cerebral thrombosis                           | 6           | 0.81 (0.40-1.48) |
| Cerebrovascular accident                      | 303         | 0.83 (0.75-0.91) |
| Diplegia                                      | 4           | 0.69 (0.30-1.41) |
| Disseminated intravascular coagulation        | 15          | 0.5 (0.32-0.74)  |
| Embolic stroke                                | 3           | 0.27 (0.10-0.61) |
| Embolism                                      | 10          | 0.53 (0.31-0.85) |
| Haemorrhagic stroke                           | 7           | 0.26 (0.13-0.45) |
| Hemiparesis                                   | 5           | 0.11 (0.05-0.21) |
| Hemiplegia                                    | 7           | 0.32 (0.17-0.56) |
| Infarction                                    | 9           | 0.48 (0.27-0.80) |
| Intestinal infarction                         | 1           | 0.48 (0.10-1.58) |
| Intracardiac mass                             | 1           | 0.8 (0.17-2.62)  |
| Intracardiac thrombus                         | 2           | 0.28 (0.09-0.73) |
| Monoplegia                                    | 5           | 0.43 (0.20-0.83) |
| Paraplegia                                    | 3           | 0.42 (0.16-0.95) |
| Paresis                                       | 1           | 0.21 (0.05-0.70) |
### Prosthetic cardiac valve thrombosis

| Event Type                                      | N  | ROR (CI)           | EB5, lower 5% | EB95, upper 5% |
|------------------------------------------------|----|--------------------|---------------|---------------|
| Prosthetic cardiac valve thrombosis            | 1  | 1.03 (0.22-3.40)   |               |               |
| Renal vascular thrombosis                      | 1  | 0.91 (0.19-2.99)   |               |               |
| Splenic infarction                             | 1  | 0.27 (0.06-0.89)   |               |               |
| Thrombosis                                     | 173| 0.94 (0.82-1.06)   |               |               |
| Vascular stent insertion                       | 1  | 0.98 (0.21-3.22)   |               |               |

‘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) |
**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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