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AN INTEGRATED ANALYSIS OF CHANGES IN LIPID LEVELS AND INCIDENCE OF CARDIOVASCULAR EVENTS FOLLOWING TOFACITINIB TREATMENT IN PATIENTS WITH PSORIATIC ARTHRITIS ACROSS PHASE 3 AND LONG-TERM EXTENSION STUDIES

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Background: Cardiovascular (CV) disease and cardiometabolic syndrome are common comorbidities/causes of mortality in patients (pts) with psoriatic arthritis (PsA). Tofacitinib is an oral JAK inhibitor for the treatment of PsA.

Objectives: To investigate changes in lipid levels and incidence of CV events in pts with PsA treated with tofacitinib in Phase (P) 3 and long-term extension (LTE) studies.

Methods: Data were analysed for pts who received ≥ 1 dose of tofacitinib 5 or 10 mg BID or placebo (PBO), integrated across 2 P3 studies (OPAL Broaden [12 months (m); NCT01877668, including adalimumab control]; OPAL Beyond [6 m; NCT01882439]) and 1 LTE study (OPAL Balance [data cut-off May 2016; ongoing, database not locked; NCT01976364]). Lipid levels were assessed throughout P3 and LTE studies; this analysis included data from the PBO-controlled period (M0–3) of P3 studies. Blood pressure, hypertension events (standardised MedDRA query [narrow]) and adjudicated (independent/blinded to treatment) major adverse cardiovascular events (MACE) are reported for all pts who received ≥ 1 dose of tofacitinib (pooled across doses for hypertension and MACE). Incidence rates (IR; pts with events/100 pt-years [PY]) and 95% CI are reported.

Results: Overall, 783 pts (776 PY of tofacitinib exposure) were included in P3 and LTE studies; treatment duration was 1–927 days. After 3 m of tofacitinib treatment in P3 studies, dose-dependent increases in lipid levels were observed with tofacitinib; minimal changes were observed with PBO, except for triglycerides (figure 1). Concurrent increases in high-density and low-density lipoprotein (HDL/LDL) and no change in the total cholesterol/HDL ratio were shown. Across P3 and LTE studies, no clinically significant changes in mean systolic or diastolic blood pressure were seen to 24 m. Hypertension events were reported in 38 (4.9%) pts: IR 4.93 [95% CI 3.49, 6.77]. Of these events, 4 led to pt discontinuation and 2 were serious adverse events. MACE were reported for 3 (0.4%) pts receiving tofacitinib (IR 0.38 [95% CI 0.08, 1.11]) and included sudden cardiac death (57 days of exposure at time of event), myocardial infarction (197 days) and ischaemic stroke (80 days). This is within the range reported in tofacitinib studies in pts with psoriasis (IR 0.24 [0.15, 0.37]; 8,759 PY of exposure) and rheumatoid arthritis (RA) (IR 0.38 [0.30, 0.47]; 21,286 PY of exposure). No dose-dependent effects on blood pressure were apparent.

Figure. Mean % change from baseline in lipid levels to Month 3 integrated across Phase 3 studies

BID, twice daily; SE, standard error

Abstract THU0299 – Figure 1. Mean% change from baseline in lipid levels to Month 3 integrated across Phase 3 studies. BID, twice daily; SE, standard error

Conclusions: In pts with PsA, the magnitude and dose dependency of increases in lipid levels to M3 were consistent with findings in tofacitinib studies in pts with psoriasis and RA. In P3 and LTE studies, no clinically significant changes were seen in blood pressure or incidence of hypertension. Incidence of MACE was within the range reported in prior tofacitinib studies in psoriasis and RA; however, the long latency of MACE requires longer-term observation.

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NETWORK META-ANALYSIS OF TOFACITINIB VS bDMARDS OR APREMILAST FOR THE TREATMENT OF TNF INHIBITOR-NAÏVE PATIENTS WITH PSORIATIC ARTHRITIS

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Background: Tofacitinib is an oral JAK inhibitor for the treatment of psoriatic arthritis (PsA).

Objectives: To perform a systematic literature review (SLR) and network meta-analysis (NMA) to evaluate the efficacy of tofacitinib 5 and 10 mg BID relative to biologic disease-modifying antirheumatic drugs (bDMARDs) or a targeted synthetic DMARD (apremilast [APR]) in tumour necrosis factor inhibitor-naïve (TNFi-N) patients with active PsA.

Methods: The SLR identified randomised controlled clinical trials (RCTs) evaluating tofacitinib, bDMARDs or APR to treat patients with active PsA who were TNFi-N. Outcomes included American College of Rheumatology (ACR)20 response and change from baseline in Health Assessment Questionnaire-Disability Index (Δ HAQ-DI), Dactylitis Severity Score (Δ DSS) and Leeds Enthesitis Index (Δ LEI). Treatment effects were only evaluated during placebo (PBO)-controlled trial phases. The Bayesian NMA (with non-informative priors) was conducted using WinBUGS. The binomial logit model was used for ACR20, Δ HAQ-DI, Δ DSS and Δ LEI were analysed using the normal identity link model. A fixed-effect model was fitted to the data. Median treatment rankings represent data from each iteration of the model from which inferences are based, following model convergence.

Results: The SLR identified 25 RCTs and 21 were included in the NMA (see treatments in table 1). All trials allowed methotrexate use. PBO-controlled treatment durations ranged from 12–24 weeks. In general, patient characteristics were similar across trials. All treatments were associated with improvements in ACR20 and Δ HAQ-DI vs PBO. Tofacitinib 5 mg BID was associated with substantially decreased odds ratios (ORs) for ACR20 vs golimumab 50 and 100 mg Q4W, etanercept 25 mg BW, infliximab 5 mg/kg and secukinumab 150 mg QW-Q4W (table 1); ORs for all remaining comparators were not substantially different. Tofacitinib 10 mg BID was associated with a substantially increased OR for ACR20 vs APR 20 mg BID. Etanercept was associated with an improvement in Δ HAQ-DI vs tofacitinib 5 and 10 mg BID. There was no difference in Δ HAQ-DI for tofacitinib vs other bDMARDs. For ACR20, tofacitinib 5 and 10 mg BID were median ranked 14 (95% credible interval: 8, 17) and 9, ^{5, 14} respectively, among 18 comparators. For Δ HAQ-DI, tofacitinib 5 and 10 mg BID were median ranked 11 ^{4, 13} and 8, ^{2, 13} respectively, among 14 comparators. Two studies evaluated Δ DSS and Δ LEI; there were no substantial differences in Δ DSS and Δ LEI for tofacitinib 5 and 10 mg BID vs adalimumab 40 mg Q2W and ixekizumab 80 mg Q2W and Q4W.