ONLINE SUPPLEMENTARY MATERIAL

Table S1. Summary of phase 1, phase 2, phase 3, phase 3/4b and LTE studies included in the safety analysis

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
RA clinical trials						
Phase 1						
NCT01262118[1]	A3921130	36 (RA), 33 (healthy volunteers)	Active RA and healthy volunteers	10 mg BID (background methotrexate permitted)	None	6 weeks
NCT01484561[2]	A3921152	97	Active RA with inadequate response to ≥1 DMARD	10 mg BID (background csDMARDs permitted)	Placebo BID	6 weeks (for tofacitinib treatment)

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
Phase 2						
NCT00147498[3]	A3921019	199	Active RA with inadequate response or unacceptable toxicity to methotrexate or to any of the following: etanercept, infliximab or adalimumab	5 mg BID, 15 mg BID, 30 mg BID monotherapy	Placebo BID	6 weeks
NCT00413660[4]	A3921025	438	Active RA with inadequate response to methotrexate	1, 3, 5, 10 or 15 mg BID or 20 mg QD with background methotrexate	Placebo	24 weeks
NCT00550446[5]	A3921035	272	Active RA with inadequate response or toxicity to ≥1 DMARD	1, 3, 5, 10 or 15 mg BID monotherapy	Adalimumab SC 40 mg Q2W; placebo	24 weeks

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
NCT00603512[6]	A3921039	108	Active RA with inadequate response to methotrexate	1, 3, 5, 10 mg BID plus background methotrexate	Placebo	12 weeks
NCT00687193[7]	A3921040	265	Active RA with inadequate response to ≥1 DMARD	1, 3, 5, 10 or 15 mg BID monotherapy	Placebo	12 weeks
NCT01164579[8]	A3921068	72	Early active RA, methotrexate-naïve	10 mg BID plus methotrexate, 10 mg BID monotherapy	Methotrexate	12 months
NCT00976599[9]	A3921073	15	Active RA with inadequate response to methotrexate	10 mg BID plus background methotrexate	Placebo	4 weeks

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
NCT01059864[10]	A3291109	111	Active RA	10 mg BID, half of patients received concomitant atorvastatin 10 mg QD for Weeks 6-12	None	12 weeks
NCT01359150[11]	A3921129	102	Active RA	10 mg BID monotherapy (half of patients) or with background methotrexate	Placebo only (half of patients), or placebo plus methotrexate	9 weeks
NCT02147587[12]	A3921237	55	Moderate to severe RA inadequately controlled by methotrexate	5 mg BID plus background methotrexate; 2-3 weeks post-HZ vaccination	Placebo	14 weeks

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
Phase 3						
NCT00960440[13]	ORAL Step, A3921032	267	Moderate to severe RA with inadequate response to TNFi	5 or 10 mg BID with background methotrexate	Placebo (advanced to tofacitinib at Month 3)	6 months
NCT00847613[14]	ORAL Scan, A3921044	637	Active RA with inadequate response to methotrexate	5 or 10 mg BID with background methotrexate	Placebo (advanced to tofacitinib at Month 3 (non-responders) or Month 6 (remaining patients))	24 months

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
NCT00814307[15]	ORAL Solo, A3921045	488	Active RA with inadequate response to ≥1 DMARD	5 or 10 mg BID monotherapy	Placebo (advanced to tofacitinib at Month 3)	6 months
NCT00856544[16]	ORAL Sync, A3921046	636	Active RA with inadequate response to ≥1 DMARD	5 or 10 mg BID with background csDMARD	Placebo (advanced to tofacitinib at Month 3 (non-responders) or Month 6 (remaining patients))	12 months

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
NCT00853385[17]	ORAL Standard, A3921064	405	Active RA with incomplete response to methotrexate	5 or 10 mg BID with background methotrexate	Adalimumab 40 mg SC Q2W; placebo (patients receiving placebo were advanced to tofacitinib at Month 3 (non-responders) or Month 6 (remaining patients))	12 months
NCT01039688[18]	ORAL Start, A3921069	770	Active RA, methotrexate-naïve	5 or 10 mg BID monotherapy	Methotrexate	24 months
NCT02281552[19]	A3921215	209	Japanese patients with active RA with inadequate response to methotrexate	11 mg MR QD or 5 mg IR BID with background methotrexate	None	12 weeks

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
Phase 3b/4						
NCT02187055[20]	ORAL Strategy, A3921187	760	Active RA with inadequate response to methotrexate	5 mg BID monotherapy or with background methotrexate	Adalimumab 40 mg SC Q2W with background methotrexate	12 months
NCT02831855[21]	ORAL Shift, A3921192	623	Active RA with inadequate response to methotrexate	11 mg MR QD monotherapy or with background methotrexate	None	48 weeks
LTE						
NCT00413699[22]	ORAL Sequel, A3921024	4481 (final data cut March 2017)	Active RA who participated in the above studies	5 or 10 mg BID, concomitant DMARDs permitted	None	114 months

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
NCT00661661[23]	A3921041	486	Japanese patients with active RA who participated in studies A3921039, A3921040 or A3921044	5 or 10 mg BID, concomitant DMARDs permitted after Week 12	None	72 months
Pooled LTE NCT00413699; NCT00661661[24, 25]	ORAL Sequel, A3921024; A3921041	4967 (ORAL Sequel final data cut March 2017)	Active RA who participated in the above studies	5 or 10 mg BID, concomitant DMARDs permitted	None	114 months; 72 months

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
PsA clinical trials						
Phase 3						
NCT01877668[26]	OPAL Broaden, A3921091	211	Active PsA, TNFi-naïve with an inadequate response to ≥1 csDMARD	5 or 10 mg BID with a stable dose of a single DMARD	Placebo, adalimumab 40 mg SC Q2W	12 months
NCT01882439[27]	OPAL Beyond, A3921125	263	Active PsA with an inadequate response to ≥1 TNFi	5 or 10 mg BID with a stable dose of a single DMARD	Placebo	6 months

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
LTE						
NCT01976364[28]	OPAL Balance, A3921092	686	Patients from OPAL Broaden, A3921091 and OPAL Beyond A3921125	5 mg BID or 10 mg BID, concomitant DMARDs permitted	None	36 months
UC clinical trials						
Phase 2						
NCT00787202[29]	A3921063	146	Moderate to severe UC	0.5, 3, 10 or 15 mg BID	Placebo	8 weeks

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
Phase 3						
NCT01465763[30]	OCTAVE Induction 1, A3921094	492	Moderate to severe UC with prior failure/intolerance to corticosteroids, immunomodulators and/or TNFi	10 or 15 mg BID	Placebo	8 weeks
NCT01458951[30]	OCTAVE Induction 2, A3921095	435	Moderate to severe UC with prior failure/intolerance to corticosteroids, immunomodulators and/or TNFi	10 or 15 mg BID	Placebo	8 weeks

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
NCT01458574[30]	OCTAVE Sustain, A3921096	395	Moderate to severe UC, completing OCTAVE Induction 1 or 2 with clinical response	5 or 10 mg BID	Placebo	52 weeks
LTE						
NCT01470612[31]	OCTAVE Open, A3921139	944	Patients from OCTAVE Induction 1, A3921094; OCTAVE Induction 2, A3921095; and OCTAVE Sustain, A3921096	5 or 10 mg BID	None	≥12 months
PsO clinical trials						

ClinicalTrials.gov identifier	Protocol number	Patients initially receiving tofacitinib, n	Patient population	Tofacitinib doses	Control arm	Study duration
Phase 2						
NCT00678210[32]	A3921047	147	Moderate to severe chronic PsO	2, 5 or 15 mg BID	Placebo	12 weeks
NCT01710046[33]	A3921147	9	Moderate to severe chronic PsO	10 mg BID	Placebo	12 weeks
Phase 3						
NCT01241591[34]	OPT COMPARE, A3921080	659	Moderate to severe chronic PsO who participated in the above studies	5 or 10 mg BID	Placebo, etanercept 50 mg SC Q2W	12 weeks

ClinicalTrials.gov identifier	**Protocol number**	**Patients initially receiving tofacitinib, n**	**Patient population**	**Tofacitinib doses**	**Control arm**	**Study duration**
NCT01186744[35]	A3921111	666	Moderate to severe chronic PsO	5 or 10 mg BID	Placebo (withdrawal phase)	56 weeks
NCT01276639[36]	OPT PIVOTAL 1, A3921078	723	Moderate to severe chronic PsO	5 or 10 mg BID	Placebo	16 weeks
NCT01309737[36]	OPT PIVOTAL 2, A3921079	763	Moderate to severe chronic PsO	5 or 10 mg BID	Placebo	16 weeks
LTE						
NCT01163253[37]	A3921061	2881	Moderate to severe chronic PsO	5 or 10 mg BID	None	Maximum of 66 months

BID, twice daily; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; HZ, herpes zoster; IR, immediate release; LTE, long-term extension; MR, modified release; n, number of patients; QD, once daily; Q2W, every 2 weeks; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SC, subcutaneous; TNFi, tumour necrosis factor inhibitor; UC, ulcerative colitis.

Treatment-emergent adverse events (AEs) and AEs of special interest

The most common treatment-emergent AEs by Medical Dictionary for Regulatory Activities System Organ Class for all cohorts were infections and infestations, which were reported in 60.0%, 62.7%, 55.4% and 58.4% of patients in the rheumatoid arthritis (RA), psoriatic arthritis (PsA), ulcerative colitis (UC) and psoriasis (PsO) cohorts, respectively. The most common events by Preferred Term were: nasopharyngitis (16.1%) and upper respiratory tract infection (URTI; 15.8%) for RA; URTI (20.1%) and nasopharyngitis (17.1%) for PsA; ulcerative colitis (24.2%), nasopharyngitis (21.7%) and URTI (11.1%) for UC; and viral URTI (21.4%) and blood creatine phosphokinase increased (14.7%) for PsO.

Time to mortality, serious infection events and herpes zoster was similar across diseases, and for both average tofacitinib 5 and 10 mg twice daily (BID) (online supplementary figures S1A-F and S2).

The five most common adjudicated malignancies (excluding non-melanoma skin cancer) for each cohort (including those reported outside the 28-day risk period) included lung (n=39), breast (n=36), melanoma (n=20), non-Hodgkin's lymphoma (n=19), colorectal (n=14) and prostate (n=13) for RA; breast (n=3), bladder (n=3), colorectal (n=3), prostate (n=3) and thyroid (n=2) for PsA; colorectal and breast (both n=3) and cervix, melanoma and soft tissue sarcoma (all n=2) for UC; and prostate (n=18), lung (n=10), breast (n=8), pancreatic (n=5) and melanoma (n=5) for PsO (table S3). The risk of patients experiencing malignancies, non-melanoma skin cancer, melanoma and lymphoma/lymphoproliferative disorders was consistent across time points (online supplementary figure S1G-N).

Adjudicated major adverse cardiovascular events (total events including those outside the 28-day risk period) included non-fatal myocardial infarction (MI; n=34), procedure-related MI (n=1), ischaemic stroke (n=21), haemorrhagic stroke (n=8), embolic

stroke (n=2), stroke unclassified (n=2), fatal MI (n=4), fatal stroke (n=4), sudden cardiac death (n=14), fatal heart failure (n=3) and other cardiac/vascular deaths (n=4) for RA; non-fatal MI (n=3), non-fatal ischaemic stroke (n=2), sudden cardiac death (n=3) and one other cardiovascular death in the PsA cohort; three non-fatal events each of MI and cerebrovascular accident, and one fatal event of aortic dissection in the UC cohort; and non-fatal MI (n=10), non-fatal ischaemic events (n=6), fatal MI (n=3), sudden cardiac death (n=10) and one other cardiovascular death for PsO.

Table S2. Number of adjudicated OI events by Preferred Term

Average tofacitinib 5 mg BID	**Average tofacitinib 10 mg BID**
RA	
N=3969	N=3995
Tuberculosis (n=13)	HZ (n=47)
HZ (n=9)	Tuberculosis (n=31)
Pneumocystis jirovecii pneumonia (n=6)	Oesophageal candidiasis (n=6)
Pneumonia (n=5)	Pneumonia, cryptococcal (n=2)
Oesophageal candidiasis (n=5)	CMV viremia (n=1)
CMV hepatitis (n=1)	CMV chorioretinitis (n=1)
CMV infection (n=1)	Varicella zoster (n=2)
CMV chorioretinitis (n=1)	Pneumonia, CMV (n=1)
Lower RTI (n=1)	Septic shock (n=1)
Pneumonia, cryptococcal (n=1)	Mycobacterium avium complex (n=1)
Atypical mycobacterial infection (n=1)	Sialoadenitis (n=1)
Sepsis (n=1)	
Meningitis, cryptococcal (n=1)	
PsA	
N=458	N=325
HZ (n=3)	HZ (n=4)

UC	
N=198	N=926
HZ (n=11)*	HZ (n=26)†
Pulmonary mycosis (n=1)	CMV hepatitis (n=1)
	CMV infection (n=1)
	Histoplasmosis (n=1)
PsO	
N=920	N=2743
HZ (n=4)	HZ (n=31)
Bartonellosis (n=1)	Herpes simplex meningitis (n=1)
Pneumonia, fungal (n=1)	Varicella zoster virus (n=3)
Pneumonia, cryptococcal (n=1)	Listeria encephalitis (n=1)
	Tuberculosis (n=1)
	Pleural effusion (n=1)

*Includes three events adjudicated as HZ with two adjacent dermatomes.

†Includes nine events adjudicated as HZ with two adjacent dermatomes.

BID, twice daily; CMV, cytomegalovirus; HZ, herpes zoster; N, number of patients in the disease cohort; n, number of adjudicated events; NMSC, non-melanoma skin cancer; OI, opportunistic infection; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; RTI, respiratory tract infection; UC, ulcerative colitis.

Table S3. Number of adjudicated malignancy events (excluding NMSC) by Preferred Term*

Average tofacitinib 5 mg BID	**Average tofacitinib 10 mg BID**
RA	
N=3969	N=3995
Lung (n=18)	Lung (n=21)
Breast (n=15)	Breast (n=21)
Colorectal (n=8)	Melanoma (n=17)
Non-Hodgkin's lymphoma (n=5)	Non-Hodgkin's lymphoma (n=14)
Renal (n=4)	Prostate (n=9)
Prostate (n=4)	Colorectal (n=6)
Melanoma (n=3)	Cervical (n=7)
Gastric (n=3)	Unspecified/unknown (n=7)
Thyroid (n=3)	Thyroid (n=4)
Ovarian (n=3)	Bladder (n=4)
Uterus (n=3)	Uterine (n=4)
Vulvar (n=2)	Vulvar (n=3)
Cervical (n=2)	Renal (n=3)
Pleural (n=2)	Soft tissue sarcoma (n=3)
Soft tissue sarcoma (n=2)	Gastric (n=2)
Vaginal (n=1)	Ovarian (n=2)
Fallopian (n=1)	Laryngeal (n=2)

Bladder (n=1)	Oesophageal (n=2)
Salivary (n=1)	Glioblastoma (n=2)
Oesophageal (n=1)	Lip/oral cavity (n=1)
Gall bladder/extrahepatic bile duct (n=1)	Renal/pelvic/ureter (n=1)
Laryngeal (n=1)	Liver (n=1)
Adrenal (n=1)	Gall bladder/extrahepatic bile duct (n=1)
Choroid plexus atypical papilloma (n=1)	Head/neck (ill-defined site; n=1)
Glioblastoma (n=1)	Acute myeloid leukaemia (n=1)
Acute myeloid leukaemia (n=1)	Hodgkin's lymphoma (n=1)
Myeloproliferative neoplasm (n=1)	Neuroendocrine (n=1)
Hodgkin's lymphoma (n=1)	
Unknown (n=1)	
PsA	
N=458	N=325
Breast (n=3)	Prostate (n=2)
Bladder (n=3)	Colorectal (n=1)
Colorectal (n=2)	
Pancreatic (n=1)	
Prostate (n=1)	
Thyroid (n=2)	
Renal (n=1)	

Vulvar (n=1)	
Lymphoma (n=1)	
UC	
N=198	N=926
Breast (n=2)	Colorectal (n=3)
Diffuse large B-cell lymphoma (n=1)	Cervical (n=2)
	Melanoma (n=2)
	Soft tissue sarcoma (n=2)
	Breast (n=1)
	Non-Hodgkin's lymphoma (n=1)
	Oesophageal (n=1)
	Penile (n=1)
	Gall bladder/extrahepatic bile duct (n=1)
	Liver (n=1)
	Renal (n=1)
	Lung (n=1)
	Myeloproliferative neoplasm (n=1)
	Acute myeloid leukaemia (n=1)
PsO	
N=920	N=2743
Breast (n=5)	Prostate (n=15)

Prostate (n=3)	Lung (n=7)
Lung (n=3)	Pancreatic (n=5)
Renal (n=2)	Breast (n=3)
Melanoma (n=2)	Colorectal (n=3)
Cancer of ampulla of vater (n=1)	Melanoma (n=3)
Colorectal (n=1)	Lymphoma (n=3)
Bladder (n=1)	Small intestinal (n=2)
Uterine (n=1)	Uterine (n=2)
Oesophageal (n=1)	Soft tissue sarcoma (n=2)
Nasal/sinus (n=1)	Renal (n=1)
Lymphoma (n=1)	Bladder (n=1)
	Gall bladder/extrahepatic bile duct (n=1)
	Gastric (n=1)
	Pleural (n=1)
	Laryngeal (n=1)
	Testicular (n=1)
	Vaginal (n=1)
	Oligodendroglioma (n=1)
	Head/neck (ill-defined site; n=1)
	Pharyngeal (n=1)
	Unspecified (n=1)

*****Includes all events reported for the overall risk period.

BID, twice daily; n, number of events; N, number of patients in the disease cohort; n, number of adjudicated events; NMSC, non-melanoma skin cancer; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis.

Table S4. IRs (95% CI) for adjudicated gastrointestinal perforations according to concomitant NSAID and corticosteroid use

	RA	**PsA**	**UC*,†**	**PsO**
NSAID use				
Yes, IR (95% CI)	N=5782	N=448	N=71	N=420
	0.1 (0.1-0.2) [n=24]	0.1 (0.0-0.5) [n=1]	0.0 (0.0-2.0) [n=0]	0.1 (0.0-0.5) [n=1]
No, IR (95% CI)	N=2182	N=335	N=1053	N=3243
	0.1 (0.0-0.1) [n=3]	0.0 (0.0-0.4) [n=0]	0.1 (0.0-0.4) [n=3]	0.1 (0.0-0.2) [n=6]
Corticosteroid use				
Yes, IR (95% CI)	N=4254	N=171	N=505	—‡
	0.2 (0.1-0.2) [n=20]	0.0 (0.0-0.9) [n=0]	0.2 (0.0-0.7) [n=2]	
No, IR (95% CI)	N=3710	N=612	N=619	—‡
	0.1 (0.0-0.1) [n=7]	0.1 (0.0-0.3) [n=1]	0.3 (0.1-0.7) [n=4]	

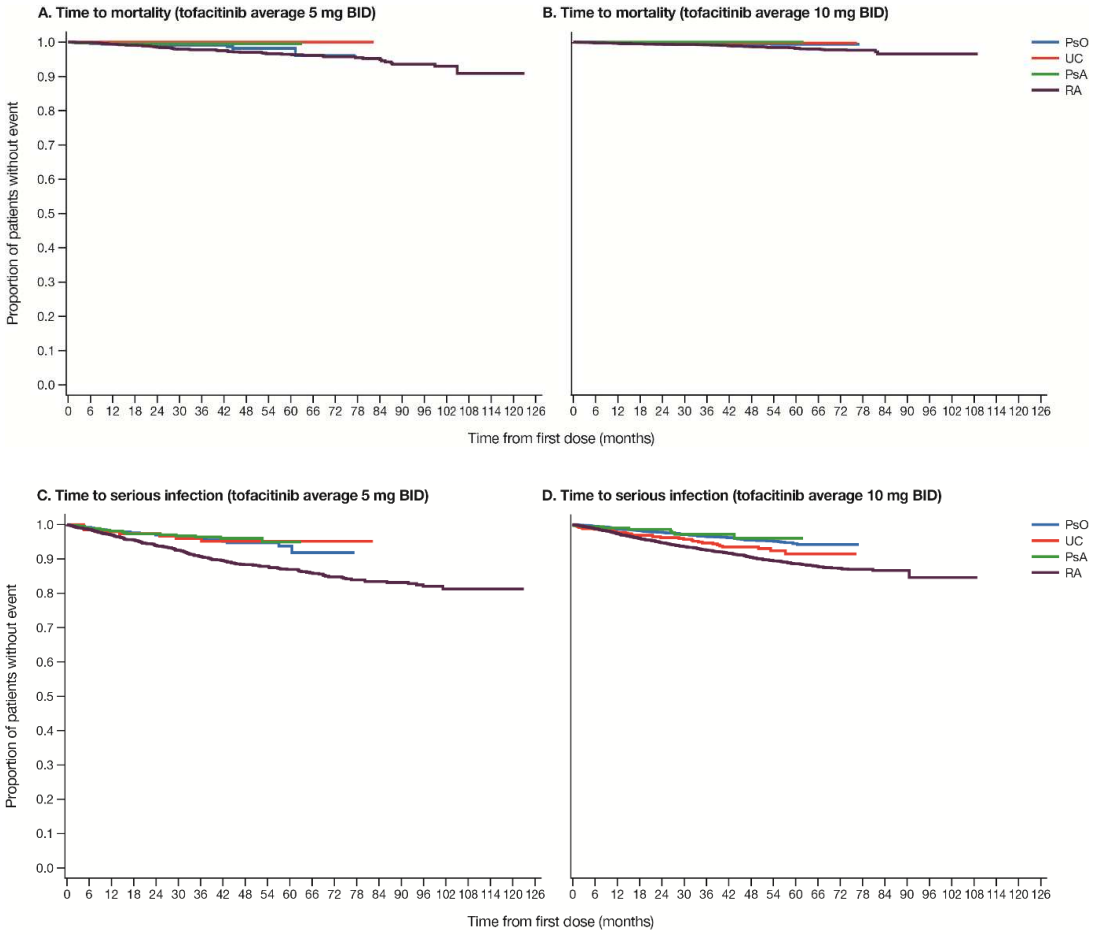
*Adjudicated data for the UC cohort does not include the phase 2 study.

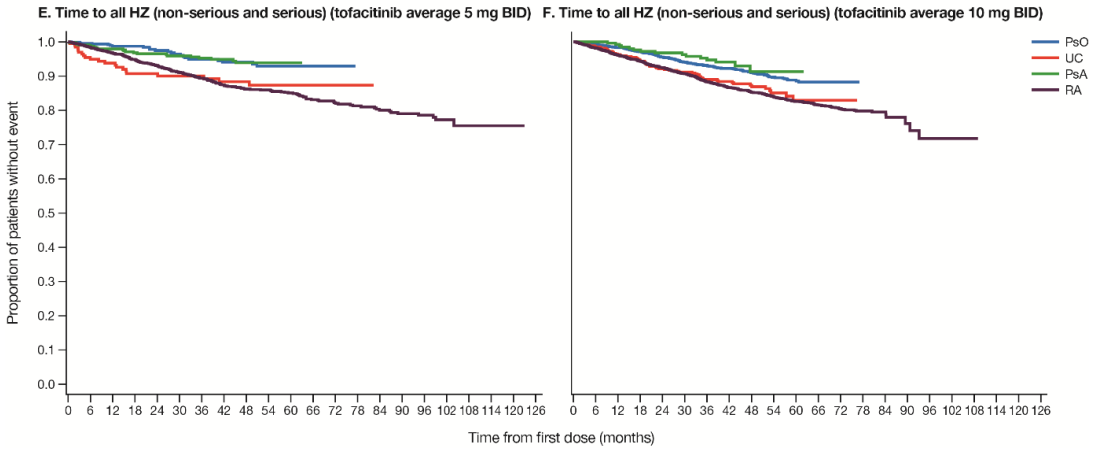
†Adjudicated gastrointestinal perforations for the UC cohort excludes Preferred Terms of pilonidal cyst, perirectal abscess, rectal abscess, anal abscess, perineal abscess and any Preferred Terms containing the term fistula.

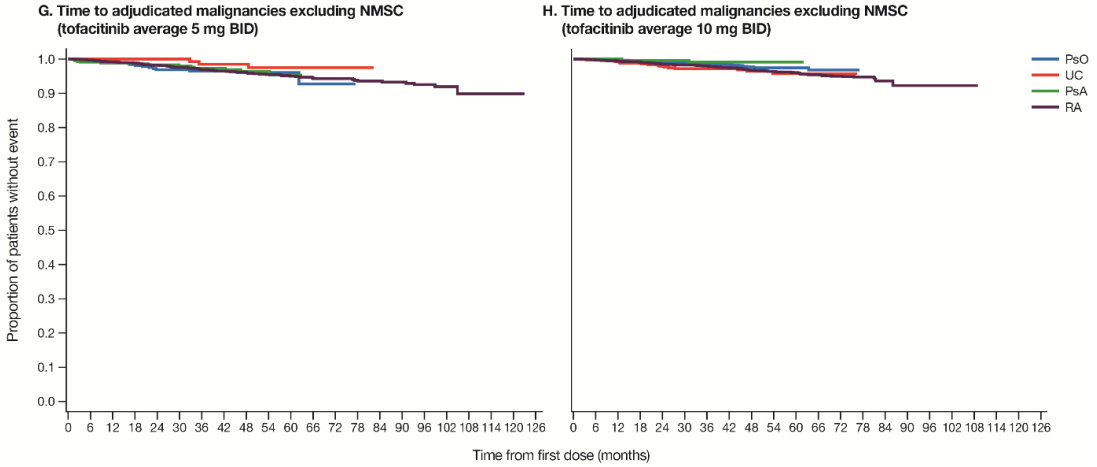
‡Concomitant corticosteroid use was not permitted in the PsO studies.

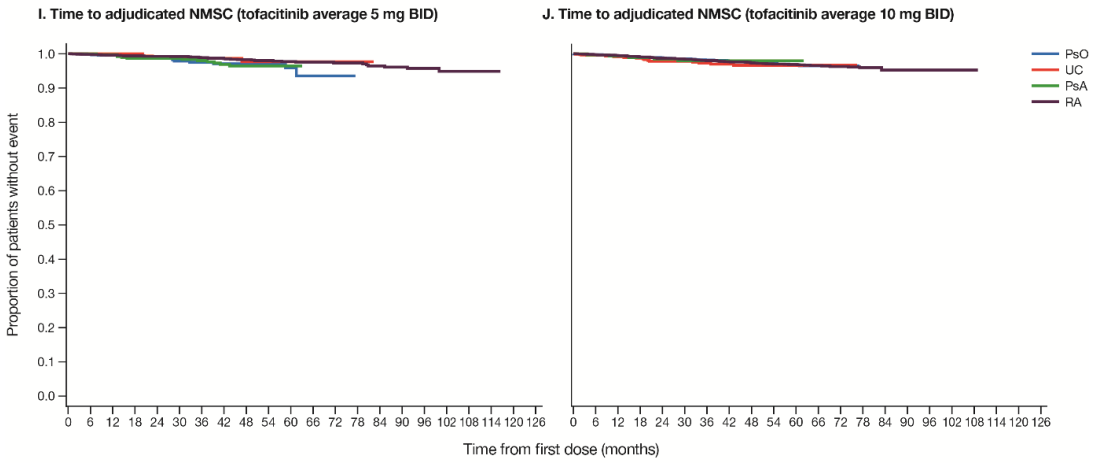
IR, incidence rate (unique patients with events per 100 patient-years); N, number of patients per category in the disease cohort; n, number of patients with the event (events are counted up to 28 days beyond the last dose or to the data cut-off date); NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; PsO psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis.

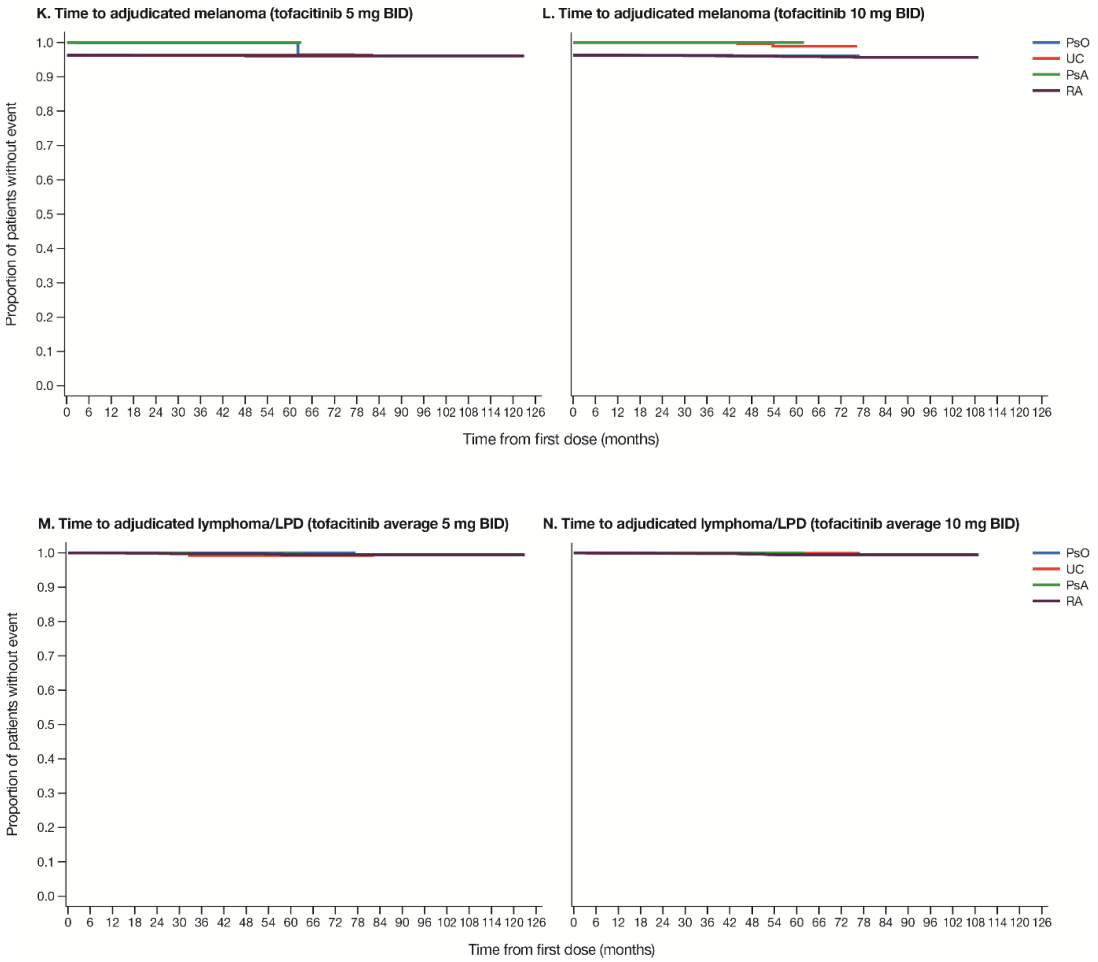
Figure S1. Kaplan-Meier plots of (A, B) time to mortality; (C, D) serious infection; (E, F) all HZ (non-serious and serious); (G, H) adjudicated malignancies excluding NMSC; (I, J) adjudicated NMSC; (K, L) adjudicated melanoma; and (M, N) lymphoma/lymphoproliferative disorder; for the average tofacitinib 5 mg BID and 10 mg BID doses.




E. Time to all HZ (non-serious and serious) (tofacitinib average 5 mg BID)
F. Time to all HZ (non-serious and serious) (tofacitinib average 10 mg BID)
PsO
UC
PsA
RA
Proportion of patients without event
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108 114 120 126
Time from first dose (months)

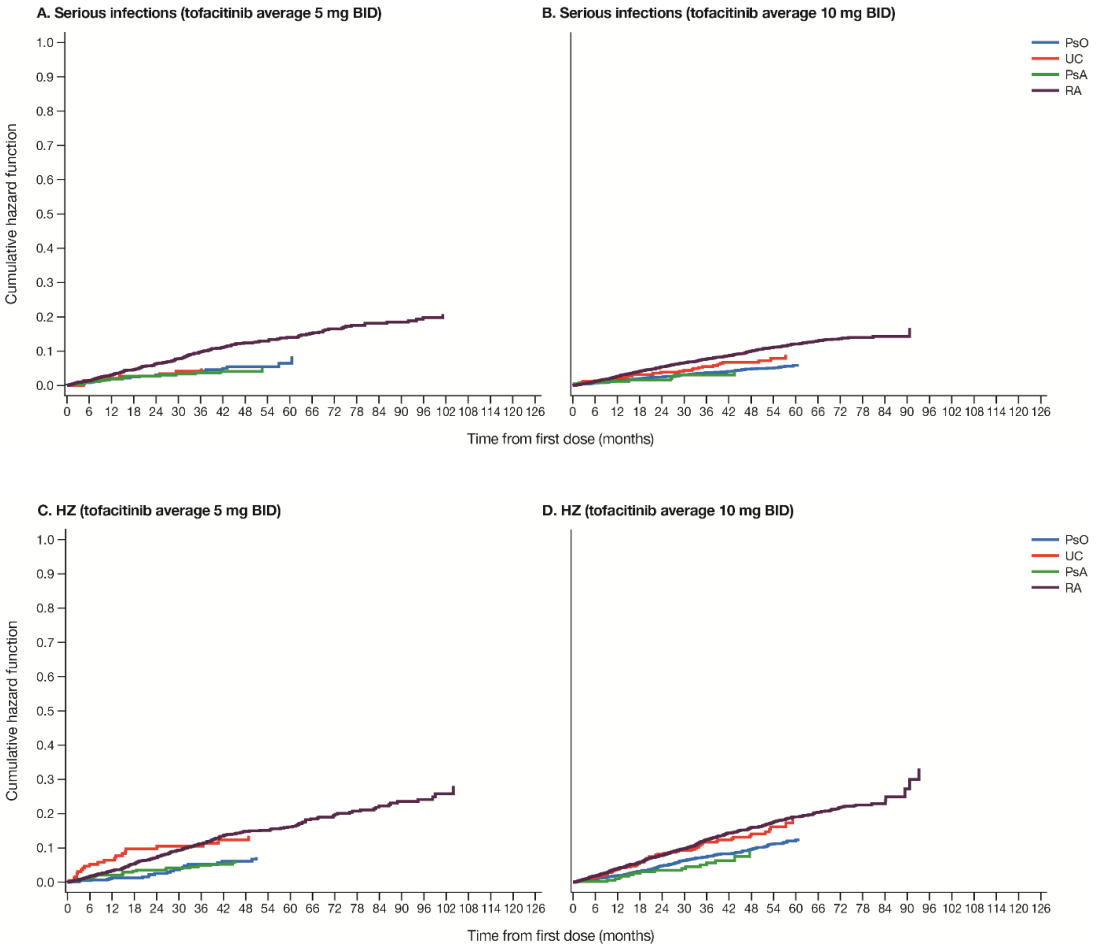

G. Time to adjudicated malignancies excluding NMSC (tofacitinib average 5 mg BID)
H. Time to adjudicated malignancies excluding NMSC (tofacitinib average 10 mg BID)
PsO
UC
PsA
RA
Proportion of patients without event
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108 114 120 126
Time from first dose (months)


I. Time to adjudicated NMSC (tofacitinib average 5 mg BID)
J. Time to adjudicated NMSC (tofacitinib average 10 mg BID)
PsO
UC
PsA
RA
Proportion of patients without event
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108 114 120 126
Time from first dose (months)



BID, twice daily; HZ, herpes zoster; NMSC, non-melanoma skin cancer; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis.

Figure S2. Cumulative probability plots of (A, B) serious infections, and (C, D) HZ (serious and non-serious).



HZ, herpes zoster; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis.

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