Impact of cardiovascular risk enrichment on incidence of major adverse cardiovascular events in the tofacitinib rheumatoid arthritis clinical programme

The ORAL Surveillance trial found that patients with rheumatoid arthritis (RA) aged ≥50 years with ≥1 additional cardiovascular (CV) risk factor had an increased risk of major adverse cardiovascular events (MACE) with tofacitinib versus tumour necrosis factor inhibitors (TNFi).[1] A post hoc analysis indicated that the increased risk of MACE with tofacitinib versus TNFi was apparent primarily in patients with a history of atherosclerotic CV disease (ASCVD), that is, pre-existing coronary artery, cerebrovascular or peripheral artery disease.[2]

Excess risk of MACE was not identified in the wider tofacitinib RA clinical trial programme (consisting of 21 phase 1–3b/4 and 2 long-term extension studies, hereafter collectively referred to as P123LTE).[3] To better understand the results from ORAL Surveillance vs P123LTE, we: (1) applied the ORAL Surveillance CV risk-enrichment criteria to P123LTE (patients who received ≥1 tofacitinib dose) to create a CV risk-enriched P123LTE cohort (P123LTE-CV+; patients aged ≥50 years who had ≥1 additional CV risk factor (current smoker, hypertension, high-density lipoprotein cholesterol <40 mg/dL, diabetes mellitus, history of coronary artery disease)) and (2) assessed MACE incidence rates (IRs) in all patients, and separately in patients with and without history of ASCVD, in P123LTE and P123LTE-CV+.

P123LTE included 7964 patients; of these, 3125 (39.2%) were included in P123LTE-CV+. MACE data were summarised by tofacitinib dose (average 5 or 10 mg two times per day, based on an average total daily dose of <15 or ≥15 mg, respectively). IRs (patients with unique events/100 patient-years) with 95% CI were evaluated for adjudicated MACE and compared with previously published data from ORAL Surveillance.[1 2] Adjudication of MACE was performed concurrently in phase 3 studies and retrospectively in phases 1 and 2 studies. Baseline CV risk profiles of P123LTE and P123LTE-CV+were determined as previously described.[2] Briefly, patients were grouped according to history of ASCVD, and patients with no history of ASCVD were further grouped by categories of predicted 10-year risk of MACE (high (≥20%), intermediate (≥7.5% to <20%), borderline (≥5% to <7.5%) and low (<5%) risk), per the ASCVD-pooled cohort equations calculator[4] with a 1.5-multiplier applied.[5]

The proportion of patients with a history of ASCVD was higher in ORAL Surveillance (15%) than in P123LTE-CV+ (8%) or P123LTE (4%). Otherwise, the baseline CV risk profile of P123LTE-CV+ was similar to that of ORAL Surveillance (figure 1A).[2] Mean baseline disease activity was high across cohorts (figure 1B). MACE IRs were highest in ORAL Surveillance followed by P123LTE-CV+and P123LTE (figure 1B). However, when comparing the patients without history of ASCVD in P123LTE-CV+ and ORAL Surveillance, MACE IRs were similar (figure 1C). There were relatively few patients with history of ASCVD in P123LTE-CV+ and few MACE. Accordingly, due to wide 95% CI for the IRs, differences comparing P123LTE-CV+ and ORAL Surveillance were difficult to interpret (figure 1D).

In ORAL Surveillance, markedly higher MACE IRs were reported in tofacitinib-treated patients with history of ASCVD than in patients who had CV risk factors but no history of ASCVD.[2] Also, excess risk of MACE with tofacitinib vs TNFi was apparent primarily in patients with history of ASCVD.[2] Data from the wider tofacitinib clinical trial programme did not indicate increased risk of MACE compared with placebo or bDMARDs[3 6]; however, the comparative analyses were limited by smaller samples and shorter exposure than ORAL Surveillance and were not enriched for CV risk.

Results presented here suggest that an important difference between P123LTE and ORAL Surveillance was the proportion of patients with a history of ASCVD (4% and 15%, respectively). While the mechanism and generalisability of these findings require further study, they provide important context regarding the CV safety of tofacitinib in patients without a history of ASCVD.

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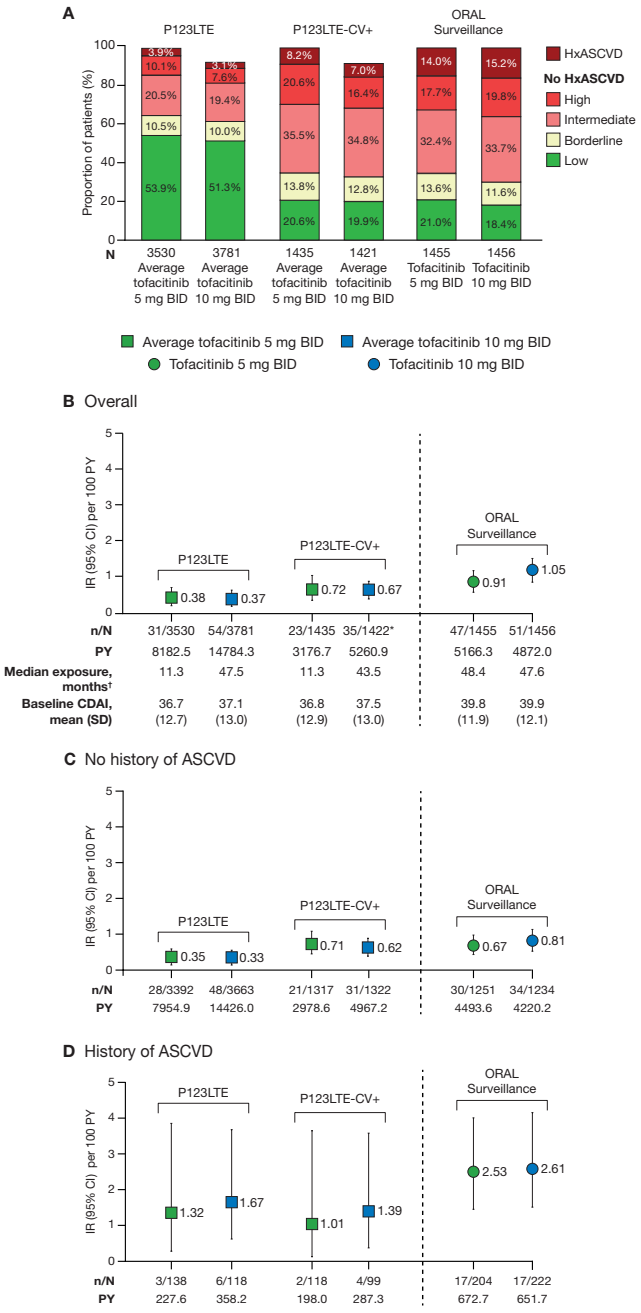

Figure 1 Risk of MACE in P123LTE, P123LTE-CV+ and ORAL Surveillance. (A) Baseline risk profiles. Patients without history of ASCVD were categorised according to their 10-year risk of MACE, per the ASCVD-PCE risk calculator[4] with a 1.5-multiplier applied.[5] The proportions of patients who had no history of ASCVD and were missing ASCVD-PCE risk category data are not shown (P123LTE: average tofacitinib 5 mg two times per day, n=42 (1.2%); average tofacitinib 10 mg two times per day n=321 (8.5%); P123LTE-CV+: average tofacitinib 5 mg two times per day, n=18 (1.3%); average tofacitinib 10 mg two times per day, n=130 (9.1%); ORAL Surveillance: tofacitinib 5 mg two times per day, n=17 (1.2%); tofacitinib 10 mg two times per day, n=18 (1.2%)). (B–D) IRs and 95% CIs (number of patients with first events per 100 PY) for MACE in: (B) all patients; (C) patients with no history of ASCVD; and (D) patients with history of ASCVD. For patients randomised to the tofacitinib 10 mg two times per day group in ORAL Surveillance who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two times per day group. Data for P123LTE cohorts included patients from RA studies (NCT01262118, NCT01484561, NCT00147498, NCT00413660, NCT00550446, NCT00603512, NCT00687193, NCT01164579, NCT00976599, NCT01059864, NCT01359150, NCT02147587, NCT00960440, NCT00847613, NCT00814307, NCT00856544, NCT00853385, NCT01039688, NCT02281552, NCT02187055, NCT02831855, NCT00413699, NCT00661661) with the CV adjudication process applied after 25 February 2009. Data from ORAL Surveillance (NCT02092467) have been published.[1 2] *One patient included in the overall analyses was excluded from the analyses by CV risk history due to an inactive Standardised MedDRA Query. †Treatment exposure was assessed in P123LTE as the time between first and last tofacitinib doses (including patients in studies prior to 25 February 2009 with no CV adjudication) and in ORAL Surveillance as the time from randomisation to last contact. ASCVD, atherosclerotic cardiovascular disease; BID, two times per day; CDAI, Clinical Disease Activity Index; CV, cardiovascular; HxASCVD, history of ASCVD; IR, incidence rate; MACE, major adverse CV events; n, number of patients with event; N, number of evaluable patients; P123LTE, Phase 1–3b/4 and long-term extension studies; P123LTE-CV+, CV risk-enriched population of P123LTE; PCE, pooled cohort equations; PY, patient-years; RA, rheumatoid arthritis.

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Upon request, and subject to review, Pfizer Inc will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer Inc may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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