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Background: ORAL Shift, a global Phase 3b/4 non-inferiority study, demonstrated sustained efficacy and safety of tofacitinib modified-release (MR) 11 mg once daily (QD) following methotrexate (MTX) withdrawal in patients with rheumatoid arthritis (RA) who achieved Clinical Disease Activity Index (CDAI) low disease activity (LDA) after treatment with tofacitinib + MTX.¹

Objectives: To assess predictors of durable clinical response in patients receiving tofacitinib MR 11 mg QD in ORAL Shift.

Methods: ORAL Shift (NCT02831855) enrolled patients aged ≥18 years with moderate to severe RA and an inadequate response to MTX. Patients received open-label tofacitinib MR 11 mg QD + MTX for 24 weeks. Patients achieving LDA (CDAI score ≤10) at Week (W)24 entered the 24-week double-blind MTX withdrawal phase and were randomised 1:1 to receive tofacitinib MR 11 mg QD + placebo (tofacitinib monotherapy; ie blinded MTX withdrawal) or continue tofacitinib + MTX. In this post hoc analysis of randomised patients, we assessed predictors of durable response (maintenance of response from W24–48) per CDAI LDA and remission (CDAI score ≤2.8) criteria. All covariates were initially assessed for significance in a univariate logistic regression. Highly correlated covariates were reviewed to assess which would be removed prior to modelling in a multivariable logistic regression. Remaining significant (p≤0.10) covariates in the univariate regression were selected in the model using a stepwise selection process with p≤0.15 entry and p≤0.05 stay criteria. From the final model, estimated odds ratios (ORs) with 95% confidence intervals (CIs) are presented.

Results: In the double-blind phase of ORAL Shift, durable CDAI LDA and remission rates were: 66.2% and 14.7%, respectively, with tofacitinib + MTX (N=266); and 55.3% and 11.0%, respectively, with tofacitinib + placebo (N=264) (Table 1). In the multivariable analysis, five patient covariates significantly predicted durable CDAI LDA (Figure 1; discussed hereafter). Each unit increase in CDAI score at W24 reduced the likelihood of maintaining CDAI LDA by 22.0%. Each unit increase in C-reactive protein (CRP) at W24 increased the likelihood of maintaining CDAI LDA by 4.0%; this may have been due to imbalanced CRP levels at W24 (randomisation) between treatment groups (Figure 1, footnote c). The odds of durable CDAI LDA were 53.0% lower in the US vs Europe and 61.0% lower in the US vs 'other' regions. Each unit increase in baseline Health Assessment Questionnaire-Disability Index (HAQ-DI) score reduced the odds of durable CDAI LDA by 34.0%. Patients receiving tofacitinib + MTX had 66.0% greater odds of durable CDAI LDA vs patients receiving tofacitinib + placebo. CDAI at W24 was the only significant predictor of durable CDAI remission in the multivariable analysis: OR (95% CI) 0.32 (0.24, 0.43); p<0.0001. Each unit increase in CDAI score at W24 reduced the odds of durable CDAI remission by 68.0%.

Table 1. Durable CDAI LDA and remission^a in patients receiving tofacitinib MR 11 mg QD with MTX or placebo in the double-blind phase of ORAL Shift

	Tofacitinib + MTX (N=266)	Tofacitinib + placebo (N=264)
Durable CDAI LDA, n (%)	176 (66.2)	146 (55.3)
Durable CDAI remission, n (%)	39 (14.7)	29 (11.0)

^aDurable CDAI LDA or remission was defined as achievement of LDA (CDAI score ≤10) or remission (CDAI score ≤2.8), respectively, at W24–48
N, number of patients in each group; n, number of patients achieving outcome

Conclusion: This post hoc analysis of data from ORAL Shift found that CDAI and CRP at W24, geographic region, baseline HAQ-DI and treatment could be predictors for durable CDAI LDA. As these findings were limited to patients who achieved CDAI LDA at W24 with tofacitinib MR 11 mg QD + MTX, additional data in the general patient population need to be investigated.

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POS0651 **CLINICAL AND FUNCTIONAL RESPONSE TO TOFACITINIB IN PATIENTS WITH RHEUMATOID ARTHRITIS: PROBABILITY PLOT ANALYSIS OF RESULTS FROM A 48-WEEK PHASE 3b/4 METHOTREXATE WITHDRAWAL STUDY**

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Background: The Phase 3b/4 study ORAL Shift (NCT02831855) demonstrated sustained efficacy/safety of tofacitinib modified-release 11 mg QD following MTX withdrawal, that was non-inferior to continued tofacitinib + MTX use, in patients (pts) with moderate to severe RA who achieved LDA with tofacitinib + MTX at Week (W)24.¹

Objectives: To assess differences and similarities in clinical/functional responses in pts receiving tofacitinib ± MTX in ORAL Shift.

Methods: In ORAL Shift, pts received open-label tofacitinib + MTX to W24; at W24, pts who achieved CDAI LDA were randomised to receive tofacitinib + MTX or tofacitinib + placebo (PBO) from W24–48. In this post hoc analysis, clinical efficacy endpoints were ACR-N (minimum % change from baseline [BL; Δ] at W48 achieved by each pt in 3 efficacy measures), ΔDAS28-4(ESR), and DAS28-4(ESR) remission/LDA (scores ≤3.2) and moderate/high disease activity (scores >3.2). Functional efficacy endpoints were ΔHAQ-DI and HAQ-DI clinically relevant functional progression (CRFP) status at W48, defined as failure to achieve improvement in HAQ-DI ≥ minimum clinically important difference (MCID; ≥0.22 decrease from BL in HAQ-DI). Thus, CRFP was defined as <0.22 decrease, no change or increase from BL in HAQ-DI at W48. All efficacy endpoints were summarised descriptively. Cumulative probability plots of ACR-N and ΔHAQ-DI were produced. Median of mean CRP values from BL–W24 and >W24–48 were assessed by response subgroups.

Results: 266 pts receiving tofacitinib + MTX and 264 pts receiving tofacitinib + PBO in W24–48 were included. At W48: mean ACR-N was numerically greater with tofacitinib + MTX vs tofacitinib + PBO (60.8 vs 53.1); mean decrease in HAQ-DI was generally similar between groups (-0.71 vs -0.67); mean decrease in DAS28-4(ESR) was numerically greater with tofacitinib + MTX vs tofacitinib + PBO (-2.95 vs -2.68). The differences/similarities between groups in ACR-N and ΔHAQ-DI were also seen in cumulative probability plots (Figure 1). CRFP rates were numerically lower with tofacitinib + MTX (18.7%) vs tofacitinib + PBO (23.5%), and in pts with remission/LDA (tofacitinib + MTX, 12.1%; tofacitinib + PBO, 16.8%) vs moderate/high disease activity (tofacitinib + MTX, 26.2%; tofacitinib + PBO, 30.8%). Median of mean CRP over time was generally numerically lower in pts with CRFP vs non-CRFP and DAS28-4(ESR)-defined remission/LDA vs moderate/high disease activity; and in those receiving tofacitinib + PBO vs tofacitinib + MTX, irrespective of CRFP or DAS28-4(ESR) disease status (Table 1).

Table 1. Median of mean CRP^a up to W48 by response subgroups

	Tofacitinib 11 mg QD + MTX		Tofacitinib 11 mg QD + PBO	
Mean CRP, ^a median (IQR) [n]	>BL–W24	>W24–48	>BL–W24	>W24–48
HAQ-DI CRFP	2.84 (1.15–7.30) [45]	2.30 (0.82–4.75) [46]	1.45 (0.77–4.42) [56]	2.28 (0.53–7.28) [56]
HAQ-DI non-CRFP	2.81 (1.09–6.19) [195]	2.91 (1.19–5.84) [195]	2.26 (0.98–4.63) [176]	2.47 (1.13–5.53) [178]
DAS28-4(ESR) remission/LDA	2.48 (1.05–4.95) [126]	2.46 (1.07–4.76) [127]	1.70 (0.89–4.14) [115]	1.95 (0.81–3.82) [117]
DAS28-4(ESR) moderate/high disease activity	3.56 (1.17–7.13) [107]	3.58 (1.36–8.33) [107]	2.60 (0.87–5.16) [115]	2.68 (1.34–8.23) [115]

^aMean CRP was calculated as the average CRP value during each time period (>BL–W24 or >W24–48)

CRP, C-reactive protein; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; IQR, interquartile range; LDA, low disease activity; MTX, methotrexate; n, number of pts meeting assessment criteria; QD, once daily

Figure. Cumulative probability plot at W48 for a) ACR-N; b) ΔHAQ-DI score

Endpoints were assessed using the full analysis set (defined as all pts receiving ≥1 dose of study drug with ≥1 value post-baseline), with no imputation for missing values.
ACR-N, American College of Rheumatology response, where N represents the minimum amount of improvement expressed by each pt in % ΔTJC28, % ΔSJC28, and the median of % Δ in PGA, Pain, HAQ-DI and CRP; CRP, C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; MR, modified release; MTX, methotrexate; PGA, Physician Global Assessment; TJC28, Patient Global Assessment; QD, once daily; SJC28, swollen joint count in 28 joints; TJC28, tender joint count in 28 joints

Conclusion: Although clinical/functional responses were generally similar between treatment groups, numerical improvements were seen for some efficacy endpoints with tofacitinib + MTX vs tofacitinib + PBO. A numerically higher CRFP rate may be associated with higher DAS28-4(ESR) disease activity. CRP changes up to W48 may not trend with CRFP status.

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POS0652

SEX DIFFERENCES IN THE EFFICACY AND SAFETY OF TOFACITINIB IN RHEUMATOID ARTHRITIS PATIENTS: A POST HOC ANALYSIS OF PHASE 3 AND LONG-TERM EXTENSION TRIALS

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Background: Differences in efficacy outcomes favouring males vs females with rheumatoid arthritis (RA) have been reported with conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs) and tumour necrosis factor inhibitors; results with Janus kinase inhibitors are less clear.

Objectives: To assess the impact of sex on efficacy, safety and persistence in tofacitinib RA clinical trials.

Methods: Efficacy and safety analyses included data pooled from Phase (P)3 randomised controlled trials (RCTs) of patients (pts) with RA and an inadequate response (IR) to methotrexate (NCT00847613; NCT00853385) or ≥1 DMARD (NCT00856544) who received tofacitinib 5 or 10 mg twice daily (BID), adalimumab (ADA) 40 mg Q2W or placebo (PBO), with background csDMARDs. Persistence analyses of pts receiving tofacitinib 5 or 10 mg BID ± csDMARDs used data pooled from two long-term extension trials (NCT00661661; NCT00413699). Efficacy outcomes to Month (M)12 included: ACR20/50/70 responses, changes from baseline (Δ; BL) in DAS28-4(ESR), CDAI, HAQ-DI and FACIT-F, and DAS28-4(ESR) remission (<2.6). Safety was evaluated to M24 for tofacitinib and ADA. Kaplan-Meier persistence analysis estimated time to discontinuation.

Results: 2265 pts were included from P3 RCTs. Demographics and BL characteristics were comparable across sexes and treatments. Tofacitinib or ADA vs PBO generally led to significantly higher ACR20/50/70 responses in both sexes through M6. To M12, ACR20/50/70 responses were broadly comparable across active treatments and between sexes, with significant differences favouring males at some time points, including M3 (Figure 1). Statistically significant differences favouring males vs females were observed in DAS28-4(ESR) remission rates at most time points, including M3 (Figure 1); a similar trend was observed for ΔDAS28-4(ESR). ΔCDAI, ΔHAQ-DI and ΔFACIT-F significantly favoured males vs females receiving tofacitinib 5mg BID at most time points, while ΔHAQ-DI and ΔFACIT-F tended to favour females receiving tofacitinib 10mg BID. Rates of adverse events (AEs), serious AEs (SAEs), severe AEs and discontinuations due to AEs were slightly higher in females vs males with tofacitinib 5mg BID; this was generally reversed with tofacitinib 10mg BID and ADA (Table 1). AEs of special interest (AESI) were comparable between sexes with tofacitinib and ADA, although low event numbers limit interpretation (Table 1). Time to all-cause discontinuation and discontinuation due to AEs/lack of efficacy with tofacitinib 5mg BID was similar between sexes. Numerical differences favouring females vs males were observed for time to all-cause discontinuation and discontinuation due to AEs with tofacitinib 10mg BID.

Table 1. Safety summary to M24 in pooled DMARD-IR P3 RCTs

	Tofacitinib 5mg BID		Tofacitinib 10mg BID		ADA	
Pts with events, n (%)	Females (N=707)	Males (N=133)	Females (N=698)	Males (N=137)	Females (N=162)	Males (N=42)
AEs	562 (79.5)	85 (63.9)	529 (75.8)	107 (78.1)	119 (73.5)	30 (71.4)
SAEs	107 (15.1)	17 (12.8)	71 (10.2)	24 (17.5)	13 (8.0)	6 (14.3)
Severe AEs	86 (12.2)	12 (9.0)	55 (7.9)	22 (16.1)	14 (8.6)	5 (11.9)
Discontinuations due to AEs	87 (12.3)	10 (7.5)	88 (12.6)	10 (7.3)	17 (10.5)	5 (11.9)
Death	6 (0.8)	4 (3.0)	0	3 (2.2)	1 (0.6)	2 (4.8)
AESI						
Serious infections	28 (4.0)	6 (4.5)	27 (3.9)	6 (4.4)	2 (1.2)	1 (2.4)
All HZ (non-serious/serious)	35 (5.0)	7 (5.3)	43 (6.2)	5 (3.6)	2 (1.2)	3 (7.1)
MACE	5 (0.7)	0	2 (0.3)	3 (2.2)	0	3 (7.1)
Malignancies (excl. NMSC)	7 (1.0)	1 (0.8)	9 (1.3)	1 (0.7)	0	1 (2.4)
NMSC	2 (0.3)	5 (3.8)	4 (0.6)	2 (1.5)	1 (0.6)	1 (2.4)
Venous thromboembolism	3 (0.4)	0	3 (0.4)	1 (0.7)	0	0

HZ, herpes zoster; MACE, major adverse cardiovascular events; NMSC, non-melanoma skin cancer