Supplementary Data

Supplementary methods

Patient populations and study designs

Full study design details of all studies included in this analysis have been published previously,[1-5] and are summarized in Supplementary Figure 1. Briefly, patients in the 8-week phase 2 induction study were randomized to receive placebo or tofacitinib 0.5, 3, 10, or 15 mg twice daily [BID]; this analysis includes only those patients who received placebo or tofacitinib 10 mg BID. Oral mesalamine or oral prednisone [≤30 mg/day] were allowed during the phase 2 study.[1]

Patients in the 8-week OCTAVE Induction 1 and 2 studies received placebo or tofacitinib 10 mg BID; concomitant therapy with oral aminosalicylates or corticosteroids [prednisone or prednisone equivalent, ≤25 mg/day] were allowed during OCTAVE Induction 1 and 2, but azathioprine, methotrexate, 6-mercaptopurine, and tumor necrosis factor inhibitors [TNFi] were prohibited. Patients entering 52-week OCTAVE Sustain maintenance study were re-randomized to placebo, tofacitinib 5 mg BID, or tofacitinib 10 mg BID; patients could remain on stable doses of concomitant medications, per protocol, although tapering of corticosteroids was mandatory upon entry into the study [any patient who experienced worsening signs or symptoms of ulcerative colitis [UC] attributable to corticosteroid dose reduction could have a one-time increase in their corticosteroid dosage during the study, after which corticosteroid taper would be resumed in order to achieve steroid-free status].[2] In OCTAVE Open, those patients in remission at Week 52 of OCTAVE Sustain received tofacitinib 5 mg BID and all other patients received tofacitinib 10 mg BID. Corticosteroid tapering was required in OCTAVE Open, although doses ≤10 mg/day were

permitted for patients who could not tolerate tapering of their corticosteroid dose.[3,6] Patients in OCTAVE Open who were in stable remission for ≥6 months after receiving tofacitinib 10 mg BID for ≥2 years were eligible to enter the double-blind, randomized RIVETING study, and received either tofacitinib 5 or 10 mg BID. Patients entering RIVETING were also required to have not received corticosteroids for UC for ≥4 weeks prior to baseline; corticosteroids were not permitted.[4]

Analysis cohorts

For contextualization of data in the Overall plus P3b/4 [2020] Cohort, data from three cohorts included in a previous integrated analysis [Induction, Maintenance, and Overall Cohorts] are also reported.[5] Briefly, the Induction Cohort comprised patients who received placebo or tofacitinib 10 mg BID in phase 2/3 induction studies for up to 8 weeks; the Maintenance Cohort comprised patients who received placebo or tofacitinib 5 or 10 mg BID in the phase 3 maintenance study for up to 52 weeks; and the Overall Cohort comprised patients who received ≥1 dose of tofacitinib 5 or 10 mg BID in any phase 2/3/open-label, long-term extension study, and included data from OCTAVE Open as of December 16, 2016 [total tofacitinib exposure ≤4.4 years; hereafter defined as the Overall [Dec 2016] Cohort].

Assessment of safety

Adverse events [AEs] and serious AEs were coded using Medical Dictionary for Regulatory Activities [MedDRA; v19.0 (Induction and Maintenance Cohorts); v19.1 (Overall [Dec 2016] Cohort); v23.0 (Overall plus P3b/4 [2020] Cohort)]. Serious AEs were defined as any events that resulted in death, were life-threatening, resulted in a significant or persistent disability or incapacity, required patient hospitalization or prolongation of existing hospitalization, or resulted in a birth defect or congenital anomaly. Serious infections were defined as infection events that required parenteral antimicrobial therapy, hospitalization, or met criteria that

required the infection to be classified as a serious AE. Patients with serious infections were required to discontinue the studies [with appropriate follow-up].

Disseminated herpes zoster [HZ] events were those that involved >6 dermatomes [diffuse rash], or had non-skin involvement [e.g., pneumonia, encephalitis]. Multidermatomal HZ events were those that involved non-adjacent or >2 adjacent dermatomes [not classified as disseminated]. Gastrointestinal perforation excluded preferred terms of pilonidal cyst, perirectal abscess, rectal abscess, anal abscess, perineal abscess, and any preferred terms containing the term fistula.

Laboratory abnormalities evaluated in the Overall plus P3b/4 [2020] Cohort included creatine kinase elevation, anemia, lymphopenia, neutropenia, acute renal failure, and rhabdomyolysis. Laboratory abnormalities were reported by preferred term, but were not confirmed events (defined as two consecutive values on different study visit dates). Creatine kinase elevation included any event coded to the MedDRA preferred term blood creatine phosphokinase increased. Lymphopenia included any event coded to the preferred terms lymphopenia and lymphocytopenia neonatal, B-lymphocyte count decreased, lymphocyte count decreased, or T-lymphocyte count decreased. Neutropenia included any event coded to the higher-level term neutropenia, or the preferred terms granulocyte count decreased or neutrophil count decreased. AEs of anemia, renal impairment, and rhabdomyolysis were analyzed based on events coded to the Standardized MedDRA Queries [SMQs] of hematopoietic erythropenia, acute renal failure, and rhabdomyolysis/myopathy, respectively. As the SMQ of acute renal failure could include a broad variety of AEs, all AEs identified by this SMQ were then reviewed for clinical relevance.

Statistical analyses

For all cohorts, proportions and incidence rates [IRs; unique patients with events per 100 patient-years of exposure] along with 95% confidence intervals [CIs] were calculated for deaths and AEs of special interest. For deaths, malignancies [excluding non-melanoma skin cancer (NMSC)], NMSC, and major adverse cardiovascular events, calculation of IRs included all events; for other AEs of special interest, events occurring >28 days after the last dose of study treatment were not included in the calculation of IRs; 95% CIs for IRs were computed using the Exact Poisson method.[7] The denominator for calculation of IRs was the exposure [in days] accrued from the date of the first dose of tofacitinib to the date of the last dose of tofacitinib [on or before the data cut-off date, or the last dose plus 28 days for patients who discontinued prematurely], or to the date of the first event, whichever occurred earlier. Events occurring within 28 days of study discontinuation were included in the numerator. Data from the phase 2 induction study were not included in the calculation of IRs for adjudicated events, as the phase 2 induction study took place prior to the establishment of the adjudication committees. Venous thromboembolic events included adjudicated events from OCTAVE Open and RIVETING plus select events from phase 2/3 studies from the Narrow Standardized MedDRA query for embolic and thrombotic events.

Risk factor analysis

Cox proportional regression models were used to assess the association of demographic and clinical factors with the risk of AEs of special interest. Models were applied to the Overall plus P3b/4 [2020] Cohort, which included all patients exposed to tofacitinib in the UC clinical program and excluded any time periods and events experienced while receiving placebo. Candidate baseline covariates included age [continuous and categorical], sex, race, geographical region [two analyses: North America, Europe, other (categorical); Asia, rest of

the world (categorical)], weight [continuous and categorical], body mass index [continuous and categorical], history of diabetes mellitus, duration of UC [continuous and categorical], prior TNFi treatment, prior TNFi failure, prior immunosuppressant treatment, prior corticosteroid use, oral corticosteroid use, corticosteroid dose group, high-density lipoprotein [categorical], total Mayo score [continuous and categorical], prior myocardial infarction, smoking status, prior NMSC, absolute lymphocyte count [continuous], and absolute neutrophil count [continuous]. In addition, tofacitinib predominant dose [tofacitinib 5 or 10 mg BID, based on average total daily dose <15 or ≥15 mg, respectively] was also included in the analysis as a candidate covariate. If multiple continuous covariates were highly correlated, only one was retained in the model in order to avoid problems with collinearity. The modeling approach for baseline characteristics first applied univariate models to identify individual risk factors with a statistically significant relationship to each AE; factors with $p < 0.10$ were then included in a stepwise multivariable model. The final model included all factors from the stepwise model with $p < 0.05$. No adjustment of p values was made for multiple comparisons.

Supplementary Table 1. Proportions of patients in the Overall plus P3b/4 [2020] Cohort with tofacitinib exposure over time

Exposure time, *n* [%]	**PD tofacitinib 5 mg BID [*N* = 202]**	**PD tofacitinib 10 mg BID [*N* = 955]**	**Tofacitinib All [N = 1157]**
<2 years	57 [28.2]	548 [57.4]	605 [52.3]
≥2 years	145 [71.8]	407 [42.6]	552 [47.7]
≥3 years	130 [64.4]	347 [36.4]	477 [41.2]
≥4 years	109 [54.0]	303 [31.7]	412 [35.6]
≥5 years	89 [44.1]	200 [20.9]	289 [25.0]
≥6 years	34 [16.8]	67 [7.0]	101 [8.7]

BID, twice daily; *N*, number of patients treated in the treatment group; *n*, number of unique patients in each category; PD, predominant dose.

Supplementary Table 2. Univariate regression analysis of risk factors for serious infections in the Overall plus P3b/4 [2020] Cohort

Covariate	HR [95% CI]	*p* value
Age, years [10-year increments]	1.09 [0.89–1.32]	0.4190
Age, years [continuous]	1.01 [0.99–1.03]	0.4190
Age, <65 vs ≥65 years	0.88 [0.32–2.44]	0.8013
Age, years [range]		0.3458
≥30–<40 vs ≥40–<50	1.66 [0.74–3.74]	
≥30–<40 vs <30	2.14 [0.84–5.44]	
≥30–<40 vs ≥50	1.20 [0.62–2.34]	
≥40–<50 vs <30	1.29 [0.46–3.63]	
≥40–<50 vs ≥50	0.72 [0.33–1.61]	
<30 vs ≥50	0.56 [0.22–1.42]	
Sex, female vs male	1.55 [0.89–2.69]	0.1239
Body weight, kg [continuous]	1.01 [0.99–1.03]	0.2662
Body weight, kg [<90 vs ≥90]	0.54 [0.29–1.01]	0.0539
BMI, kg/m^2 [continuous]	1.05 [1.00–1.10]	**0.0355**
BMI, kg/m^2 [range]		0.5022
≥25–<30 vs <25	0.95 [0.48–1.86]	
≥25–<30 vs ≥30	0.64 [0.28–1.48]	
<25 vs ≥30	0.67 [0.33–1.39]	
Geographic region		
North America/Europe/other		0.0600
North America vs Europe	2.11 [1.09–4.06]	
North America vs other	1.20 [0.57–2.52]	
Europe vs other	0.57 [0.29–1.13]	
Asia vs Rest of the World	0.87 [0.34–2.19]	0.7679
Race		
Asian vs non-Asian	0.91 [0.39–2.14]	0.8268
White vs non-White	0.82 [0.43–1.56]	0.5395
Race [comparison]		0.2228
Asian vs Black	163361.9 [0.00–NA]	
Asian vs White	0.95 [0.40–2.25]	
Asian vs other	0.36 [0.11–1.17]	
Black vs White	0.00 [0.00–NA]	
Black vs other	0.00 [0.00–NA]	
Other vs White	2.67 [1.05–6.77]	
Smoking status		0.1865
Ex-smoker vs never smoked	1.62 [0.92–2.84]	

Ex-smoker vs smoker	2.78 [0.37–20.63]	
Never smoked vs smoker	1.72 [0.23–12.65]	
Disease duration years [<6.3 vs ≥6.3 years][a]	1.29 [0.74–2.25]	0.3714
Disease duration, years [continuous]	1.01 [0.98–1.05]	0.4523
Baseline total Mayo score [continuous]	1.12 [0.96–1.31]	0.1478
Baseline total Mayo score, <9 vs ≥9	0.63 [0.35–1.14]	0.1293
Baseline ALC, cells/mm^3 [continuous]	0.96 [0.69–1.35]	0.8317
Baseline ANC, cells/mm^3 [continuous]	0.99 [0.89–1.10]	0.8672
Baseline HDL, mg/dL [continuous]	1.00 [0.99–1.02]	0.5413
Baseline HDL <40 mg/dL, no vs yes	1.00 [0.43–2.35]	0.9983
History of diabetes, no vs yes	0.76 [0.24–2.45]	0.6470
History of MI, no vs yes	1.04 [0.14–7.53]	0.9692
History of NMSC, no vs yes	458216.4 [0.00–NA]	0.9839
Prior immunosuppressant use, no vs yes	0.67 [0.32–1.38]	0.2769
Prior TNFi exposure, no vs yes	0.87 [0.49–1.53]	0.6176
Prior TNFi failure, no vs yes	1.19 [0.47–3.00]	0.7139
Baseline corticosteroid use, no vs yes	0.77 [0.44–1.36]	0.3723
Prior corticosteroid use, no vs yes	1.38 [0.77–2.47]	0.2856
Corticosteroid dose, mg/day [range][b]		0.3897
<15 vs ≥15	0.90 [0.30–2.70]	
<15 vs other	0.61 [0.24–1.55]	
≥15 vs other	0.68 [0.32–1.40]	
Tofacitinib dose, PD tofacitinib 10 vs 5 mg BID	1.40 [0.70–2.82]	0.3408

In total, 1157 patients in the Overall plus P3b/4 [2020] Cohort were included in Cox univariate models; each covariate was assessed in a separate model; covariates which significantly changed the risk of a serious infection are shown in **bold** text.

[a]Median disease duration = 6.3 years.

[b]Prednisone equivalent.

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BID, twice daily; BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; MI, myocardial infarction; NA, not available; NMSC, non-melanoma skin cancer; PD, predominant dose; TNFi, tumor necrosis factor inhibitor.

Supplementary Table 3. Univariate regression analysis of risk factors for opportunistic infections in the Overall plus P3b/4 [2020] Cohort

Covariate	HR [95% CI]	*p* value
Age, years [10-year increments]	1.18 [0.92–1.52]	0.1916
Age, years [continuous]	1.02 [0.99–1.04]	0.1916
Age <65 vs ≥65 years	0.69 [0.21–2.29]	0.5493
Age, years [range]		0.4992
≥30–<40 vs ≥40–<50	0.60 [0.19–1.89]	
≥30–<40 vs <30	0.77 [0.22–2.65]	
≥30–<40 vs ≥50	0.47 [0.17–1.32]	
≥40–<50 vs <30	1.28 [0.41–4.03]	
≥40–<50 vs ≥50	0.78 [0.31–1.96]	
<30 vs ≥50	0.61 [0.22–1.72]	
Sex, female vs male	1.25 [0.61–2.55]	0.5489
Body weight, kg [continuous]	0.98 [0.95–1.00]	**0.0458**
Body weight, kg [<90 vs ≥90]	1.22 [0.42–3.48]	0.7166
BMI, kg/m^2 [continuous]	0.93 [0.86–1.02]	0.1187
BMI, kg/m^2 [range]		0.2778
≥25–<30 vs <25	1.18 [0.55–2.55]	
≥25–<30 vs ≥30	5.36 [0.69–41.85]	
<25 vs ≥30	4.52 [0.61–33.79]	
Geographic region		0.1718
North America/Europe/other		
North America vs Europe	2.16 [0.96–4.87]	
North America vs other	1.74 [0.63–4.80]	
Europe vs other	0.81 [0.31–2.10]	
Asia vs Rest of the World	1.92 [0.78–4.69]	0.1549
Race		
Asian vs non-Asian	1.99 [0.85–4.65]	0.1106
White vs non-White	0.52 [0.24–1.11]	0.0908
Race [comparison]		0.3357
Asian vs Black	312754.5 [0.00–NA]	
Asian vs White	2.09 [0.88–4.95]	
Asian vs other	1.00 [0.21–4.80]	
Black vs White	0.00 [0.00–NA]	
Black vs other	0.00 [0.00–NA]	
Other vs White	2.10 [0.49–8.99]	

Smoking status		0.5195
Ex-smoker vs never smoked	1.52 [0.74–3.14]	
Ex-smoker vs smoker	1719150 [0.00–NA]	
Never smoked vs smoker	1127610 [0.00–NA]	
Disease duration, years [<6.3 vs ≥6.3 years][a]	0.82 [0.40–1.68]	0.5818
Disease duration, years [continuous]	1.01 [0.96–1.06]	0.6936
Baseline total Mayo score [continuous]	1.19 [0.96–1.47]	0.1216
Baseline total Mayo score, <9 vs ≥9	0.67 [0.31–1.42]	0.2953
Baseline ALC, cells/mm^3 [continuous]	0.88 [0.56–1.39]	0.5948
Baseline ANC, cells/mm^3 [continuous]	0.80 [0.66–0.97]	**0.0229**
Baseline HDL, mg/dL [continuous]	1.01 [0.99–1.03]	0.5277
Baseline HDL <40 mg/dL, no vs yes	4053059 [0.00–NA]	0.9879
History of diabetes, no vs yes	0.30 [0.11–0.86]	**0.0256**
History of MI, no vs yes	0.59 [0.08–4.30]	0.5987
History of NMSC, no vs yes	458518.3 [0.00–NA]	0.9874
Prior immunosuppressant use, no vs yes	1.05 [0.47–2.36]	0.9067
Prior TNFi exposure, no vs yes	0.44 [0.20–0.96]	**0.0401**
Prior TNFi failure, no vs yes	0.39 [0.18–0.86]	**0.0192**
Baseline corticosteroid use, no vs yes	1.24 [0.59–2.60]	0.5754
Prior corticosteroid use, no vs yes	2.02 [0.77–5.28]	0.1520
Corticosteroid dose, mg/day [range][b]		0.3427
<15 vs ≥15	2.55 [0.72–9.04]	
<15 vs other	1.34 [0.54–3.34]	
≥15 vs other	0.53 [0.18–1.54]	
Tofacitinib dose, PD tofacitinib 10 vs 5 mg BID	0.89 [0.40–2.01]	0.7839

In total, 1124 patients in the Overall plus P3b/4 [2020] Cohort were included in Cox univariate models; each covariate was assessed in a separate model; covariates which significantly changed the risk of an opportunistic infection are shown in **bold** text.

[a]Median disease duration = 6.3 years.

[b]Prednisone equivalent.

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BID, twice daily; BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; MI, myocardial infarction; NA, not available; NMSC, non-melanoma skin cancer; PD, predominant dose; TNFi, tumor necrosis factor inhibitor.

Supplementary Table 4. Proportions and IRs for adjudicated malignancy events in the Overall plus P3b/4 [2020] Cohort

***n* [%], IR [95% CI]**	**PD tofacitinib 5 mg BID [*N* = 202]**	**PD tofacitinib 10 mg BID [*N* = 955]**	**Tofacitinib All [*N* = 1124][a]**
All malignancies	9 [4.5] 1.13 [0.52–2.15]	37 [4.0] 1.66 [1.17–2.28]	46 [4.1] 1.52 [1.11–2.03]
Malignancies [excl. NMSC][b]	5 [2.5] 0.62 [0.20–1.45]	21 [2.3] 0.92 [0.57–1.41]	26 [2.3] 0.84 [0.55–1.24]
Colorectal Cancer	0 [0.0] 0.00 [0.00–0.46]	4 [0.4] 0.17 [0.05–0.45]	4 [0.4] 0.13 [0.04–0.33]
Lung Cancer	0 [0.0] 0.00 [0.00–0.46]	2 [0.2] 0.09 [0.01–0.32]	2 [0.2] 0.06 [0.01–0.23]
Breast Cancer[c]	2 [2.3] 0.61 [0.07–2.21]	1 [0.3] 0.11 [0.00–0.59]	3 [0.6] 0.24 [0.05–0.69]
Lymphoma and LPD	1 [0.5] 0.12 [0.00–0.69]	1 [0.1] 0.04 [0.00–0.24]	2 [0.2] 0.06 [0.01–0.23]
Melanoma	0 [0.0] 0.00 [0.00–0.46]	2 [0.2] 0.09 [0.01–0.32]	2 [0.2] 0.06 [0.01–0.23]
Pancreatic Cancer	0 [0.0] 0.00 [0.00–0.46]	0 [0.0] 0.00 [0.00–0.16]	0 [0.0] 0.00 [0.00–0.12]
Prostate Cancer[d]	0 [0.0] 0.00 [0.00–0.77]	0 [0.0] 0.00 [0.00–0.27]	0 [0.0] 0.00 [0.00–0.20]
NMSC	5 [2.5] 0.63 [0.20–1.47]	17 [1.8] 0.76 [0.44–1.22]	22 [2.0] 0.73 [0.45–1.10]
Basal cell carcinoma[e]	4 [2.0] 0.50 [0.14–1.29]	12 [1.3] 0.53 [0.28–0.93]	16 [1.4] 0.52 [0.30–0.85]
Squamous cell carcinoma[e]	2 [1.0] 0.25 [0.03–0.90]	9 [1.0] 0.40 [0.18–0.76]	11 [1.0] 0.36 [0.18–0.64]

[a]Adjudicated events [excludes phase 2 study data].

[b]Malignancies [excluding NMSC] reported in the Overall plus P3b/4 [2020] Cohort included one case of each of acute myeloid leukemia, Bowen's disease, diffuse large B-cell lymphoma, Epstein-Barr virus associated lymphoma, essential thrombocythemia, hepatic angiosarcoma, leiomyosarcoma, esophageal adenocarcinoma, renal cell carcinoma, penile dysplasia, and vulvar cancer; two cases of cervical dysplasia, cholangiocarcinoma, lung cancer, and malignant melanoma; three cases of breast cancer; and four cases of colorectal cancer.

[c]*N* = 86, *N* = 380, and *N* = 466 for PD tofacitinib 5 mg BID, PD tofacitinib 10 mg BID, and tofacitinib all groups, respectively

[d]*N* = 116, *N* = 542, and *N* = 658 for PD tofacitinib 5 mg BID, PD tofacitinib 10 mg BID, and tofacitinib all

groups, respectively

[e]There were five patients who experienced both basal cell carcinoma and squamous cell carcinoma.

BID, twice daily; CI, confidence interval; IR, incidence rate [unique patients with events/100 PY of exposure]; LPD, lymphoproliferative disease; *N*, number of patients treated in the treatment group; *n*, number of unique patients with a particular malignancy; NMSC, non-melanoma skin cancer; PD, predominant dose; PY, patient-years.

Supplementary Table 5. Univariate regression analysis of risk factors for malignancy [excluding NMSC] in the Overall plus P3b/4 [2020] Cohort

Covariate	HR [95% CI]	*p* value
Age, years [10-year increments]	1.54 [1.17–2.03]	**0.0023**
Age, years [continuous]	1.04 [1.02–1.07]	**0.0023**
Age <65 vs ≥65 years	0.22 [0.09–0.53]	**0.0007**
Age, years [range]		0.0975
≥30–<40 vs ≥40–<50	1.11 [0.30–4.13]	
≥30–<40 vs <30	1.80 [0.35–9.27]	
≥30–<40 vs ≥50	0.44 [0.16–1.22]	
≥40–<50 vs <30	1.62 [0.30–8.88]	
≥40–<50 vs ≥50	0.40 [0.13–1.21]	
<30 vs ≥50	0.25 [0.06–1.08]	
Sex, female vs male	0.77 [0.34–1.74]	0.5348
Body weight, kg [continuous]	1.02 [0.99–1.04]	0.1539
Body weight, kg [<90 vs ≥90]	0.84 [0.32–2.23]	0.7260
BMI, kg/m^2 [continuous]	1.06 [1.00–1.13]	**0.0385**
BMI, kg/m^2 [range]		0.0544
≥25–<30 vs <25	1.81 [0.72–4.60]	
≥25–<30 vs ≥30	0.58 [0.22–1.54]	
<25 vs ≥30	0.32 [0.13–0.81]	
Geographic region		**0.0060**
North America/Europe/other		
North America vs Europe	4.01 [1.68–9.54]	
North America vs other	2.51 [0.88–7.16]	
Europe vs Other	0.63 [0.21–1.87]	
Asia vs Rest of the World	0.30 [0.04–2.20]	0.2348
Race		
Asian vs non-Asian	0.26 [0.03–1.90]	0.1834
White vs non-White	1.99 [0.60–6.64]	0.2625
Race [comparison]		0.6200
Asian vs Black	49472.83 [0.00–NA]	
Asian vs White	0.26 [0.03–1.90]	
Asian vs other	0.29 [0.02–4.64]	
Black vs White	0.00 [0.00–NA]	
Black vs other	0.00 [0.00–NA]	
Other vs White	0.88 [0.12–6.56]	
Smoking status		0.2723
Ex-smoker vs never smoked	1.89 [0.87–4.07]	

Ex-smoker vs smoker	1955749 [0.00–NA]	
Never smoked vs smoker	1037391 [0.00–NA]	
Disease duration, years [<6.3 vs ≥6.3 years][a]	0.27 [0.10–0.72]	**0.0085**
Disease duration, years [continuous]	1.07 [1.03–1.11]	**0.0002**
Baseline total Mayo score [continuous]	1.07 [0.87–1.31]	0.5313
Baseline total Mayo score, <9 vs ≥9	0.82 [0.37–1.81]	0.6212
Baseline ALC, cells/mm^3 [continuous]	0.58 [0.32–1.04]	0.0679
Baseline ANC, cells/mm^3 [continuous]	1.04 [0.91–1.18]	0.5525
History of diabetes, yes vs no	0.39 [0.12–1.30]	0.1259
History of NMSC, no vs yes	0.17 [0.05–0.57]	**0.0039**
Prior immunosuppressant use, no vs yes	0.38 [0.11–1.26]	0.1145
Prior TNFi exposure, no vs yes	0.54 [0.24–1.21]	0.1341
Prior TNFi failure, no vs yes	0.48 [0.21–1.07]	0.0715
Baseline corticosteroid use, no vs yes	0.95 [0.43–2.06]	0.8907
Prior corticosteroid use, no vs yes	1.34 [0.40–4.47]	0.6343
Corticosteroid dose, mg/day [range][b]		0.6058
<15 vs ≥15	1.95 [0.52–7.29]	
<15 vs other	1.28 [0.47–3.49]	
≥15 vs other	0.66 [0.22– 1.96]	
Tofacitinib dose, PD tofacitinib 10 vs 5 mg BID	1.51 [0.57–4.01]	0.4097

In total, 1124 patients in the Overall plus P3b/4 [2020] Cohort were included in Cox univariate models; each covariate was assessed in a separate model; covariates which significantly changed the risk of malignancies [excluding NMSC] are shown in **bold** text.

[a]Median disease duration = 6.3 years.

[b]Prednisone equivalent.

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BID, twice daily; BMI, body mass index; CI, confidence interval; HR, hazard ratio; NA, not available; NMSC, non-melanoma skin cancer; PD, predominant dose; TNFi, tumor necrosis factor inhibitor.

Supplementary Table 6. Univariate regression analysis of risk factors for NMSC in the Overall plus P3b/4 [2020] Cohort

Covariate	HR [95% CI]	*p* value
Age, years [10-year increments]	2.67 [1.88–3.80]	**<0.0001**
Age, years [continuous]	1.10 [1.07–1.14]	**<0.0001**
Age <65 vs ≥65 years	0.11 [0.05–0.25]	**<0.0001**
Age, years [range]		0.2302
≥30–<40 vs ≥40–<50	0.00 [0.00–NA]	
≥30–<40 vs <30	1.01 [0.00–NA]	
≥30–<40 vs ≥50	0.00 [0.00–NA]	
≥40–<50 vs <30	14841738 [0.00–NA]	
≥40–<50 vs ≥50	0.32 [0.11–0.94]	
<30 vs ≥50	0.00 [0.00–NA]	
Sex, female vs male	0.42 [0.15–1.13]	0.0867
Body weight, kg [continuous]	1.02 [1.00–1.04]	0.0866
Body weight, kg [<90 vs ≥90]	0.52 [0.20–1.32]	0.1687
BMI, kg/m^2 [continuous]	1.03 [0.95–1.11]	0.4848
BMI, kg/m^2 [range]		0.7140
≥25–<30 vs <25	1.42 [0.55–3.67]	
≥25–<30 vs ≥30	1.00 [0.29–3.43]	
<25 vs ≥30	0.70 [0.22–2.23]	
Geographic region		**0.0008**
North America/Europe/other		
North America vs Europe	5.35 [2.10–13.65]	
North America vs other	4.39 [1.23–15.63]	
Europe vs Other	0.82 [0.21–3.17]	
Asia vs Rest of the World	0.00 [0.00–NA]	0.9895
Race		
Asian vs non-Asian	0.00 [0.00–NA]	0.9889
White vs non-White	2.65 [0.62–11.35]	0.1902
Race [comparison]		1.0000
Asian vs Black	1.00 [0.00–NA]	
Asian vs White	0.00 [0.00–NA]	
Asian vs other	0.00 [0.00–NA]	
Black vs White	0.00 [0.00–NA]	
Black vs other	0.00 [0.00–NA]	
Other vs White	1.04 [0.14–7.77]	
Smoking status		**0.0130**
Ex-smoker vs never smoked	3.92 [1.58–9.73]	

Ex-smoker vs smoker	1.70 [0.22–12.93]	
Never smoked vs smoker	0.43 [0.05–3.52]	
Disease duration, years [<6.3 vs ≥6.3 years][a]	0.66 [0.27–1.57]	0.3421
Disease duration, years [continuous]	1.05 [1.01–1.10]	**0.0136**
Baseline total Mayo score [continuous]	1.12 [0.89–1.42]	0.3227
Baseline total Mayo score, <9 vs ≥9	0.90 [0.39–2.11]	0.8131
Baseline ALC, cells/mm^3 [continuous]	0.68 [0.38–1.23]	0.2036
Baseline ANC, cells/mm^3 [continuous]	0.94 [0.79–1.13]	0.5345
Baseline HDL, mg/dL [continuous]	1.01 [0.99–1.03]	0.2124
Baseline HDL <40 mg/dL, no vs yes	0.89 [0.26–3.00]	0.8458
History of diabetes, no vs yes	1.18 [0.16–8.93]	0.8736
History of MI, no vs yes	0.24 [0.05–1.03]	0.0543
History of NMSC, no vs yes	0.02 [0.01–0.06]	**<0.0001**
Prior immunosuppressant use, no vs yes	0.29 [0.07–1.23]	0.0924
Prior TNFi exposure, no vs yes	0.30 [0.11–0.81]	**0.0177**
Prior TNFi failure, no vs yes	0.34 [0.13–0.86]	**0.0231**
Baseline corticosteroid use, no vs yes	1.06 [0.45–2.49]	0.8940
Prior corticosteroid use, no vs yes	3.14 [1.15–8.54]	**0.0249**
Corticosteroid dose, mg/day [range][b]		0.5265
<15 vs ≥15	0.43 [0.09–2.08]	
<15 vs other	0.61 [0.14–2.75]	
≥15 vs other	1.44 [0.57–3.62]	
Tofacitinib dose, PD tofacitinib 10 vs 5 mg BID	1.18 [0.44–3.22]	0.7401

In total, 1124 patients in the Overall plus P3b/4 [2020] Cohort were included in Cox univariate models; each covariate was assessed in a separate model; covariates which significantly changed the risk of NMSC are shown in **bold** text.

[a]Median disease duration = 6.3 years.

[b]Prednisone equivalent.

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BID, twice daily; BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; MI, myocardial infarction; NA, not available; NMSC, non-melanoma skin cancer; PD, predominant dose; TNFi, tumor necrosis factor inhibitor.

Supplementary Table 7. Proportions and IRs for adjudicated MACE in the Overall plus P3b/4 [2020] Cohort

***n* [%], IR [95% CI]**	**PD tofacitinib 5 mg BID [*N* = 202]**	**PD tofacitinib 10 mg BID [*N* = 922]**	**Tofacitinib All [*N* = 1124][a]**
MACE	4 [2.0] 0.50 [0.14–1.29]	5 [0.5] 0.22 [0.07–0.51]	9 [0.8] 0.29 [0.13–0.55]
Fatal MACE	0 [0.0] 0.00 [0.00–0.46]	2 [0.2] 0.09 [0.01–0.32]	2 [0.2] 0.06 [0.01–0.23]
Non-fatal MACE	4 [2.0] 0.50 [0.14–1.29]	3 [0.3] 0.13 [0.03–0.38]	7 [0.6] 0.23 [0.09–0.47]
MI	3 [1.5] 0.38 [0.08–1.10]	0 [0.0] 0.00 [0.00–0.16]	3 [0.3] 0.10 [0.02–0.28]
Cerebrovascular accident	1 [0.5] 0.12 [0.00–0.69]	3 [0.3] 0.13 [0.03–0.38]	4 [0.4] 0.13 [0.04–0.33]

MACE were adjudicated by an independent review committee and defined as any MI, stroke, or CV death.

[a]Adjudicated events [excludes phase 2 study data].

BID, twice daily; CI, confidence interval; CV, cardiovascular; IR, incidence rate [unique patients with events/100 PY of exposure]; MACE, major adverse cardiovascular events; MI, myocardial infarction; *N*, number of patients treated in the treatment group; *n*, number of unique patients with a particular AE; PD, predominant dose.

178 **Supplementary Table 8.** Listing of adjudicated MACE

	Acute coronary syndrome	**Acute MI**	**Cerebellar hemorrhage**	**MI**	**Cerebrovascular accident**	**Hemorrhagic stroke**	**Aortic dissection**	**Cardiac arrest**	**Cerebrovascular accident**
Tofacitinib dose at onset	5 mg BID	5 mg BID	5 mg BID	5 mg BID	5 mg BID	10 mg BID	10 mg BID	10 mg BID	10 mg BID
Sex	Male	Male	Male	Male	Female	Female	Male	Male	Male
Age [years][a]	66	64	55	74	62	55	39	67	56
Day of onset[b]	28	1540	1438	142	1681	148	31	1725	951
Baseline CV risk factors									
Smoking status	Ex-smoker	Non-smoker	Non-smoker	Ex-smoker	Non-smoker	Non-smoker	Non-smoker	Ex-smoker	Smoker
BMI [kg/m^2]	≥25–<30	<25	<25	<25	<25	≥25–<30	<25	≥30	≥30
Medical history	Angina pectoris; arrhythmia; MI	No significant medical history	Left ventricular hypertrophy; hypertension	Hyperlipidemia; hypertension; DVT	Arterial hypertension	Hypertension; hypercholesterolemia; diabetes mellitus	Hyperlipidemia	PE; dyslipidemia	Diabetes mellitus; hypertension
Concomitant medications									
Lipid-lowering	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Anti-diabetic	Yes	No	No	No	No	Yes	No	No	Yes
Anti-hypertension	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes
Baseline serum lipid concentrations [mg/dL][c]									
TC	192	220	258	161	209	183	308	130	242
HDL-c	112	79	47	63	56	63	80	43	39
LDL-c	59	118	162	71	131	94	189	70	128
Triglycerides	105	116	246	134	109	132	194	84	373

Outcome	Temporary discontinuation	Temporary discontinuation	Permanent discontinuation	Temporary discontinuation	Permanent discontinuation	Permanent discontinuation	Death	Death	Permanent discontinuation

MACE were adjudicated by an independent review committee and defined as any MI, stroke, or CV death.

[a]Age at induction baseline

[b]Day of onset was computed as difference between onset date of event and date of first dose of study drug +1.

[c]Reference ranges: TC, 130–200 mg/dL; HDL-c, 40–80 mg/dL; LDL-c, 0–130 mg/dL; triglycerides, 45–250 mg/dL.

BID, twice daily; BMI, body mass index; CV, cardiovascular; DVT, deep vein thrombosis; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; PE, pulmonary embolism; TC, total cholesterol.

Supplementary Table 9. Univariate regression analysis of risk factors for MACE in the Overall plus P3b/4 [2020] Cohort

Covariate	HR [95% CI]	*p* value
Age, years [10-year increments]	2.54 [1.48–4.38]	**0.0008**
Age, years [continuous]	1.10 [1.04–1.16]	**0.0008**
Age <65 vs ≥65 years	0.15 [0.04–0.59]	**0.0069**
Age, years [range]		0.3716
≥30–<40 vs ≥40–<50	3250141 [0.00–NA]	
≥30–<40 vs <30	3299729 [0.00–NA]	
≥30–<40 vs ≥50	0.15 [0.02–1.22]	
≥40–<50 vs <30	1.02 [0.00–NA]	
≥40–<50 vs ≥50	0.00 [0.00–NA]	
<30 vs ≥50	0.00 [0.00–NA]	
Sex, female vs male	0.42 [0.09–2.04]	0.2828
Body weight, kg [continuous]	1.00 [0.97–1.04]	0.8559
Body weight, kg [<90 vs ≥90]	0.67 [0.14–3.21]	0.6124
BMI, kg/m^2 [continuous]	1.02 [0.90–1.15]	0.7534
BMI, kg/m^2 [range]		0.8806
≥25–<30 vs <25	1.37 [0.33–5.71]	
≥25–<30 vs ≥30	1.62 [0.17–15.55]	
<25 vs ≥30	1.18 [0.14–10.14]	
Geographic region		0.7929
North America/Europe/other		
North America vs Europe	1.00 [0.20–4.98]	
North America vs other	2.07 [0.19–22.80]	
Europe vs other	2.06 [0.25–17.09]	
Asia vs Rest of the World	0.95 [0.12–7.59]	0.9604
Race		
Asian vs non-Asian	0.82 [0.10–6.55]	0.8505
White vs non-White	2.05 [0.26–16.39]	0.4988
Race [comparison]		0.9949
Asian vs Black	1013483 [0.00–NA]	
Asian vs White	0.75 [0.09–6.01]	
Asian vs other	1013955 [0.00–NA]	
Black vs White	0.00 [0.00–NA]	
Black vs other	1.00 [0.00–NA]	
Other vs White	0.00 [0.00–NA]	
Smoking status		0.5702
Ex-smoker vs never smoked	1.19 [0.28–4.99]	

Ex-smoker vs smoker	0.37 [0.04–3.60]	
Never smoked vs smoker	0.31 [0.04–2.69]	
Disease duration, years [<6.3 vs ≥6.3 years][a]	0.88 [0.23–3.26]	0.8433
Disease duration, years [continuous]	1.02 [0.94–1.10]	0.6834
Baseline total Mayo score [continuous]	0.97 [0.71–1.31]	0.8261
Baseline total Mayo score, <9 vs ≥9	1.70 [0.46–6.32]	0.4314
Baseline ALC, cells/mm^3 [continuous]	0.80 [0.32–2.01]	0.6409
Baseline ANC, cells/mm^3 [continuous]	1.14 [0.98–1.32]	0.0929
Baseline HDL, mg/dL [continuous]	1.01 [0.97–1.04]	0.6584
Baseline HDL <40 mg/dL, no vs yes	0.28 [0.07–1.13]	0.0744
History of diabetes, no vs yes	10.96 [2.74–43.88]	**0.0007**
History of MI, no vs yes	0.14 [0.02–1.11]	0.0627
History of NMSC, no vs yes	458782.7 [0.00–NA]	0.9930
Prior immunosuppressant use, no vs yes	2.28 [0.61–8.49]	0.2198
Prior TNFi exposure, no vs yes	1.31 [0.35–4.89]	0.6863
Prior TNFi failure, no vs yes	1.87 [0.47–7.48]	0.3772
Baseline corticosteroid use, no vs yes	0.37 [0.09–1.47]	0.1555
Prior corticosteroid use, no vs yes	1.33 [0.17–10.67]	0.7874
Corticosteroid dose, mg/day [range][b]		0.4008
<15 vs ≥15	0.44 [0.05–3.96]	
<15 vs other	1.12 [0.13–10.01]	
≥15 vs other	2.53 [0.63–10.13]	
Tofacitinib dose, PD tofacitinib 10 vs 5 mg BID	0.39 [0.10–1.46]	0.1609

In total, 1124 patients in the Overall plus P3b/4 [2020] Cohort were included in Cox univariate models; each covariate was assessed in a separate model; covariates which significantly changed the risk of MACE are shown in **bold** text.

[a]Median disease duration = 6.3 years.

[b]Prednisone equivalent.

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BID, twice daily; BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; NA, not available; NMSC, non-melanoma skin cancer; PD, predominant dose; TNFi, tumor necrosis factor inhibitor.

Supplementary Table 10. Changes in lipid-lowering agents in the Overall plus P3b/4 [2020] Cohort

***n* [%]**	**PD tofacitinib 5 mg BID [*N* = 202]**	**PD tofacitinib 10 mg BID [*N* = 955]**	**Tofacitinib All [*N* = 1157]**
Patients receiving lipid-lowering agents at baseline	17 [8.4]	57 [6.0]	74 [6.4]
Patients who began lipid-lowering agents	26 [12.9]	64 [6.7]	90 [7.8]
Patients who had an increase in their dose of lipid-lowering agents	8 [4.0]	14 [1.5]	22 [1.9]

BID, twice daily; *N*, number of patients treated in the treatment group; *n*, number of unique patients in each category; PD, predominant dose.

Supplementary Table 11. Proportions and IRs for thromboembolic events in the Overall plus P3b/4 [2020] Cohort

***n* [%], IR [95% CI]**	**PD tofacitinib 5 mg BID [*N* = 202]**	**PD tofacitinib 10 mg BID [*N* = 955]**	**Tofacitinib All [*N* = 1157]**
VTEs	0 [0.0] 0.00 [0.00–0.46]	7 [0.7] 0.31 [0.12–0.63]	7 [0.6] 0.23 [0.09–0.47]
DVT	0 [0.0] 0.00 [0.00–0.46]	1 [0.1] 0.04 [0.00–0.24]	1 [0.1] 0.03 [0.00–0.18]]
PE[a]	0 [0.0] 0.00 [0.00–0.46]	6 [0.6] 0.26 [0.10–0.57]	6 [0.5] 0.19 [0.07–0.42]
DVT or PE[a]	0 [0.0] 0.00 [0.00–0.46]	7 [0.7] 0.31 [0.12–0.63]	7 [0.6] 0.23 [0.09–0.47]
DVT and PE[a]	0 [0.0] 0.00 [0.00–0.46]	0 [0.0] 0.00 [0.00–0.16]	0 [0.0] 0.00 [0.00–0.12]
Arterial thromboembolism	3 [1.5] 0.38 [0.08–1.10]	1 [0.1] 0.04 [0.00–0.24]	4 [0.3] 0.13 [0.04–0.33]

[a]Adjudicated events.

AE, adverse event; BID, twice daily; CI, confidence interval; DVT, deep vein thrombosis; IR, incidence rate [unique patients with events/100 PY of exposure]; *N*, number of patients treated in the treatment group; *n*, number of unique patients with a particular AE; PD, predominant dose; PE, pulmonary embolism; PY, patient-years; VTE, venous thromboembolic event.

Supplementary Table 12. Listing of adjudicated VTEs

	DVT	PE	PE	PE	PE	PE	PE
Tofacitinib dose at onset	10 mg BID	10 mg BID	10 mg BID	10 mg BID	10 mg BID	10 mg BID	10 mg BID
Sex	Female	Male	Male	Female	Male	Male	Male
Age [years] at event onset	58	25	57	21	70	59	33
Day of onset[a]	1149	216	236	570	384	1473	2564
Baseline CV risk factors							
Smoking status	Non-smoker	Non-smoker	Ex-smoker	Non-smoker	Ex-smoker	Non-smoker	Non-smoker
BMI [kg/m^2]	<25	≥25–<30	≥25–<30	>30	>30	≥25–<30	<25
Medical history	Motorcycle accident[b]	DVT; PE	Phlebothrombosis Stroke	Receiving oral contraceptives for dysfunctional uterine bleeding	Cholangiocarcinoma metastases to the peritoneum	None	None

[a]Day of onset was computed as difference between onset date of event and date of first dose of study drug +1.

[b]Patient was diagnosed following a long-haul flight and management of an infected leg wound sustained in a recent motorcycle accident.

BID, twice daily; BMI, body mass index; CV, cardiovascular; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolic event.

Supplementary Table 13. Univariate regression analysis of risk factors for VTEs in the Overall plus P3b/4 [2020] Cohort

Covariate	HR [95% CI]	*p* value
Age, years [10-year increments]	1.03 [0.61–1.76]	0.8997
Age, years [continuous]	1.00 [0.95–1.06]	0.8997
Age <65 vs ≥65 years	0.54 [0.06–4.51]	0.5657
Age, years [range]		0.7826
≥30–<40 vs ≥40–<50	2317803 [0.00–NA]	
≥30–<40 vs <30	0.33 [0.03–3.68]	
≥30–<40 vs ≥50	0.32 [0.04–2.89]	
≥40–<50 vs <30	0.00 [0.00–NA]	
≥40–<50 vs ≥50	0.00 [0.00–NA]	
<30 vs ≥50	0.97 [0.18–5.38]	
Sex, female vs male	0.53 [0.10–2.75]	0.4516
Body weight, kg [continuous]	1.03 [0.99–1.06]	0.1456
Body weight, kg [<90 vs ≥90]	0.49 [0.09–2.51]	0.3882
BMI, kg/m^2 [continuous]	1.04 [0.93–1.17]	0.4888
BMI, kg/m^2 [range]		0.3268
≥25–<30 vs <25	3.31 [0.55–19.81]	
≥25–<30 vs ≥30	0.87 [0.15–5.26]	
<25 vs ≥30	0.26 [0.04–1.90]	
Geographic region		0.1356
North America/Europe/other		
North America vs Europe	5.31 [0.94–29.93]	
North America vs other	3.70 [0.40–34.16]	
Europe vs other	0.70 [0.06–7.70]	
Asia vs Rest of the World	0.00 [0.00–NA]	0.9943
Race		
Asian vs non-Asian	0.00 [0.00–NA]	0.9940
White vs non-White	0.59 [0.11–3.11]	0.5292
Race [comparison]		**0.0325**
Asian vs Black	0.00 [0.00–NA]	
Asian vs White	0.00 [0.00–NA]	
Asian vs other	0.00 [0.00–NA]	
Black vs White	23.71 [2.64–212.83]	
Black vs other	4.81 [0.30–77.13]	
Other vs White	4.93 [0.55–44.10]	
Smoking status		0.9330
Ex-smoker vs never smoked	0.73 [0.14–3.79]	

Ex-smoker vs smoker	1050462 [0.00–NA]	
Never smoked vs smoker	1435927 [0.00–NA]	
Disease duration, years [<6.3 vs ≥6.3 years][a]	0.47 [0.09–2.43]	0.3683
Disease duration, years [continuous]	1.04 [0.96–1.12]	0.3261
Baseline total Mayo score [continuous]	1.60 [0.93–2.77]	0.0919
Baseline total Mayo score, <9 vs ≥9	0.20 [0.02–1.71]	0.1426
Baseline ALC, cells/mm^3 [continuous]	0.31 [0.08–1.24]	0.0990
Baseline ANC, cells/mm^3 [continuous]	0.97 [0.71–1.33]	0.8511
Baseline HDL, mg/dL [continuous]	0.99 [0.94–1.04]	0.6139
Baseline HDL <40 mg/dL, no vs yes	4019474 [0.00–NA]	0.9942
History of diabetes, no vs yes	1442778 [0.00–NA]	0.9931
History of MI, no vs yes	463112.2 [0.00–NA]	0.9935
History of NMSC, no vs yes	458226.5 [0.00–NA]	0.9944
Prior immunosuppressant use, no vs yes	2.30 [0.51–10.30]	0.2771
Prior TNFi exposure, no vs yes	1.46 [0.32–6.61]	0.6214
Prior TNFi failure, no vs yes	1.25 [0.28–5.59]	0.7736
Baseline corticosteroid use, no vs yes	0.98 [0.22–4.42]	0.9830
Prior corticosteroid use, no vs yes	0.00 [0.00–NA]	0.9950
Corticosteroid dose, mg/day [range][b]		0.8975
<15 vs ≥15	0.61 [0.05–7.05]	
<15 vs other	0.86 [0.09–8.04]	
≥15 vs other	1.41 [0.26–7.71]	
Tofacitinib dose, PD tofacitinib 10 vs 5 mg BID	14910431 [0.00–NA]	0.9945

In total, 1157 patients in the Overall plus P3b/4 [2020] Cohort were included in Cox univariate models; each covariate was assessed in a separate model; covariates which significantly changed the risk of VTEs are shown in **bold** text.

[a]Median disease duration = 6.3 years.

[b]Prednisone equivalent.

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BID, twice daily; BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; MI, myocardial infarction; NA, not available; NMSC, non-melanoma skin cancer; PD, predominant dose; TNFi, tumor necrosis factor inhibitor; VTE, venous thromboembolic event.

Supplementary Table 14. Univariate regression analysis of risk factors for GI perforations in the Overall plus P3b/4 [2020] Cohort

Covariate	HR [95% CI]	*p* value
Age, years [10-year increments]	0.96 [0.56–1.65]	0.8769
Age, years [continuous]	1.00 [0.94–1.05]	0.8769
Age <65 vs ≥65 years	1352036 [0.00–NA]	0.9929
Age, years [range]		0.7965
≥30–<40 vs ≥40–<50	2.49 [0.26–23.95]	
≥30–<40 vs <30	2.34 [0.24–22.49]	
≥30–<40 vs ≥50	1.82 [0.30–10.93]	
≥40–<50 vs <30	0.94 [0.06–15.03]	
≥40–<50 vs ≥50	0.73 [0.07–8.07]	
<30 vs ≥50	0.78 [0.07–8.65]	
Sex, female vs male	0.58 [0.11–2.98]	0.5135
Body weight, kg [continuous]	1.03 [0.99–1.07]	0.1105
Body weight, kg [<90 vs ≥90]	0.46 [0.09–2.36]	0.3514
BMI, kg/m^2 [continuous]	1.05 [0.93–1.19]	0.3994
BMI, kg/m^2 [range]		0.5098
≥25–<30 vs <25	0.56 [0.06–5.01]	
≥25–<30 vs ≥30	0.26 [0.02–2.91]	
<25 vs ≥30	0.47 [0.09–2.57]	
Geographic region		0.8133
North America/Europe/other		
North America vs Europe	1.49 [0.27–8.16]	
North America vs other	2.12 [0.19–23.35]	
Europe vs other	1.42 [0.16–12.67]	
Asia vs Rest of the World	0.00 [0.00–NA]	0.9941
Race		
Asian vs non-Asian	0.00 [0.00–NA]	0.9937
White vs non-White	1.62 [0.19–13.42]	0.6572
Race [comparison]		0.7288
Asian vs Black	1.00 [0.00–NA]	
Asian vs White	0.00 [0.00–NA]	
Asian vs other	0.00 [0.00–NA]	
Black vs White	0.00 [0.00–NA]	
Black vs other	0.00 [0.00–NA]	
Other vs White	3.43 [0.41–28.52]	
Smoking status		0.9600
Ex-smoker vs never smoked	0.79 [0.15–4.06]	

Ex-smoker vs smoker	1102507 [0.00–NA]	
Never smoked vs smoker	1400010 [0.00–NA]	
Disease duration, years [<6.3 vs ≥6.3 years][a]	0.81 [0.18–3.62]	0.7823
Disease duration, years [continuous]	1.05 [0.97–1.13]	0.2233
Baseline total Mayo score [continuous]	1.11 [0.73–1.68]	0.6304
Baseline total Mayo score, <9 vs ≥9	0.54 [0.11–2.81]	0.4677
Baseline ALC, cells/mm^3 [continuous]	0.46 [0.14–1.55]	0.2120
Baseline ANC, cells/mm^3 [continuous]	0.99 [0.74–1.31]	0.9380
Baseline HDL, mg/dL [continuous]	0.91 [0.85–0.98]	**0.0081**
Baseline HDL <40 mg/dL, no vs yes	0.19 [0.04–0.85]	**0.0296**
History of diabetes, no vs yes	1293308 [0.00–NA]	0.9944
History of MI, no vs yes	456356.6 [0.00–NA]	0.9943
History of NMSC, no vs yes	458194.2 [0.00–NA]	0.9939
Prior immunosuppressant use, no vs yes	0.48 [0.06–4.02]	0.5013
Prior TNFi exposure, no vs yes	0.79 [0.18–3.55]	0.7624
Prior TNFi failure, no vs yes	0.71 [0.16–3.18]	0.6532
Baseline corticosteroid use, no vs yes	1.84 [0.36–9.48]	0.4675
Prior corticosteroid use, no vs yes	1.71 [0.20–14.18]	0.6216
Corticosteroid dose, mg/day [range][b]		0.8210
<15 vs ≥15	1.77 [0.11–28.32]	
<15 vs other	0.89 [0.10–7.61]	
≥15 vs other	0.50 [0.06–4.31]	
Tofacitinib dose, PD tofacitinib 10 vs 5 mg BID	1.83 [0.22–15.27]	0.5772

In total, 1124 patients in the Overall plus P3b/4 [2020] Cohort were included in Cox univariate models; each covariate was assessed in a separate model; covariates which significantly changed the risk of a GI perforation are shown in **bold** text.

[a]Median disease duration = 6.3 years.

[b]Prednisone equivalent.

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BID, twice daily; BMI, body mass index; CI, confidence interval; GI, gastrointestinal; HDL, high-density lipoprotein; HR, hazard ratio; MI, myocardial infarction; NA, not available; NMSC, non-melanoma skin cancer; PD, predominant dose; TNFi, tumor necrosis factor inhibitor.

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