Long-term Safety of Tofacitinib for the Treatment of Rheumatoid Arthritis up to 8.5 years: Integrated Analysis of Data from the Global Clinical Trials

SUPPLEMENTARY TEXT

Case ascertainment for gastrointestinal perforation

Clinical events reflecting an opening in the gastrointestinal (GI) tract, including those associated with appendicitis and diverticulitis, were classified as confirmed GI perforations.

In addition, all serious adverse events coding to the following Medical Dictionary for Regulatory Activities preferred terms were submitted for independent review: peridiverticular abscess, abscess bacterial, abscess rupture, liver abscess, rectovaginal septum abscess, peritoneal abscess, splenic abscess, appendiceal abscess, pelvic abscess, biliary abscess, gallbladder abscess, mesenteric abscess, colitis, subdiaphragmatic abscess, pancreatic abscess, pyloric abscess, appendectomy, appendicitis, abdominal abscess, diverticulitis, diverticulum, peritonitis and postoperative abscess.

Major adverse cardiovascular events

In Phase 3 and LTE studies, cardiovascular events were blindly adjudicated by a sponsor-independent committee from February 25, 2009. Major adverse cardiovascular events (MACE) were defined as cardiovascular, non-fatal myocardial infarction (MI) or non-fatal stroke.

The most common cardiac disorders categorised as SAEs were atrial fibrillation (n=24), MI (n=21) and coronary artery disease (n=15). Total tofacitinib exposure for adjudicated composite MACE was 18,400 patient-years. Adjudicated MACE were reported in 71 patients, with an IR

(95% CI) of 0.4 (0.3–0.5). IRs were 0.4 (0.3–0.6) and 0.4 (0.3–0.5) for average 5 and 10 mg BID; and 0.4 (0.3–0.7) and 0.4 (0.2–0.5) for constant 5 and 10 mg BID. Analysis of IR by 1-year intervals did not reveal any trends for increases over time; IRs were small with wide and overlapping CIs (Supplementary Figure 2).

MACE IRs with tofacitinib were similar to those with placebo in Phase 3 trials, and earlier analyses of LTE studies did not reveal increased risk versus short-term controlled trials.[1] Here, the MACE IR was 0.4, with no increase over time. Long-term comparative studies are required to assess whether tofacitinib increases MACE risk versus bDMARDs; a Phase 4 trial is underway to investigate this (NCT02092467). Phase 3 trials revealed increased total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels in patients receiving tofacitinib, although the LDL-C/HDL-C ratio remained largely unchanged.[1] Further research revealed that tofacitinib improved the anti-atherogenic protein profile of HDL-C and decreased cholesterol ester catabolism, which was elevated in patients with RA versus matched healthy controls.[2]

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Supplementary Table 1 Phase 1, Phase 2, Phase 3 and LTE studies included in the present analysis

Clinicaltrials.gov identifier	Sponsor ID	Patients receiving tofacitinib, n	Patient population	Tofacitinib doses	Control group	Study duration
Phase 1						
NCT01262118[2]	A3921130	36 (RA), 33 (healthy volunteers)	Active RA and healthy volunteers	10 mg BID (background MTX permitted)	None	6 weeks
NCT01484561[3]	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	Sponsor ID	Patients receiving tofacitinib, n	Patient population	Tofacitinib doses	Control group	Study duration
Phase 2						
NCT00147498[4]	A3921019	199	Active RA with inadequate or unacceptable toxicity to MTX, etanercept, infliximab or adalimumab	5 mg BID, 15 mg BID, 30 mg BID monotherapy	Placebo BID	6 weeks
NCT00413660[5]	A3921025	438	Active RA with inadequate response to MTX	1, 3, 5, 10, or 15 mg BID or 20 mg QD with background MTX	Placebo	24 weeks

Clinicaltrials.gov identifier	Sponsor ID	Patients receiving tofacitinib, n	Patient population	Tofacitinib doses	Control group	Study duration
NCT00550446[6]	A3921035	272	Active RA with inadequate response to ≥1 DMARD	1, 3, 5, 10, or 15 mg BID monotherapy	Adalimumab sc 40 mg Q2W; placebo	24 weeks
NCT00603512[7]	A3921039	108	Active RA with inadequate response to MTX	1, 3, 5, 10 mg BID plus background MTX	Placebo	12 weeks
NCT00687193[8]	A3921040	265	Active RA with inadequate response to ≥1 DMARD	1, 3, 5, 10, or 15 mg BID monotherapy	Placebo	12 weeks

Clinicaltrials.gov identifier	Sponsor ID	Patients receiving tofacitinib, n	Patient population	Tofacitinib doses	Control group	Study duration
NCT01164579[9]	A3921068	72	Early active RA, MTX-naïve	10 mg BID plus MTX, 10 mg BID monotherapy	MTX	52 weeks
NCT00976599[10]	A3921073	15	Active RA with inadequate response to MTX	10 mg BID plus background MTX	Placebo	4 weeks

Clinicaltrials.gov identifier	Sponsor ID	Patients receiving tofacitinib, n	Patient population	Tofacitinib doses	Control group	Study duration
NCT01059864[11]	A3291109	111	Active RA	10 mg BID, half of patients received concomitant atorvastatin 10 mg QD for Weeks 6–12	None	12 weeks
NCT01359150 [12]	A3921129	102	Active RA	10 mg BID, monotherapy (half of patients) or with background MTX	Placebo	9 weeks

Phase 3

Clinicaltrials.gov identifier	Sponsor ID	Patients receiving tofacitinib, n	Patient population	Tofacitinib doses	Control group	Study duration
NCT00960440[13]	ORAL Step, A3921032	267	Moderate to severe RA with inadequate response to TNFi	5 or 10 mg BID with background MTX	Placebo	6 months
NCT00847613[14]	ORAL Scan, A3921044	797	Active RA with inadequate response to MTX	5 or 10 mg BID with background MTX	Placebo (advanced to tofacitinib at Month 3 [non-responders] or 6 [remaining patients])	24 months

Clinicaltrials.gov identifier	Sponsor ID	Patients receiving tofacitinib, n	Patient population	Tofacitinib doses	Control group	Study duration
NCT00814307[15]	ORAL Solo, A3921045	610	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	792	Active RA with inadequate response to ≥1 DMARD	5 or 10 mg BID with background MTX	Placebo (advanced to tofacitinib at Month 3 [non-responders] or 6 [remaining patients])	12 months

Clinicaltrials.gov identifier	Sponsor ID	Patients receiving tofacitinib, n	Patient population	Tofacitinib doses	Control group	Study duration
NCT00853385[17]	ORAL Standard, A3921064	513	Active RA with incomplete response to MTX	5 or 10 mg BID with background MTX	Adalimumab 40 mg sc Q2W; placebo (patients receiving placebo were advanced to tofacitinib at Month 3 [non-responders] or 6 [remaining patients])	12 months

Clinicaltrials.gov identifier	Sponsor ID	Patients receiving tofacitinib, n	Patient population	Tofacitinib doses	Control group	Study duration
NCT01039688[18]	ORAL Start, A3921069	770	Active RA, MTX-naïve	5 or 10 mg BID monotherapy	MTX	24 months

Clinicaltrials.gov identifier	Sponsor ID	Patients receiving tofacitinib, n	Patient population	Tofacitinib doses	Control group	Study duration
LTE						
NCT00413699[19]	ORAL Sequel, A3921024	2,308 (as of March 31, 2015)	Active RA who participated in the above studies	5 or 10 mg BID, concomitant DMARDs permitted	None	Ongoing
NCT00661661[19]	A3921041	486	Japanese patients with active RA who participated in studies A3921039, A3921040 or A3921044	5 or 10 mg BID, concomitant DMARDs permitted	None	72 months

BID, twice daily; csDMARD, conventional synthetic disease-modifying antirheumatic drug; LTE, long-term extension; MTX, methotrexate; Q2W, every 2 weeks; QD, once daily; RA, rheumatoid arthritis; sc, subcutaneous; TNFi, tumour necrosis factor inhibitor.

Supplementary Table 2 Geographical distribution of non-serious and serious HZ cases, for all tofacitinib doses

Geographical region	Patients, n/N (%)	IR (95% CI)
US/Canada	163/1,505 (10.8)	4.3 (3.6–5.0)
Europe	166/2,065 (8.0)	2.5 (2.1–2.9)
Latin America	111/1,037 (10.7)	3.7 (3.0–4.4)
Asia	263/1,587 (16.6)	5.9 (5.2–6.6)
Japan/Korea	182/847 (21.5)	8.1 (7.0–9.4)
India	16/197 (8.1)	3.4 (1.9–5.5)
Thailand/Malaysia/Philippines	22/171 (12.9)	4.2 (2.6–6.4)
China/Taiwan	23/249 (9.2)	2.7 (1.7–4.0)
Australia/New Zealand	20/123 (16.3)	5.3 (3.2–8.1)

CI, confidence interval; HZ, herpes zoster; IR, incidence rate.

Supplementary Table 3 List of opportunistic infections excluding TB

Patients, n	All tofacitinib, n (N=61)*
HZ (multidermatomal HZ [non-adjacent or >2 adjacent dermatomes] and disseminated)	29
Oesophageal candidiasis	12
Cytomegalovirus	7
Pneumocystosis	5
Cryptococcosis	5
Non-TB mycobacteria	2
Nocardiosis	1
BK encephalitis	1

*One patient experienced two events of oesophageal candidiasis.

BK, BK virus; HZ, herpes zoster; TB, tuberculosis.

Supplementary Table 4 TB cases in tofacitinib-treated patients (all doses) according to geographical background rates (WHO categorisation [20]).

Geographical region	Patients, n/N (%)	IR, patients with event/100 patient-years (95% CI)
High (>50 per 100,000 populations per year)	28/1,360 (2.1)	0.6 (0.4–0.9)
Intermediate (10–≤ 50 per 100,000 populations/year)	7/2,281 (0.3)	0.1 (0.04–0.2)
Low (<10 per 100,000 populations/year)	1/2,553 (0.04)	0.01 (0.0–0.07)

CI, confidence interval; IR, incidence rate; TB, tuberculosis; WHO, World Health Organization.

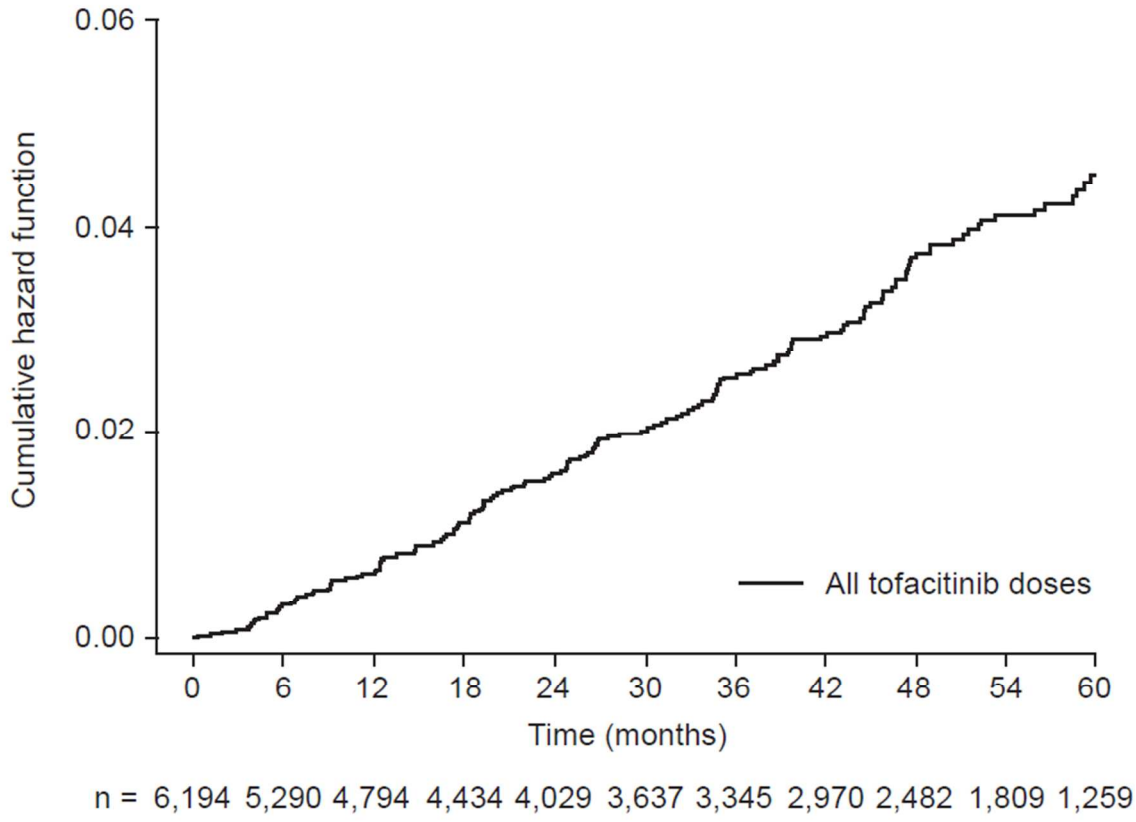
Supplementary Table 5 Geographical distribution of NMSC

Geographic region/country, n (%)	All tofacitinib doses (N=118)
Asia	28 (23.7)
Australia	27 (22.9)
Japan	1 (0.8)
Europe	19 (16.1)
Austria	1 (0.8)
Bulgaria	1 (0.8)
Czech Republic	3 (2.5)
Denmark	1 (0.8)
Germany	5 (4.2)
Poland	4 (3.4)
Slovakia	1 (0.8)

Spain	3 (2.5)
Latin America	6 (5.1)
Brazil	3 (2.5)
Chile	1 (0.8)
Colombia	2 (1.7)
North America	65 (55.1)
Canada	4 (3.4)
United States	61 (51.7)

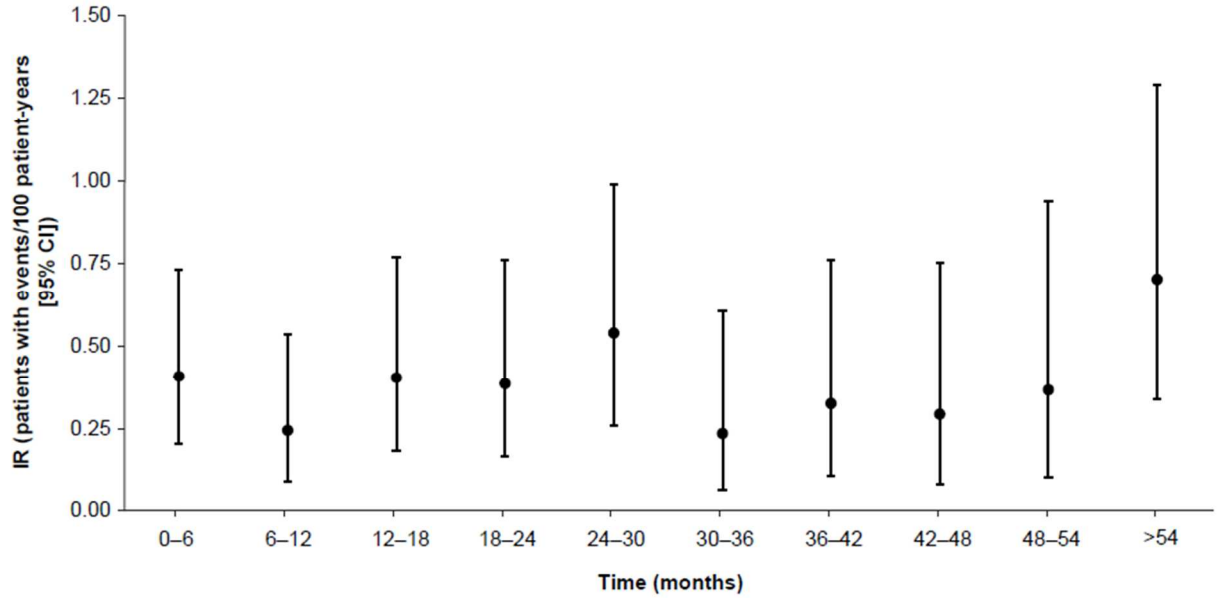
NMSC, non-melanoma skin cancer.

Supplementary Figure 1 Cumulative hazard function to assess the hazard for developing a malignancy (excluding NMSC) over time.



NMSC, non-melanoma skin cancer.

Supplementary Figure 2 IRs of MACE over time* for all tofacitinib doses.



	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	>54
Total patient exposure, n	5,756	5,186	4,756	4,352	4,051	3,597	3,329	2,949	2,569	1,924
Patients with MACE, n	11	6	9	8	10	4	5	4	4	10
Total patient-year exposure for event	2,694.3	2,446.1	2,228.5	2,073.4	1,855.0	1,696.8	1,533.8	1,358.3	1,089.0	1,425.0
IR, patients with events/100 patient-years (95% CI)	0.4 (0.2–0.7)	0.2 (0.1–0.5)	0.4 (0.2–0.8)	0.4 (0.2–0.8)	0.5 (0.3–1.0)	0.2 (0.1–0.6)	0.3 (0.1–0.8)	0.3 (0.1–0.8)	0.4 (0.1–0.9)	0.7 (0.3–1.3)

*Exposure appears lower than for other adverse events, since the cardiovascular adjudication process only applied to data after February 25, 2009.

CI, confidence interval; IR, incidence rate; MACE, major adverse cardiovascular event.