SUPPLEMENTARY FILE 1

SUPPLEMENTARY METHODS

Statistical analyses

Below is the full categorical listing of hypotheses tested. Notably, each of these represents multiple comparisons to be made via contrast between groups and/or treatment arms, and potentially by case status, treatment arm, or visit (baseline or month 12). Categorically, each continuous biomarker was tested for the following:

- *Hypothesis A*: Whether the biomarker is prospectively associated with incident venous thromboembolism (VTE) events at baseline (or on subsequent events at month 12) in at least one arm, but particularly within the tofacitinib 10 mg BID arm, which would be necessary for the biomarker to be useful to identify patients at risk. This was assessed via survival analysis (Cox proportional hazards regression).
- *Hypothesis B*: Whether the biomarker is prospectively associated with incident VTE events differently between treatment arms (at baseline or at month 12 on subsequent events), particularly with the magnitude of association elevated in the tofacitinib 10 mg BID arm compared with the tumour necrosis factor inhibitor (TNFi) arm. This was assessed by testing for an interaction between treatment arm and the baseline biomarker value on incident VTE via survival analysis (via the Cox proportional hazards regression model used for Hypothesis A).
- *Hypothesis C*: Whether the biomarker happens to differ at baseline between treatment arms, particularly if it happens to differ in the direction of an association with incident VTE events (from Hypotheses A and B) more strongly in the tofacitinib 10 mg BID arm than in the TNFi arm. This involved testing for a treatment difference in baseline

values of the biomarker (via simple linear regression), and then comparing with the results from Hypotheses A and B.

- *Hypothesis D*: Whether there is a treatment effect on changes in the biomarker from baseline. This was assessed by testing for a treatment effect on the change from baseline at month 12 of the biomarker by simple linear regression, both in all patients and separately in cases and controls. (A treatment-specific risk biomarker may give a false signal in cases by ascertainment, but treatment-related changes in controls will unambiguously reflect a treatment effect.) In the D-dimer dataset, as data were available from the end-of-study visit, this time point was assessed by a separate longitudinal mixed model in controls only.
- *Hypothesis E*: Whether the change from baseline at month 12 of the biomarker is prospectively associated with incident VTE events in at least one arm, but particularly within the tofacitinib 10 mg BID arm and, in particular, if matching the direction of treatment-related changes from Hypothesis D. This was assessed via survival analysis (Cox proportional hazards regression).
- *Hypothesis F*: Whether the change from baseline at month 12 of the biomarker is prospectively associated with incident VTE events differently between arms, but particularly within the tofacitinib 10 mg BID arm and, in particular, if matching the direction of treatment-related changes from Hypothesis D. This was assessed via the interaction term between treatment arm and the biomarker change from baseline at month 12 in the survival analysis (Cox proportional hazards regression using model from Hypothesis E).
- *Hypothesis G* (not applicable in the D-dimer dataset): A check that the biomarker levels are different between tofacitinib 10 mg BID cases and strongly matched 2:1 TNFi controls (the secondary cohort), validating that any differences observed in

Hypotheses A through F were not due to ascertainment bias from unmatched risk factors.

As a result of the large number of biomarkers assessed and the many relevant contrasts within each hypothesis, biomarkers were filtered for significance (and hence further examination) based on global testing (across the entire cohort) of full statistical models. Generally, these were assessed by analysis of variance (ANOVA) using model comparison. This approach allowed a single P value to assess simultaneously either a uniform prospective association of the biomarker with incident VTE events, or an interaction between treatment arm and the biomarker association with VTE incident events, or any combination of the 2 (see online supplemental table 3, Hypothesis A.0). Similarly, when biomarker levels or changes of biomarker levels are the endpoint, this permitted simultaneous evaluation of a treatment effect or a treatment-by-case-status interaction. This approach allowed for a substantial reduction in the number of tests used to identify biomarkers for follow-up and allowed for a multiple-testing procedure that considered only the number of biomarkers for each test.

Five global tests were used to filter biomarkers for further examination; these are marked as ‘primary test’ in online supplemental table 3 and are listed together with ‘subtests’ (which include all contrasts evaluated within the corresponding primary test). Hypotheses and contrasts not included in online supplemental table 3 are subsets of those shown (eg, Hypothesis B.0 is a sub-hypothesis of Hypothesis A.0) or can be partially inferred by the displayed contrasts.

Biomarkers identified as significant by any of the five primary tests described above were evaluated further for potential use as a biomarker to identify patients at risk of VTE events if prescribed tofacitinib, or for potential utility in explaining increased VTE risk in the

tofacitinib treatment arms relative to TNFi. This evaluation was conducted by employing all the tests and subtests enumerated in online supplemental table 3. The criteria for being of potential use for either of the above purposes included meeting any one of the following:

1. If the biomarker was prospectively associated (false discovery rate [FDR]≤0.05 in both the contrast and the corresponding primary test) with incident risk of VTE or pulmonary embolism (PE) events within the tofacitinib 10 mg BID arm, either at baseline or at month 12 on subsequent events (subtests of Hypothesis A within tofacitinib 10 mg BID; online supplemental table 3).

2. If the change from baseline at month 12 of the biomarker was prospectively associated (FDR≤0.05 in both the contrast and the corresponding primary test) with incident risk of VTE or PE events within the tofacitinib 10 mg BID arm at month 12 on subsequent events (subtest of Hypothesis E within tofacitinib 10 mg BID; online supplemental table 3).

3. If there was a significant difference in baseline levels between treatment arms (FDR ≤0.05 for Hypothesis C.0; online supplemental table 3) and the direction of a nominally significant (P≤0.05) difference between the tofacitinib 10 mg BID and TNFi arms in matched controls matches the direction of a filtered nominally significant association (primary test FDR≤0.05, contrast P≤0.05) with incident VTE or PE events in the tofacitinib 10 mg BID arm. This association with events was assessed as described in point 1 or point 2 above; that is, either prospectively at baseline, prospectively at month 12, or prospectively for change from baseline at month 12.

4. If there was a significant difference in change from baseline at month 12 levels between treatment arms (FDR≤0.05 for Hypothesis D.0; online supplemental table 3), and the direction of a nominally significant (P≤0.05) difference between the tofacitinib 10 mg BID and TNFi arms in matched controls matches the direction of a filtered nominally significant association (primary test FDR≤0.05, contrast P≤0.05) with incident PE or VTE in the tofacitinib 10 mg BID arm. Association with incident events was assessed as described in point 3 above.

Any biomarker passing FDR≤0.05 for a primary test and satisfying any of the four criteria above is discussed in this manuscript. Furthermore, any biomarker meeting the aforementioned criteria was also examined for significant effects between the tofacitinib 5 mg BID arm and TNFi treatment arms, using the same tests that were applied to the tofacitinib 10 mg BID treatment arm.

SUPPLEMENTARY RESULTS

Risk factor analyses

Analyses were performed to explore the potential incremental value of D-dimer monitoring in patients treated with tofacitinib with known VTE risk factors. Of the patients enrolled in ORAL Surveillance who were eligible for D-dimer analysis, the majority had at least one VTE risk factor (namely, previous VTE, major surgery, immobilization, myocardial infarction within the previous 3 months, heart failure, use of combined hormonal contraceptives or hormone replacement therapy, thrombophilia [including factor V Leiden mutation, and antithrombin, protein C, and protein S deficiency], malignancy, advanced age, obesity [body mass index (BMI) ≥30 kg/m^2], diabetes, hypertension, or smoking). This is primarily attributable to a study population that was, by design, older (age ≥50 years) with at

least one additional cardiovascular risk factor. All VTE events occurred in patients with at least one VTE risk factor.

The number of cases in patients with and without the risk factors of age ≥65 years, BMI ≥30 kg/m^2, history of smoking, and history of hypertension was assessed by D-dimer levels <2×ULN and ≥2×ULN (other risk factors were investigated but not presented due to low event numbers).

In patients ≥65 years at baseline, in the tofacitinib 10 mg BID arm, a higher proportion of patients with D-dimer levels ≥2×ULN developed VTE events compared with those with lower D-dimer levels and also compared with patients receiving TNFi with high D-dimer levels (online supplemental table 8). A similar trend, but less evident, was observed with tofacitinib 5 mg BID. The difference was even more evident when month 12 levels were assessed. These effects, both at baseline and at month 12, were less evident in patients <65 years.

Similar general trends were also observed when the dichotomous D-dimer cutoff, either at baseline or at month 12, was used to analyse BMI (online supplemental table 9), smoking history (online supplemental table 10), or hypertension (online supplemental table 11) as risk factors for VTE events. However, these observations should be interpreted with caution because of the low number of VTE cases overall.

Table S 1 Biomarkers assessed and assays used

Biomarker evaluated	Test assay name (supplier, catalogue no.)	Mode of action/pathway involved
Tier 1		
D-dimer	Tina-quant D-Dimer (Roche Diagnostics, 3001245322)	Formed as a product of fibrin degradation; present in blood after blood clot is degraded by fibrinolysis (19)
CRP	Cardiophase hsCRP (Siemens Healthineers, OQIY21)	Marker of systemic inflammation, regulated by IL-6, which signals through JAKs (26,30)
TPO	U-PLEX Human TPO ECL Assay (Meso Scale Diagnostics, K151VKK)	Growth factor that is central to the regulation of platelet levels (31); platelets are produced by megakaryocytes that require TPO signalling via JAK2-dependent MPL receptors for development and maturation (27)
Tier 2		
Factor VIII	VisuLize FVIII ELISA (Affinity Biologicals, FVIII-AG)	Blood clotting protein in the coagulation cascade (32)
TAT	Enzygnost TAT Micro ELISA (Siemens Healthcare Diagnostic Products, 10446632)	Formed when thrombin concentrations are elevated (33)
TFPI	Human TFPI Quantikine ELISA (R&D Systems, DTFP10)	Reversibly inhibits FXa (34)
PAI-1	Human PAI-1 Quantikine ELISA (R&D Systems, DSE100)	Inhibits fibrinolysis (35)
Protein C	ZYMUTEST Protein C Antigen (HYPHEN BioMed, RK027A)	Activated protein C neutralizes FVa and FVIIIa (36,37)

Biomarker evaluated	Test assay name (supplier, catalogue no.)	Mode of action/pathway involved
AT	Human ATIII Quantikine ELISA (R&D Systems, DSPC10)	Inhibits thrombin and FXa (38)
ApoCIII	Human Apolipoprotein CIII ELISA (Abcam, ab154131)	Marker of triglyceride-rich lipoproteins; elevated levels predispose to development of atherosclerotic disease (39)
Leptin	Human Leptin ECL Assay (Meso Scale Diagnostics, K151BYC)	Adipokine; mediates prothrombotic risk in obesity by promoting platelet adhesion/activation/aggregation (40)
Tiers 3 and 4		
Proteomic arrays (276 markers)	Olink Cardiometabolic (Olink Proteomics, 95360) • *Tier 3:* CCL14, CCL18, CCL5, F7, F11, GP1BA, ICAM1, ICAM3, OSMR, PLA2G7, VCAM1, PROC, CST3, MBL2, LCN2, and SELL • *Tier 4:* All other markers not named above Olink Cardiovascular II (Olink Proteomics, 95500) • *Tier 3:* ADAM-TS13, ANGPT1, CCL17, CCL3, CD40-L, CXCL1, IL-6, LEP, PDGF subunit B, TF, THBS2, TM, THPO, TIE2, TRAIL-R2, VEGF-D, BNP, PTX3, LPL, IL-18, IL-27, and RAGE • *Tier 4:* All markers not named above Olink Cardiovascular III (Olink Proteomics, 95611) • *Tier 3:* CCL15, CCL16, CCL24, CXCL16, EGFR, KLK6, PAI, PDGF subunit A, SELE, SELP, TFPI, tPA, uPA, VWF, OPG, Gal-3, MCP-1, MPO, OPN, CD163, PON3, TNFR1, and TNFR2	Proteins including cytokines and chemokines based on known role in platelet activation, the coagulation cascade, endothelial function, or inflammation (41)

Biomarker evaluated	Test assay name (supplier, catalogue no.)	Mode of action/pathway involved
	• *Tier 4:* All markers not named above	
Genetic biomarkers		
Factor V Leiden (FVL/F5 R506Q)	TaqMan assay (Thermo Fisher Scientific)	Mutation associated with increased risk of VTE (11)
Prothrombin (F2, G20210A)	TaqMan assay (Thermo Fisher Scientific)	Mutation associated with increased risk of VTE (12)
JAK2 V617F mutations	TaqMan assay (Thermo Fisher Scientific)	Mutation associated with myeloproliferative disorders (42); known association with VTE (13)
Antibody biomarkers		
ACA IgG	QUANTA Lite ACA IgG III ELISA (Inova Diagnostics, 708625.10)	Acquired thrombophilia (14)
ACA IgM	QUANTA Lite ACA IgM III ELISA (Inova Diagnostics, 708630.10)	Acquired thrombophilia (14)
Anti-β2GP1 IgG	QUANTA Lite β2GP1 IgG ELISA (Inova Diagnostics, 708665.10)	Acquired thrombophilia (14)
Anti-β2GP1 IgM	QUANTA Lite β2GP1 IgM ELISA (Inova Diagnostics, 708670.10)	Acquired thrombophilia (14)

ACA, anticardiolipin antibody; ADAM-TS13, a disintegrin and metalloproteinase with thrombospondin motifs 13; ANGPT1, angiopoietin-1; apoCIII, apolipoprotein C-III; AT, antithrombin; ATIII, antithrombin-III; β2GP1, beta-2-glycoprotein 1; BNP, B-type natriuretic peptide; CCL, Cys-Cys motif chemokine ligand; CD40-L, cluster of differentiation 40 ligand; CD163, cluster of differentiation 163; CRP, C-reactive protein; CST3, cystatin-3; CXCL, C-X-C motif chemokine ligand; EGFR, epidermal growth

factor receptor; ELISA, enzyme-linked immunosorbent assay; F2, factor II; F7, factor VII; F11, factor XI; FVa, factor Va; FVIII, factor VIII; FVIIIa, factor VIIIa; FXa, factor Xa; Gal-3, galectin-3; GP1BA, platelet glycoprotein Ib alpha chain; hsCRP, high-sensitivity C-reactive protein; ICAM, intercellular adhesion molecule; IgG, immunoglobulin G; IgM, immunoglobulin M; IL, interleukin; JAK, Janus kinase; KLK6, kallikrein-6; LCN2, neutrophil gelatinase-associated lipocalin; LEP, leptin; LPL, lipoprotein lipase; MBL2, mannose-binding protein C; MCP-1, monocyte chemotactic protein-1; MPL, myeloproliferative leukaemia protein; MPO, myeloperoxidase; OPG, osteoprotegerin; OPN, osteopontin; OSMR, oncostatin-M-specific receptor subunit beta; PAI, plasminogen activator inhibitor 1; PDGF, platelet-derived growth factor; PLA2G7, platelet-activating factor acetylhydrolase; PON3, paraoxonase 3; PROC, vitamin K-dependent protein C; PTX3, pentraxin-related protein 3; RAGE, advanced glycosylation end product-specific receptor; SELE, E-selectin; SELL, L-selectin; SELP, P-selectin; TAT, thrombin-antithrombin complex; TF, tissue factor; TFPI, tissue factor pathway inhibitor; THBS2, thrombospondin-2; THPO/TPO, thrombopoietin; TIE2, angiopoietin-1 receptor; TM, thrombomodulin; TNFR, tumour necrosis factor receptor; tPA, tissue-type plasminogen activator; TRAIL-R2, TNF-related apoptosis-inducing ligand receptor 2; uPA, urokinase-type plasminogen activator; VCAM1, vascular cell adhesion protein 1; VEGF-D, vascular endothelial growth factor D; VTE, venous thromboembolism; VWF, von Willebrand factor.

Table S 2 Sample availability by event type (early or late), time point, and treatment arm

Data source	Treatment arm	No VTE/PE (controls), n (%)	Early VTE event (before month 12), n (%)	Late VTE event (after month 12), n (%)	Early PE event (before month 12), n (%)	Late PE event (after month 12), n (%)
Exploratory biomarker dataset						
Total patients	Tofacitinib 5 mg BID	57 (25)	4 (21)	10 (26)	2 (15)	7 (37)
	Tofacitinib 10 mg BID*	117 (51)	10 (53)	20 (53)	8 (62)	12 (63)
	TNFi	54 (24)	5 (26)	8 (21)	3 (23)	0 (0)
Baseline sample	Tofacitinib 5 mg BID	57 (25)	4 (21)	10 (26)	2 (15)	7 (37)
	Tofacitinib 10 mg BID*	117 (51)	10 (53)	20 (53)	8 (62)	12 (63)
	TNFi	54 (24)	5 (26)	8 (21)	3 (23)	0 (0)
Baseline and month 12 samples	Tofacitinib 5 mg BID	57 (25)	3 (23)	9 (25)	1 (11)	6 (35)
	Tofacitinib 10 mg BID*	117 (51)	9 (69)	19 (53)	7 (78)	11 (65)
	TNFi	54 (24)	1 (8)	8 (22)	1 (11)	0 (0)
D-dimer dataset						
Total patients	Tofacitinib 5 mg BID	1392 (34)	5 (28)	11 (28)	2 (17)	7 (30)
	Tofacitinib 10 mg BID*	1357 (33)	10 (56)	23 (57)	8 (67)	15 (65)
	TNFi	1380 (33)	3 (17)	6 (15)	2 (17)	1 (4)

Data source	Treatment arm	No VTE/PE (controls), n (%)	Early VTE event (before month 12), n (%)	Late VTE event (after month 12), n (%)	Early PE event (before month 12), n (%)	Late PE event (after month 12), n (%)
Baseline sample	Tofacitinib 5 mg BID	1243 (34)	4 (24)	10 (27)	2 (17)	7 (33)
	Tofacitinib 10 mg BID*	1194 (32)	10 (59)	21 (57)	8 (67)	13 (62)
	TNFi	1241 (34)	3 (18)	6 (16)	2 (17)	1 (5)
Baseline and month 12 samples	Tofacitinib 5 mg BID	1057 (34)	–	6 (21)	–	5 (29)
	Tofacitinib 10 mg BID*	985 (32)	–	18 (62)	–	11 (65)
	TNFi	1042 (34)	–	5 (17)	–	1 (6)
Baseline and end-of-study samples†	Tofacitinib 5 mg BID	427 (34)	–	–	–	–
	Tofacitinib 10 mg BID*	382 (30)	–	–	–	–
	TNFi	444 (35)	–	–	–	–

Percentage values refer to the proportion of patients in each treatment arm for a given category.

*For patients assigned to receive tofacitinib at a dose of 10 mg BID who had their dose reduced to 5 mg BID, the data collected after patients had been switched to 5 mg BID were counted in the arm receiving 10 mg BID. †No end-of-study samples from VTE/PE cases were analysed due to the confounding effect of anti-coagulant therapy.

BID, twice daily; PE, pulmonary embolism; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism.

Table S 3 Primary statistical tests and hypotheses

Hypothesis reference	Hypothesis description	Sub-hypothesis name†	Role	Sub-hypothesis description	Additional subsetting	Statistical method
A	Biomarker X is prospectively associated with incident events in at least one treatment arm	A.0.bl Overall, possible interaction	Primary test	Any combination of a uniform effect and a differing effect by arm	Baseline	Cox regression (D-dimer and full clinical datasets) Cox regression with IPW (exploratory biomarker dataset)
		A.1.bl Tofacitinib 5 mg	Subtest	Test association (HR per unit X) on incident events in each arm		
		A.1.bl Tofacitinib 10 mg	Subtest			
		A.1.bl TNFi	Subtest			
		A.0.12m Overall, possible interaction	Primary test	Any combination of a uniform effect and a differing effect by arm	Month 12	
		A.1.12m Tofacitinib 5 mg	Subtest	Test association (HR per unit X) on incident events in each arm		
		A.1.12m Tofacitinib 10 mg	Subtest			
		A.1.12m TNFi	Subtest			
C	Baseline levels of biomarker X differed by treatment arm	C.0 Overall	Primary test	Test difference in baseline X across all arms	Baseline	Linear regression
		C.2.ctrl Tofacitinib 5 mg vs TNFi	Subtest	Test difference in baseline X between 2 arms in controls only		
		C.2.ctrl Tofacitinib 10 mg vs TNFi	Subtest			
		C.3.case Tofacitinib 5 mg vs TNFi	Subtest	Test difference in baseline X between 2 arms in cases only		
		C.3.case Tofacitinib 10 mg vs TNFi	Subtest			

Hypothesis reference	Hypothesis description	Sub-hypothesis name†	Role	Sub-hypothesis description	Additional subsetting	Statistical method
D	Biomarker X experienced treatment-dependent changes	D.0 Overall	Primary test	Test difference in CFB.X across all arms	Only CFB.X at month 12 (for controls in D-dimer dataset, CFB.X at month 12 and EOS)	Linear regression
		D.2.ctrl Tofacitinib 5 mg vs TNFi	Subtest	Test difference in CFB.X between 2 arms in controls only		
		D.2.ctrl Tofacitinib 10 mg vs TNFi	Subtest			
		D.3.case Tofacitinib 5 mg vs TNFi	Subtest	Test difference in CFB.X between 2 arms in cases only		
		D.3.case Tofacitinib 10 mg vs TNFi	Subtest			
E	CFB.X is prospectively associated with incident events in at least one treatment arm	E.0 Overall	Primary test	Any association on incident events from CFB.X in addition to from baseline X	Only CFB.X at month 12	Cox regression (D-dimer and full clinical datasets) Cox regression with IPW (exploratory biomarker dataset)
		E.1 Tofacitinib 5 mg	Subtest	Test association (HR per unit CFB.X) on incident events in each arm		
		E.1 Tofacitinib 10 mg	Subtest			
		E.1 TNFi	Subtest			

[†]Hypotheses with names of the form *.*.bl were assessed at baseline, whereas those with names of the form *.*.12m were assessed at month 12. Hypotheses of the form *.0.* were global tests from full statistical models run across the cohort, possibly assessing multiple effects at once, and were typically assessed via comparison with a null model via ANOVA. Hypotheses of the form *.1.*, *.2.*, etc. were subtests of the corresponding *.0.* hypotheses, and were assessed by contrasts within that full model. Hypotheses and contrasts not shown in the table either are subsets of those shown (eg, Hypothesis B.0 is a sub-hypothesis of Hypothesis A.0) or can be partially inferred by the displayed contrasts.

ANOVA, analysis of variance; BID, twice daily; bl, baseline; CFB, change from baseline; ctrl, control; EOS, end of study; HR, hazard ratio; IPW, inverse probability weighting; TNFi, tumour necrosis factor inhibitor.

Table S 4 Patient demographics and baseline disease characteristics (exploratory biomarker dataset*)

Biomarker subpopulation (N=285)	Matched controls (n=228)			VTE cases (n=57)		
	Tofacitinib 5 mg BID (N=57)	Tofacitinib 10 mg BID (N=117)†	TNFi (N=54)	Tofacitinib 5 mg BID (N=14)	Tofacitinib 10 mg BID (N=30)†	TNFi (N=13)
Age (years), mean (SD)	65.8 (6)	63.2 (6)	61.1 (4)	65.8 (7)	64 (6)	61.1 (5)
Female sex, n (%)	47 (82.5)	72 (61.5)	53 (98.1)	12 (85.7)	18 (60)	13 (100)
White race, n (%)	47 (82.5)	91 (77.8)	45 (83.3)	14 (100)	25 (83.3)	11 (84.6)
BMI (kg/m^2), mean (SD)	29.6 (6)	30.3 (6)	29.9 (7)	31.5 (8)	33.5 (7)	35.2 (10)
Current smoker, n (%)	20 (35.1)	27 (23.1)	12 (22.2)	4 (28.6)	4 (13.3)	1 (7.7)
Hypertension at baseline, n (%)	37 (64.9)	81 (69.2)	38 (70.4)	11 (78.6)	23 (76.7)	12 (92.3)
Diabetes mellitus at baseline, n (%)	8 (14.0)	30 (25.6)	7 (13.0)	1 (7.1)	6 (20.0)	3 (23.1)
Coronary heart disease at baseline, n (%)	4 (7.0)	7 (6.0)	3 (5.6)	1 (7.1)	3 (10.0)	1 (7.7)
Extra-articular disease‡, n (%)	22 (38.6)	43 (36.8)	20 (37)	3 (21.4)	11 (36.7)	5 (38.5)
Baseline HDL-C <40 mg/dL, n (%)	5 (8.8)	19 (16.2)	5 (9.3)	0 (0)	6 (20.0)	1 (7.7)
Previous VTE (DVT or PE), n (%)	3 (5.3)	5 (4.3)	0 (0)	1 (7.1)	3 (10.0)	3 (23.1)
Oestrogen replacement at baseline, n (%)	2 (3.5)	2 (1.7)	2 (3.7)	2 (14.3)	1 (3.3)	0 (0)

Biomarker subpopulation (N=285)	Matched controls (n=228)			VTE cases (n=57)		
	Tofacitinib 5 mg BID (N=57)	Tofacitinib 10 mg BID (N=117)†	TNFi (N=54)	Tofacitinib 5 mg BID (N=14)	Tofacitinib 10 mg BID (N=30)†	TNFi (N=13)
Aspirin at baseline, n (%)	14 (24.6)	29 (24.8)	3 (5.6)	1 (7.1)	11 (36.7)	2 (15.4)
Genotyping	n=47	n=91	n=45	n=14	n=25	n=11
F2 risk allele carriers, n (%)	0	3 (3.3)	0	2 (14.3)	2 (8.0)	0
F5 risk allele carriers, n (%)	3 (6.4)	1 (1.1)	1 (2.2)	0	5 (20.0)	2 (18.2)

*Data obtained from the unplanned interim 22 February 2019, data cut; data had not been subject to all source verification and adjudication activities associated with a final dataset in a prospectively defined interim analysis or at study completion. †For patients assigned to receive tofacitinib at a dose of 10 mg BID who had their dose reduced to 5 mg BID, the data collected after patients had been switched to 5 mg BID were counted in the arm receiving 10 mg BID. ‡Includes nodules, Sjögren's syndrome, anaemia of chronic disease, pulmonary manifestations, and other. BID, twice daily; BMI, body mass index; DVT, deep vein thrombosis; F2, factor II; F5, factor V; HDL-C, high-density lipoprotein cholesterol; n, number of patients meeting baseline criteria; N, number of patients in each treatment arm in the biomarker subpopulation; PE, pulmonary embolism; SD, standard deviation; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism.

Table S 5 Key statistical comparisons* for Tier 1 and 2 biomarkers and VTE (exploratory biomarker dataset)

Biomarker name	Sub-hypothesis name	P-value type	Effect size type	Effect size	95% CI	P value
Tier 1						
CRP (assessed in the full clinical dataset)	A.1.bl Tofacitinib 5 mg	Contrast (X)	HR	0.769	0.476, 1.242	0.283
	A.1.bl Tofacitinib 10 mg			0.962	0.684, 1.352	0.822
	A.1.bl TNFi			0.609	0.349, 1.064	0.081
	A.1.12m Tofacitinib 5 mg			1.222	0.735, 2.033	0.439
	A.1.12m Tofacitinib 10 mg			1.160	0.830, 1.620	0.385
	A.1.12m TNFi			1.142	0.576, 2.261	0.704
	B.0.bl Overall	Interaction	NA			0.371
	B.0.12m Overall					0.982
	D.2.ctrl Tofacitinib 5 mg vs TNFi	Contrast (Arm)	DeltaLog	−0.173	−0.266, −0.080	2.70e-04
	D.2.ctrl Tofacitinib 10 mg vs TNFi			−0.324	−0.418, −0.23	1.51e-11
	D.3.case Tofacitinib 5 mg vs TNFi			−0.182	−1.329, 0.964	0.755
	D.3.case Tofacitinib 10 mg vs TNFi			−0.365	−1.389, 0.659	0.485
	E.1 Tofacitinib 5 mg	Contrast (CFB)	HR	1.196	0.704, 2.032	0.508
	E.1 Tofacitinib 10 mg			1.172	0.831, 1.655	0.366
	E.1 TNFi			1.276	0.620, 2.625	0.508
TPO	A.1.bl Tofacitinib 5 mg	Contrast (X)	HR	1.259	0.630, 2.514	0.514
	A.1.bl Tofacitinib 10 mg			1.555	0.913, 2.649	0.105
	A.1.bl TNFi			1.108	0.578, 2.124	0.758
	A.1.12m Tofacitinib 5 mg			1.313	0.668, 2.581	0.429
	A.1.12m Tofacitinib 10 mg			1.752	1.160, 2.645	0.008
	A.1.12m TNFi			0.838	0.419, 1.678	0.618
	B.0.bl Overall	Interaction	NA			0.582
	B.0.12m Overall					0.175
	D.2.ctrl Tofacitinib 5 mg vs TNFi	Contrast (Arm)	DeltaLog	0.096	−0.013, 0.204	0.085
	D.2.ctrl Tofacitinib 10 mg vs TNFi			0.083	−0.012, 0.177	0.087
	D.3.case Tofacitinib 5 mg vs TNFi			0.242	−0.035, 0.518	0.086
	D.3.case Tofacitinib 10 mg vs TNFi			0.319	0.080, 0.559	0.009

Biomarker name	Sub-hypothesis name	P-value type	Effect size type	Effect size	95% CI	P value
	E.1 Tofacitinib 5 mg	Contrast (CFB)	HR	1.195	0.546, 2.615	0.656
	E.1 Tofacitinib 10 mg			1.571	0.914, 2.700	0.102
	E.1 TNFi			0.587	0.157, 2.195	0.428
Tier 2						
ApoCIII	A.1.bl Tofacitinib 5 mg	Contrast (X)	HR	0.809	0.458, 1.429	0.465
	A.1.bl Tofacitinib 10 mg			1.090	0.821, 1.447	0.552
	A.1.bl TNFi			1.164	0.690, 1.965	0.569
	A.1.12m Tofacitinib 5 mg			0.885	0.415, 1.891	0.753
	A.1.12m Tofacitinib 10 mg			0.915	0.594, 1.407	0.684
	A.1.12m TNFi			1.115	0.469, 2.652	0.805
	B.0.bl Overall	Interaction	NA			0.551
	B.0.12m Overall					0.901
	D.2.ctrl Tofacitinib 5 mg vs TNFi	Contrast (Arm)	DeltaLog	0.083	−0.058, 0.223	0.248
	D.2.ctrl Tofacitinib 10 mg vs TNFi			0.057	−0.064, 0.178	0.358
	D.3.case Tofacitinib 5 mg vs TNFi			0.056	−0.301, 0.413	0.759
	D.3.case Tofacitinib 10 mg vs TNFi			−0.042	−0.352, 0.268	0.791
	E.1 Tofacitinib 5 mg	Contrast (CFB)	HR	1.223	0.588, 2.543	0.590
	E.1 Tofacitinib 10 mg			0.860	0.367, 2.018	0.729
	E.1 TNFi			1.263	0.503, 3.172	0.619
AT	A.1.bl Tofacitinib 5 mg	Contrast (X)	HR	0.616	0.225, 1.688	0.346
	A.1.bl Tofacitinib 10 mg			0.883	0.61, 1.279	0.510
	A.1.bl TNFi			0.624	0.283, 1.373	0.241
	A.1.12m Tofacitinib 5 mg			1.185	0.733, 1.915	0.488
	A.1.12m Tofacitinib 10 mg			0.983	0.594, 1.626	0.946
	A.1.12m TNFi			1.006	0.598, 1.691	0.982
	B.0.bl Overall	Interaction	NA			0.444
	B.0.12m Overall					0.823
	D.2.ctrl Tofacitinib 5 mg vs TNFi	Contrast (Arm)	DeltaLog	0.024	−0.06, 0.108	0.577
	D.2.ctrl Tofacitinib 10 mg vs TNFi			0.009	−0.064, 0.083	0.799
	D.3.case Tofacitinib 5 mg vs TNFi			0.031	−0.182, 0.244	0.776
	D.3.case Tofacitinib 10 mg vs TNFi			0.011	−0.174, 0.195	0.910

Biomarker name	Sub-hypothesis name	P-value type	Effect size type	Effect size	95% CI	P value
	E.1 Tofacitinib 5 mg	Contrast (CFB)	HR	1.210	0.791, 1.85	0.379
	E.1 Tofacitinib 10 mg			1.114	0.677, 1.833	0.670
	E.1 TNFi			1.079	0.632, 1.841	0.780
Factor VIII	A.1.bl Tofacitinib 5 mg	Contrast (X)	HR	0.766	0.500, 1.174	0.221
	A.1.bl Tofacitinib 10 mg			1.226	0.883, 1.703	0.224
	A.1.bl TNFi			1.446	0.853, 2.451	0.170
	A.1.12m Tofacitinib 5 mg			0.772	0.521, 1.144	0.197
	A.1.12m Tofacitinib 10 mg			1.097	0.699, 1.721	0.688
	A.1.12m TNFi			0.943	0.647, 1.376	0.762
	B.0.bl Overall	Interaction	NA			0.188
	B.0.12m Overall					0.649
	D.2.ctrl Tofacitinib 5 mg vs TNFi	Contrast (Arm)	DeltaLog	−0.090	−0.235, 0.055	0.226
	D.2.ctrl Tofacitinib 10 mg vs TNFi			−0.301	−0.428, −0.174	3.31e-06
	D.3.case Tofacitinib 5 mg vs TNFi			−0.093	−0.458, 0.271	0.616
	D.3.case Tofacitinib 10 mg vs TNFi			−0.180	−0.496, 0.136	0.263
	E.1 Tofacitinib 5 mg	Contrast (CFB)	HR	0.736	0.282, 1.925	0.532
	E.1 Tofacitinib 10 mg			1.089	0.439, 2.703	0.855
	E.1 TNFi			0.627	0.225, 1.752	0.373
Leptin	A.1.bl Tofacitinib 5 mg	Contrast (X)	HR	2.064	0.893, 4.770	0.090
	A.1.bl Tofacitinib 10 mg			1.500	1.029, 2.187	0.035
	A.1.bl TNFi			2.495	0.956, 6.508	0.062
	A.1.12m Tofacitinib 5 mg			2.986	1.172, 7.608	0.022
	A.1.12m Tofacitinib 10 mg			1.123	0.721, 1.75	0.607
	A.1.12m TNFi			2.431	1.02, 5.794	0.045
	B.0.bl Overall	Interaction	NA			0.357
	B.0.12m Overall					0.045
	D.2.ctrl Tofacitinib 5 mg vs TNFi	Contrast (Arm)	DeltaLog	0.218	−0.021, 0.457	0.073
	D.2.ctrl Tofacitinib 10 mg vs TNFi			0.222	0.015, 0.429	0.036
	D.3.case Tofacitinib 5 mg vs TNFi			0.446	−0.164, 1.057	0.152
	D.3.case Tofacitinib 10 mg vs TNFi			0.153	−0.379, 0.686	0.573

Biomarker name	Sub-hypothesis name	P-value type	Effect size type	Effect size	95% CI	P value
	E.1 Tofacitinib 5 mg	Contrast (CFB)	HR	1.881	0.588, 6.012	0.287
	E.1 Tofacitinib 10 mg			0.694	0.269, 1.795	0.452
	E.1 TNFi			0.982	0.169, 5.695	0.984
PAI-1	A.1.bl Tofacitinib 5 mg	Contrast (X)	HR	2.167	0.896, 5.244	0.086
	A.1.bl Tofacitinib 10 mg			0.915	0.545, 1.534	0.735
	A.1.bl TNFi			0.937	0.628, 1.400	0.752
	A.1.12m Tofacitinib 5 mg			1.300	0.295, 5.718	0.729
	A.1.12m Tofacitinib 10 mg			0.955	0.527, 1.729	0.879
	A.1.12m TNFi			1.379	0.745, 2.552	0.307
	B.0.bl Overall	Interaction	NA			0.075
	B.0.12m Overall					0.635
	D.2.ctrl Tofacitinib 5 mg vs TNFi	Contrast (Arm)	DeltaLog	0.224	0.008, 0.440	0.042
	D.2.ctrl Tofacitinib 10 mg vs TNFi			0.114	−0.072, 0.300	0.231
	D.3.case Tofacitinib 5 mg vs TNFi			0.081	−0.465, 0.627	0.771
	D.3.case Tofacitinib 10 mg vs TNFi			−0.020	−0.493, 0.453	0.934
	E.1 Tofacitinib 5 mg	Contrast (CFB)	HR	0.952	0.213, 4.255	0.948
	E.1 Tofacitinib 10 mg			0.910	0.469, 1.768	0.781
	E.1 TNFi			1.366	0.624, 2.991	0.436
Protein C	A.1.bl Tofacitinib 5 mg	Contrast (X)	HR	0.478	0.202, 1.129	0.092
	A.1.bl Tofacitinib 10 mg			1.168	0.792, 1.721	0.433
	A.1.bl TNFi			1.383	0.686, 2.787	0.365
	A.1.12m Tofacitinib 5 mg			0.746	0.228, 2.446	0.629
	A.1.12m Tofacitinib 10 mg			1.106	0.681, 1.795	0.684
	A.1.12m TNFi			0.718	0.406, 1.268	0.253
	B.0.bl Overall	Interaction	NA			0.021
	B.0.12m Overall					0.447
	D.2.ctrl Tofacitinib 5 mg vs TNFi	Contrast (Arm)	DeltaLog	−0.042	−0.141, 0.056	0.403
	D.2.ctrl Tofacitinib 10 mg vs TNFi			−0.082	−0.167, 0.003	0.057
	D.3.case Tofacitinib 5 mg vs TNFi			0.211	−0.033, 0.454	0.090
	D.3.case Tofacitinib 10 mg vs TNFi			0.025	−0.187, 0.237	0.817

Biomarker name	Sub-hypothesis name	P-value type	Effect size type	Effect size	95% CI	P value
	E.1 Tofacitinib 5 mg	Contrast (CFB)	HR	4.201	0.387, 45.633	0.238
	E.1 Tofacitinib 10 mg			0.909	0.422, 1.960	0.808
	E.1 TNFi			0.429	0.180, 1.020	0.055
TAT	A.1.bl Tofacitinib 5 mg	Contrast (X)	HR	0.573	0.281, 1.168	0.126
	A.1.bl Tofacitinib 10 mg			1.115	0.839, 1.481	0.454
	A.1.bl TNFi			1.345	0.717, 2.525	0.356
	A.1.12m Tofacitinib 5 mg			1.535	0.815, 2.891	0.185
	A.1.12m Tofacitinib 10 mg			1.624	0.972, 2.712	0.064
	A.1.12m TNFi			0.667	0.262, 1.701	0.397
	B.0.bl Overall	Interaction	NA			0.139
	B.0.12m Overall					0.165
	D.2.ctrl Tofacitinib 5 mg vs TNFi	Contrast (Arm)	DeltaLog	−0.216	−0.553, 0.121	0.209
	D.2.ctrl Tofacitinib 10 mg vs TNFi			−0.094	−0.384, 0.196	0.526
	D.3.case Tofacitinib 5 mg vs TNFi			0.271	−0.583, 1.126	0.533
	D.3.case Tofacitinib 10 mg vs TNFi			0.516	−0.222, 1.255	0.171
	E.1 Tofacitinib 5 mg	Contrast (CFB)	HR	5.674	0.856, 37.612	0.072
	E.1 Tofacitinib 10 mg			1.662	0.992, 2.783	0.054
	E.1 TNFi			0.645	0.276, 1.509	0.312
TFPI	A.1.bl Tofacitinib 5 mg	Contrast (X)	HR	0.719	0.328, 1.577	0.411
	A.1.bl Tofacitinib 10 mg			0.829	0.391, 1.759	0.625
	A.1.bl TNFi			1.149	0.787, 1.677	0.473
	A.1.12m Tofacitinib 5 mg			1.303	0.729, 2.331	0.372
	A.1.12m Tofacitinib 10 mg			1.221	0.662, 2.254	0.523
	A.1.12m TNFi			1.080	0.474, 2.457	0.855
	B.0.bl Overall	Interaction	NA			0.425
	B.0.12m Overall					0.938
	D.2.ctrl Tofacitinib 5 mg vs TNFi	Contrast (Arm)	DeltaLog	0.053	−0.033, 0.138	0.229
	D.2.ctrl Tofacitinib 10 mg vs TNFi			0.076	0.003, 0.149	0.041
	D.3.case Tofacitinib 5 mg vs TNFi			0.180	−0.035, 0.395	0.102
	D.3.case Tofacitinib 10 mg vs TNFi			0.158	−0.028, 0.344	0.095

Biomarker name	Sub-hypothesis name	P-value type	Effect size type	Effect size	95% CI	P value
	E.1 Tofacitinib 5 mg	Contrast (CFB)	HR	1.779	0.706, 4.484	0.222
	E.1 Tofacitinib 10 mg			1.257	0.663, 2.383	0.484
	E.1 TNFi			0.998	0.311, 3.207	0.997

For patients assigned to receive tofacitinib at a dose of 10 mg BID who had their dose reduced to 5 mg BID, the data collected after patients had been switched to 5 mg BID were counted in the arm receiving 10 mg BID. *For hypothesis definitions, see online supplemental table 3.

ApoCIII, apolipoprotein C-III; AT, antithrombin; BID, twice daily; CFB, change from baseline; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; PAI-1, plasminogen activator inhibitor-1; TAT, thrombin-antithrombin complex; TFPI, tissue factor pathway inhibitor; TNFi, tumour necrosis factor inhibitor; TPO, thrombopoietin; VTE, venous thromboembolism.

Table S 6 Key statistical comparisons* for D-dimer and VTE (D-dimer dataset)

Sub-hypothesis name	P-value type	Effect size type	Effect size	95% CI	P value
A.1.bl Tofacitinib 5 mg	Contrast (X)	HR	0.943	0.548, 1.621	0.831
A.1.bl Tofacitinib 10 mg			1.101	0.785, 1.544	0.576
A.1.bl TNFi			1.193	0.656, 2.170	0.562
A.1.12m Tofacitinib 5 mg			4.676	2.098, 10.421	1.61e-04
A.1.12m Tofacitinib 10 mg			1.922	1.283, 2.880	0.002
A.1.12m TNFi			1.510	0.695, 3.284	0.298
B.0.bl Overall	Interaction	NA			0.833
B.0.12m Overall					0.088
C.2 ctrl Tofacitinib 5 mg vs TNFi	Contrast (X)	Delta Log	0.044	−0.018, 0.105	0.165
C.2.ctrl Tofacitinib 10 mg vs TNFi			0.050	−0.012, 0.112	0.116
C.3 case Tofacitinib 5 mg vs TNFi			−0.138	−0.794, 0.517	0.679
C.3.case Tofacitinib 10 mg vs TNFi			−0.002	−0.583, 0.579	0.995
D.2.ctrl.12m Tofacitinib 5 mg vs TNFi	Contrast (CFB)	Delta CFB Log	−0.075	−0.131, −0.019	0.009
D.2.ctrl.12m Tofacitinib 10 mg vs TNFi			−0.045	−0.102, 0.012	0.119
D.3.case.12m Tofacitinib 5 mg vs TNFi			0.728	−0.049, 1.505	0.066
D.3.case.12m Tofacitinib 10 mg vs TNFi			0.119	−0.529, 0.768	0.719
D.2.ctrl.eos Tofacitinib 5 mg vs TNFi			0.006	−0.079, 0.091	0.892
D.2.ctrl.eos Tofacitinib 10 mg vs TNFi			−0.009	−0.097, 0.078	0.832
E.1 Tofacitinib 5 mg	Contrast (CFB)	HR	5.774	2.348, 14.203	1.34e-04
E.1 Tofacitinib 10 mg			1.966	1.256, 3.078	0.003
E.1 TNFi			1.403	0.542, 3.627	0.485

For patients assigned to receive tofacitinib at a dose of 10 mg BID who had their dose reduced to 5 mg BID, the data collected after patients had been switched to 5 mg BID were counted in the arm receiving 10 mg BID. *For hypothesis definitions, see Supplementary Table 3.

BID, twice daily; CFB, change from baseline; CI, confidence interval; HR, hazard ratio; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism.

Table S 7 Levels of D-dimer in PE cases and controls using a cutoff of 2×ULN at baseline and month 12 (D-dimer dataset)

Treatment arm	ULN	Baseline		Month 12	
		Controls, n (%)	PE cases, n (%)	Controls, n (%)	PE cases, n (%)
Tofacitinib 5 mg BID	≥2×ULN	618 (50)	5 (56)	282 (26)	5 (100)
	<2×ULN	625 (50)	4 (44)	798 (74)	0 (0)
Tofacitinib 10 mg BID*	≥2×ULN	602 (50)	15 (71)	290 (29)	9 (75)
	<2×ULN	592 (50)	6 (29)	717 (71)	3 (25)
TNFi	≥2×ULN	599 (48)	1 (33)	316 (30)	0 (0)
	<2×ULN	642 (52)	2 (67)	740 (70)	1 (100)

*For patients assigned to receive tofacitinib at a dose of 10 mg BID who had their dose reduced to 5 mg BID, the data collected after patients had been switched to 5 mg BID were counted in the arm receiving 10 mg BID.

BID, twice daily; PE, pulmonary embolism; TNFi, tumour necrosis factor inhibitor; ULN, upper limit of normal.

Table S 8 VTE case counts by binary D-dimer status, age, and treatment arm (D-dimer dataset)

		D-dimer status			
		<2×ULN		≥2×ULN	
Age	Treatment	VTE cases/total	Proportion (%)	VTE cases/total	Proportion (%)
Baseline					
≥65 years	Tofacitinib 5 mg BID	3/160	1.9	4/177	2.3
	Tofacitinib 10 mg BID*	3/175	1.7	10/220	4.5
	TNFi	0/188	0	3/197	1.5
<65 years	Tofacitinib 5 mg BID	2/470	0.4	5/450	1.1
	Tofacitinib 10 mg BID*	7/427	1.6	11/403	2.7
	TNFi	3/457	0.7	3/408	0.7
Month 12					
≥65 years	Tofacitinib 5 mg BID	0/184	0	4/92	4.3
	Tofacitinib 10 mg BID*	2/178	1.1	6/123	4.9
	TNFi	2/205	1.0	0/118	0
<65 years	Tofacitinib 5 mg BID	0/614	0	2/196	1.0
	Tofacitinib 10 mg BID*	6/547	1.1	5/178	2.8
	TNFi	1/538	0.2	2/200	1.0

*For patients assigned to receive tofacitinib at a dose of 10 mg BID who had their dose reduced to 5 mg BID, the data collected after patients had been switched to 5 mg BID were counted in the arm receiving 10 mg BID.

BID, twice daily; TNFi, tumour necrosis factor inhibitor; ULN, upper limit of normal; VTE, venous thromboembolism.

Table S 9 VTE case counts by binary D-dimer status, BMI, and treatment arm (D-dimer dataset)

		D-dimer status			
		<2×ULN		≥2×ULN	
BMI	Treatment	VTE cases/total	Proportion (%)	VTE cases/total	Proportion (%)
Baseline					
≥30 kg/m^2	Tofacitinib 5 mg BID	3/273	1.1	3/242	1.2
	Tofacitinib 10 mg BID*	6/270	2.2	15/237	6.3
	TNFi	3/303	1.0	3/240	1.2
<30 kg/m^2	Tofacitinib 5 mg BID	2/354	0.6	5/382	1.3
	Tofacitinib 10 mg BID*	4/330	1.2	6/385	1.6
	TNFi	0/336	0	3/364	0.8
Month 12					
≥30 kg/m^2	Tofacitinib 5 mg BID	0/316	0	4/122	3.3
	Tofacitinib 10 mg BID*	4/286	1.4	9/132	6.8
	TNFi	2/325	0.6	0/135	0
<30 kg/m^2	Tofacitinib 5 mg BID	0/479	0	1/164	0.6
	Tofacitinib 10 mg BID*	4/436	0.9	2/169	1.2
	TNFi	1/414	0.2	2/183	1.1

*For patients assigned to receive tofacitinib at a dose of 10 mg BID who had their dose reduced to 5 mg BID, the data collected after patients had been switched to 5 mg BID were counted in the arm receiving 10 mg BID.

BID, twice daily; BMI, body mass index; TNFi, tumour necrosis factor inhibitor; ULN, upper limit of normal; VTE, venous thromboembolism.

Table S 10 VTE case counts by binary D-dimer status, smoking status, and treatment arm (D-dimer dataset)

		D-dimer status			
		<2×ULN		≥2×ULN	
Smoking status	Treatment	VTE cases/total	Proportion (%)	VTE cases/total	Proportion (%)
Baseline					
Current or ex-smoker	Tofacitinib 5 mg BID	1/330	0.3	6/291	2.1
	Tofacitinib 10 mg BID*	7/296	2.4	12/293	4.1
	TNFi	0/320	0	3/267	1.1
Lifetime non-smoker	Tofacitinib 5 mg BID	4/300	1.3	3/336	0.9
	Tofacitinib 10 mg BID*	3/306	1.0	9/330	2.7
	TNFi	3/325	0.9	3/338	0.9
Month 12					
Current or ex-smoker	Tofacitinib 5 mg BID	0/395	0	4/136	2.9
	Tofacitinib 10 mg BID*	5/347	1.4	7/139	5.0
	TNFi	2/347	0.6	0/126	0
Lifetime non-smoker	Tofacitinib 5 mg BID	0/403	0	2/152	1.3
	Tofacitinib 10 mg BID*	3/378	0.8	4/162	2.5
	TNFi	1/396	0.3	2/192	1.0

*For patients assigned to receive tofacitinib at a dose of 10 mg BID who had their dose reduced to 5 mg BID, the data collected after patients had been switched to 5 mg BID were counted in the arm receiving 10 mg BID.

BID, twice daily; TNFi, tumour necrosis factor inhibitor; ULN, upper limit of normal; VTE, venous thromboembolism.

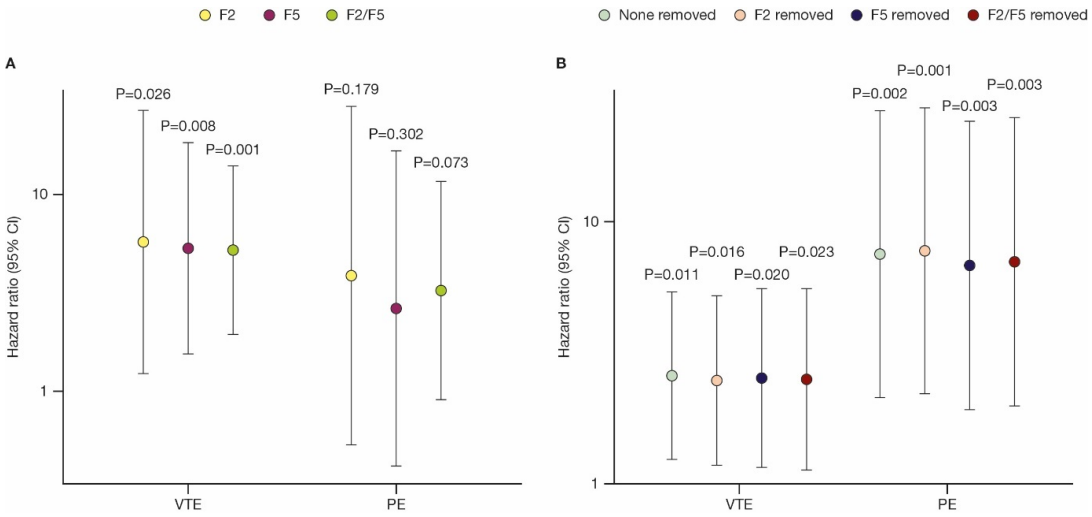
Table S 11 VTE case counts by binary D-dimer status, history of hypertension, and treatment arm (D-dimer dataset)

		D-dimer status			
		<2×ULN		≥2×ULN	
History of hypertension	Treatment	VTE cases/total	Proportion (%)	VTE cases/total	Proportion (%)
Baseline					
Yes	Tofacitinib 5 mg BID	5/415	1.2	6/394	1.5
	Tofacitinib 10 mg BID*	5/400	1.2	19/403	4.7
	TNFi	3/434	0.7	5/398	1.3
No	Tofacitinib 5 mg BID	0/215	0	3/233	1.3
	Tofacitinib 10 mg BID*	5/202	2.5	2/220	0.9
	TNFi	0/211	0	1/207	0.5
Month 12					
Yes	Tofacitinib 5 mg BID	0/500	0	4/190	2.1
	Tofacitinib 10 mg BID*	6/445	1.3	10/213	4.7
	TNFi	3/488	0.6	1/223	0.4
No	Tofacitinib 5 mg BID	0/298	0	2/98	2
	Tofacitinib 10 mg BID*	2/280	0.7	1/88	1.1
	TNFi	0/255	0	1/95	1.1

*For patients assigned to receive tofacitinib at a dose of 10 mg BID who had their dose reduced to 5 mg BID, the data collected after patients had been switched to 5 mg BID were counted in the arm receiving 10 mg BID.

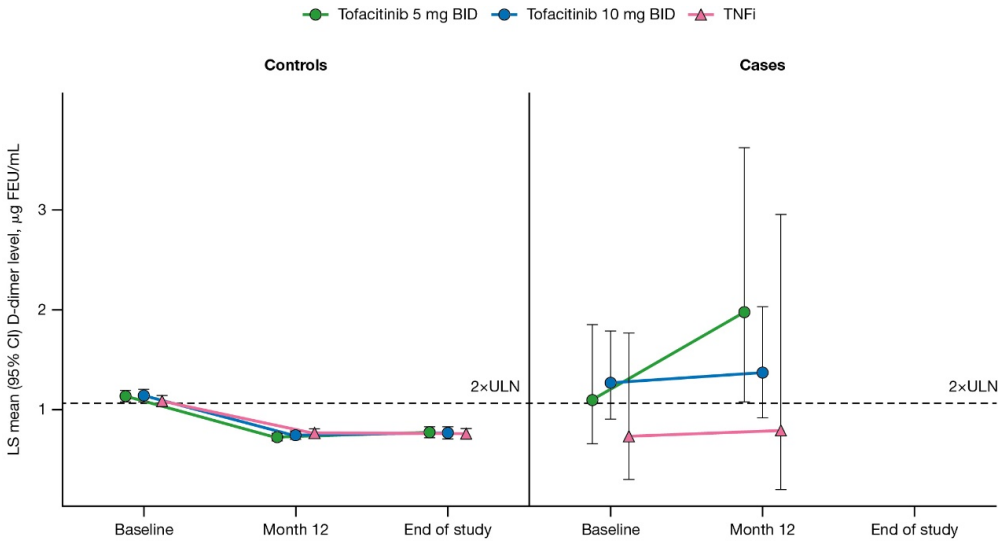
BID, twice daily; TNFi, tumour necrosis factor inhibitor; ULN, upper limit of normal; VTE, venous thromboembolism.

Figure S 1 Effect of genotype on risk of VTE events or PE events: comparing carriers versus non-carriers of F2 and/or F5 risk alleles* (**A**) and comparing tofacitinib 10 mg BID versus TNFi after removal of carriers of F2 and/or F5 (**B**) (exploratory biomarker dataset).



*By standard practice for genetic analyses, data were analysed by ancestry, but only the number of white (Caucasian) patients in each group had sufficient patients to permit this analysis; therefore, results are shown for Caucasian patients only. BID, twice daily; CI, confidence interval; F2, factor II (prothrombin) G20210A/ rs1799963 mutation; F5, factor V Leiden R506Q/rs6025 mutation; HR, hazard ratio; PE, pulmonary embolism; TNFi, tumour necrosis factor inhibitor; VTE, venous thromboembolism.

Figure S 2 D-dimer at baseline, month 12, and end of study by treatment arm in controls and PE cases (D-dimer dataset).



n						
Tofacitinib 5 mg BID	1243	1080	436	9	5	N/A
Tofacitinib 10 mg BID	1194	1007	388	21	12	N/A
TNFi	1241	1056	451	3	1	N/A

Normal assay range: <0.53 µg FEU/mL. For patients assigned to receive tofacitinib at a dose of 10 mg BID who had their dose reduced to 5 mg BID, the data collected after patients had been switched to 5 mg BID were counted in the arm receiving 10 mg BID. BID, twice daily; CI, confidence interval; FEU, fibrinogen equivalent units; LS, least squares; PE, pulmonary embolism; TNFi, tumour necrosis factor inhibitor; ULN, upper limit of normal.