SUPPLEMENTAL MATERIAL

Definitions of infection events

All infections were assessed, regardless of severity, including any adverse event (AE) in the 'infections and infestations' System Organ Class (based on the Medical Dictionary for Regulatory Activities [MedDRA] version 23.1).

Serious infection events (SIEs) were defined as any treated infection requiring hospitalisation or parenteral antimicrobial therapy, or meeting other criteria for a serious AE.

Non-serious infections (NSIs) were defined as any infection event that was not indicated as a SIE. If a patient had a SIE and a NSI, the patient was included in both reports.

Herpes zoster (HZ) events included all HZ (non-serious/serious), including adjudicated HZ events and non-adjudicated HZ events from the clinical database; adjudicated multidermatomal HZ (non-adjacent dermatomes or >2 adjacent dermatomes); and adjudicated special interest HZ (two adjacent dermatomes).

Adjudicated HZ and opportunistic infections were assessed via an external, independent committee to determine if events met predefined criteria.

Post hoc Cox proportional hazards (simple and multi-variable) regression models

Potential baseline risk factors (online supplemental table 1) were screened using simple Cox analyses, with each model including treatment group and a single candidate risk factor as predictors. All baseline risk factors with $p<0.10$ in simple analyses were incorporated in a multi-variable model with a backwards selection algorithm, including the effects of treatment group (not subjected to backward selection), and all potential baseline risk factors identified in simple analyses; risk factors with $p<0.10$ were retained in the multi-variable model.

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Finally, the multi-variable model was re-run to include the effects of treatment group and any risk factors that were selected via the backwards selection algorithm, with $p<0.05$ interpreted as predictive. Note that, for baseline risk factors with two or more levels (eg, smoking status or BMI), a factor was included within the multi-variable model if one or more of the pairwise comparisons had $p<0.1$ in the simple analyses. Hazard ratios (HRs), associated 95% confidence intervals (CIs) and nominal p values of treatment comparisons and baseline risk factors were reported from this model. Simple and multi-variable Cox models were also generated for each treatment group separately, to assess potential similarities or differences in baseline risk factors for infections between treatments.

Time-dependent multi-variable Cox models included treatment group as a factor, the baseline risk factors retained by the backward selection algorithm, and a time-dependent risk factor of interest (separate model for each time-dependent risk factor). Time-dependent risk factors were derived using a counting process derivation algorithm including all baseline and post-baseline repeated measurements.[1, 2] HRs, 95% CIs and nominal p values for time-dependent risk factors of interest were reported from these models.

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SUPPLEMENTARY TABLES

Supplemental table 1 Baseline and time-dependent risk factors considered in the Cox proportional hazard models

Risk factor	Categories compared
Baseline risk factors	
Age*	Increase of 5 years
Sex	Male versus female
Race	Non-White versus White
RA disease duration (years)	≥1–<5 versus <1; ≥5–<10 versus <1; ≥10 years versus <1
Smoking status	Past smoker versus never smoked; current smoker versus never smoked
Geographic region (proxy for TNFi)	North America (adalimumab) versus ROW (etanercept)
Positive for anti-citrullinated protein antibodies	Yes versus no
Rheumatoid factor	Positive versus negative
BMI (kg/m^2)	≥30–<35 versus <30 kg/m^2; ≥35 versus <30
HAQ-DI*	Increase of 0.375
Prior bDMARD (TNFi/non-TNFi) use	Yes versus no
Opioid use on day 1	Yes versus no
History of diabetes	Yes versus no
History of inflammatory bowel disease	Yes versus no
History of chronic lung disease (COPD or ILD)	Yes versus no

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History of chronic renal disease	Yes versus no
History of extra-articular disease	Yes versus no
History of Sjogren's syndrome	Yes versus no
History of nodules	Yes versus no
History of coronary artery disease	Yes versus no
History of heart failure	Yes versus no
History of infection	Yes versus no
Time-dependent risk factors	
HDL-C (mg/dL)	<40 versus ≥60; ≥40–<60 versus ≥60
LDL-C (mg/dL)	≥100–<130 versus <100; ≥130 versus <100
DAS28-4(CRP)	≥2.6–≤3.2 versus <2.6; >3.2–≤5.1 versus <2.6; >5.1 versus<2.6
Absolute neutrophil count (10^3/mm^3)	<2 versus ≥2
Absolute lymphocyte count (10^3/mm^3)	<1.5 versus ≥2; ≥1.5–<2 versus ≥2
eGFR by Cockcroft–Gault equation*	Decrease of 10 mL/min
First occurrence of malignancies	Yes versus no
Oral corticosteroid use	Yes versus no

*Risk factor treated as a continuous covariate in the Cox proportional hazard model. All other risk factors were treated as categorical covariates.

bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DAS28-4(CRP), Disease Activity Score in 28 joints, C-reactive protein; eGFR, estimated glomerular filtration rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; HDL-C, high-density lipoprotein cholesterol; ILD, interstitial lung disease; LDL-C, low-density lipoprotein cholesterol; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitors.

Supplemental table 2 HRs (95% CI) for the combined tofacitinib doses (5 and 10 mg BID) versus TNFi for all infections, all infections excluding HZ, SIEs, NSIs, NSIs excluding HZ, and all HZ (non-serious/serious), in ORAL Surveillance

	Combined tofacitinib doses (5 and 10 mg BID) versus TNFi, HR (95% CI)
All infections	1.28 (1.18–1.38)
All infections excluding HZ*	1.23 (1.14–1.33)
SIEs	1.32 (1.07–1.63)
NSIs	1.28 (1.18–1.38)
NSIs excluding HZ*	1.23 (1.13–1.33)
All HZ (non-serious/serious)[†]	3.33 (2.52–4.40)[‡]

For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group.

HRs (95% CIs) were based on a simple Cox proportional hazard model for pairwise treatment comparisons, with treatment as covariate.

*Excludes HZ adjudicated as opportunistic infections and non-adjudicated HZ events from the clinical database.

[†]Includes HZ adjudicated as opportunistic infections and non-adjudicated HZ events from the clinical database.

[‡]HR (95% CI) was based on a simple Cox proportional hazard model for pairwise treatment comparisons with treatment, age, region, smoking and baseline corticosteroid use as covariates.

BID, twice daily; CI, confidence interval, HR, hazard ratio; HZ, herpes zoster; NSI, non-serious infection; SIE, serious infection event; TNFi, tumour necrosis factor inhibitors.

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Supplemental table 3 HRs (95% CIs) of potential baseline risk factors for SIEs, NSIs and all HZ (non-serious/serious) in ORAL Surveillance (simple Cox analyses across treatment groups)

Risk factor comparisons, HR (95% CI)	**SIEs**	**NSIs**	**All HZ[†] (non-serious/serious)**
Age: increase of 5 years	1.33 (1.24–1.41)***		1.13 (1.05–1.21)***
Sex: male versus female	1.34 (1.08–1.66)**	0.75 (0.68–0.82)***	0.77 (0.60–0.99)*
Smoking status: past smoker versus never smoked	1.49 (1.19–1.87)***	1.16 (1.06–1.28)**	
Smoking status: current smoker versus never smoked			0.79 (0.62–1.00)*
Geographic region: North America versus ROW[‡]	1.19 (0.97–1.47)		
BMI: ≥30–<35 versus <30 kg/m^2	1.39 (1.12–1.73)**		
BMI: ≥35 versus <30 kg/m^2		1.12 (1.02–1.24)*	
HAQ-DI: increase of 0.375	1.05 (0.99–1.11)*	1.03 (1.01–1.05)**	
Opioid use on day 1: yes versus no	1.92 (1.57–2.36)***	1.18 (1.08–1.29)***	
History of diabetes	1.28 (1.01–1.62)*		
History of inflammatory bowel disease		2.50 (1.12–5.58)*	
History of chronic lung disease (COPD or ILD)	2.25 (1.78–2.84)***	1.38 (1.24–1.54)***	
History of chronic renal disease		1.85 (1.28–2.66)**	3.14 (1.56–6.33)**
History of extra-articular disease	1.35 (1.11–1.63)**	1.17 (1.09–1.27)***	1.20 (0.98–1.45)

History of Sjogren's syndrome		1.19 (1.08–1.31)***	
History of nodules	1.33 (1.06–1.65)*		
History of coronary artery disease	1.66 (1.28–2.14)***		1.39 (1.05–1.83)*
History of heart failure	3.12 (1.80–5.43)***		1.85 (0.92–3.72)
History of infection	1.48 (1.23–1.79)***	1.29 (1.20–1.39)***	

For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group.

HRs (95% CIs) were based on a simple Cox model (separate model for each risk factor). Blank cells indicate risk factors with p≥0.10.

*p<0.05; **p<0.01; ***p<0.001.

[†]Includes HZ adjudicated as opportunistic infections and non-adjudicated HZ events from the clinical database.

[‡]In North America (US, Puerto Rico and Canada), patients randomised to TNFi received adalimumab 40 mg once every 2 weeks; in the ROW, patients randomised to TNFi received etanercept 50 mg once weekly.

BID, twice daily; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HAQ-DI, Health Assessment Questionnaire-Disability Index; HR, hazard ratio; HZ, herpes zoster; ILD, interstitial lung disease; NSI, non-serious infection; ROW, rest of the world; SIE, serious infection event; TNFi, tumour necrosis factor inhibitors.

Supplemental table 4 HRs (95% CIs) of potential baseline risk factors for SIEs and NSIs in ORAL Surveillance; simple Cox analyses performed for individual treatment groups

Baseline risk factor comparisons, HR (95% CI)	**Tofacitinib 5 mg BID (N=1455)**	**Tofacitinib 10 mg BID (N=1456)**	**TNFi (N=1451)**
SIEs			
Age: increase of 5 years	1.29 (1.15–1.45)***	1.37 (1.23–1.51)***	1.31 (1.18–1.47)***
Sex: male versus female		1.46 (1.05–2.03)*	1.48 (1.00–2.20)
Smoking status: past smoker versus never smoked		1.46 (1.01–2.12)*	1.65 (1.09–2.51)*
Geographic region: North America versus ROW[†]			1.49 (1.03–2.17)*
Positive for anti-citrullinated protein antibodies: yes versus no	1.70 (1.08–2.67)*		
BMI: ≥30–<35 versus <30 kg/m^2	1.67 (1.15–2.45)**	1.50 (1.07–2.11)*	
BMI: ≥35 versus <30 kg/m^2	1.48 (0.95–2.30)		
Opioid use on day 1: yes versus no	1.93 (1.36–2.75)***	1.65 (1.18–2.31)**	2.34 (1.61–3.41)***
History of diabetes: yes versus no	1.45 (0.97–2.16)		
History of chronic lung disease (COPD or ILD): yes versus no	2.50 (1.69–3.71)***	1.92 (1.30–2.86)**	2.42 (1.57–3.74)***

History of extra-articular disease: yes versus no	1.56 (1.12–2.18)**	1.31 (0.97–1.78)	
History of coronary artery disease: yes versus no		1.68 (1.12–2.52)*	2.10 (1.33–3.30)**
History of heart failure: yes versus no		3.44 (1.52–7.80)**	4.25 (1.57–11.54)**
History of infection: yes versus no	1.35 (0.97–1.88)	1.48 (1.09–2.00)*	1.65 (1.15–2.36)**
NSIs			
Sex: male versus female	0.74 (0.63–0.88)***	0.71 (0.61–0.83)***	0.79 (0.67–0.94)**
Race: non-White versus White	1.18 (1.02–1.36)*	1.13 (0.98–1.30)	
Smoking status: past smoker versus never smoked	1.24 (1.06–1.46)**		
BMI: ≥35 versus <30 kg/m^2			1.19 (1.00–1.42)*
HAQ-DI: increase of 0.375		1.05 (1.02–1.10)**	
Opioid use day 1: yes versus no		1.19 (1.02–1.39)*	1.24 (1.05–1.45)*
History of chronic lung disease (COPD or ILD): yes versus no	1.40 (1.17–1.68)***	1.44 (1.20–1.73)***	1.30 (1.06–1.58)*
History of chronic renal disease: yes versus no	2.45 (1.35–4.44)**	2.25 (1.24–4.08)**	
History of extra-articular disease: yes versus no	1.12 (0.99–1.28)	1.27 (1.11–1.44)***	1.14 (0.99–1.30)

History of Sjogren's syndrome	1.22 (1.03–1.44)*	1.21 (1.03–1.43)*	
History of infection: yes versus no	1.23 (1.08–1.39)**	1.36 (1.20–1.54)***	1.28 (1.12–1.47)***

For patients randomised to the tofacitinib 10 mg BID group who had their dose of tofacitinib reduced to 5 mg BID, the data collected after patients were switched to tofacitinib 5 mg BID were counted in the tofacitinib 10 mg BID group.

HRs (95% CIs) were based on a simple Cox model (separate model for each risk factor). Blank cells indicate risk factors with p≥0.10.

*p<0.05; **p<0.01; ***p<0.001.

[†]In North America (US, Puerto Rico and Canada), patients randomised to TNFi received adalimumab 40 mg once every 2 weeks; in the ROW, patients randomised to TNFi received etanercept 50 mg once weekly.

BID, twice daily; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HAQ-DI, Health Assessment Questionnaire-Disability Index; HR, hazard ratio; ILD, interstitial lung disease; NSI, non-serious infection; ROW, rest of the world; SIE, serious infection event; TNFi, tumour necrosis factor inhibitors.

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