Figure 1. Kaplan-Meier curves of MTX and HCQ monotherapies and MTX+HCQ combination therapy, with (a) survival to first ADR and (b) drug survival.

Conclusion: Patients using MTX+HCQ combination therapy are more likely to experience an ADR during the first time drug use compared to MTX and HCQ monotherapies. MTX+HCQ combination therapy also leads to experiencing an ADR sooner compared to both monotherapies. Drug survival of patients treated with HCQ monotherapy as well as MTX+HCQ combination therapy is shorter compared to MTX monotherapy.

Disclosure of Interests: Kimberly Velthuis: None declared, My Nguyen: None declared, Joep Scholl: None declared, Jurriaan Jansen: None declared, Jette van Lint: None declared, Peter ten Klooster: None declared, Harald Vonkeman Consultant of: BMS, Celgene, Celltrion, Galapagos, Gilead, Janssen-Cilag, Lilly, Novartis, Pfizer, Sanofi-Genzyme, Grant/research support from: Abbvie, Naomi Jessurun: None declared

DOI: 10.1136/annrheumdis-2021-eular.181

POS0649

BARICITINIB PROVIDES GREATER IMPROVEMENTS IN PATIENT-REPORTED OUTCOMES ACROSS ALL DISEASE ACTIVITY LEVELS COMPARED TO PLACEBO AND ADALIMUMAB IN RHEUMATOID ARTHRITIS

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Background: Baricitinib (BARI) is a JAK1/JAK2 inhibitor which provides improvements to clinical signs, symptoms, and patient-reported outcomes (PROs) in patients with rheumatoid arthritis [1, 2].

Objectives: The effect of BARI on the relationship between disease activity and pain has been explored previously [3]. The purpose of this post hoc analysis was to determine the association between additional PROs (physical function, fatigue, and duration of morning joint stiffness) and disease activity status after 12 weeks of treatment and to evaluate whether patients with an inadequate response to methotrexate treated with BARI 4mg experienced greater PRO improvement than patients treated with either placebo (PBO) or adalimumab (ADA) across all levels of disease activity.

Methods: Data for these analyses were derived from the Phase 3 study RA-BEAM (N=1305; NCT01710358). Pain was evaluated using a 0-100mm visual analog scale, physical function was assessed using the Health Assessment Questionnaire-Disability Index (HAQ-DI), fatigue was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale, and

duration of morning joint stiffness (MJS, minutes) was reported by the patient. Disease activity was measured using the Clinical Disease Activity Index (CDAI) and categorized as remission (REM, ≤ 2.8), low disease activity (LDA, >2.8 to ≤ 10), moderate disease activity (MDA, >10 to ≤ 22), or high disease activity (HDA, >22). Linear regression was used to model the relationship between change in PROs at Week 12 (response) and CDAI values at Week 12 (primary explanatory variable) to evaluate the extent of improvement in PROs with BARI relative to PBO and ADA across a spectrum of disease activity levels. Last observation carried forward was used to impute missing values.

Results: At baseline, 91% of patients were classified as having HDA and 9% as having MDA by CDAI across all treatment groups. After 12 weeks of treatment, 2%, 7%, and 9% of patients achieved REM; 16%, 27%, and 33% of patients achieved LDA; and 33%, 40%, and 38% of patients achieved MDA with PBO, ADA, and BARI, respectively [3].

At Week 12, the estimated changes in measures of pain and physical function, as well as duration of MJS, for BARI 4mg were greater than both PBO and ADA at all disease activity level threshold values of CDAI (Table 1). The estimated change in fatigue for BARI 4mg was similar to that of ADA, and greater than PBO, at all disease activity level threshold values (Table 1).

Table 1. Estimate of PRO Improvement by Disease Activity Threshold Level (CDAI) at Week 12

PRO	CDAI=2.8			CDAI=10			CDAI=22		
	PBO	ADA	BARI 4 mg	PBO	ADA	BARI 4 mg	PBO	ADA	BARI 4 mg
Pain VAS ^a (mm)	-28.4	-37.9	-40.9	-24.5	-32.6	-36.1	-18.0	-23.7	-28.1
HAQ-DI ^b	-0.6	-0.7	-0.9	-0.5	-0.7	-0.7	-0.4	-0.5	-0.6
FACIT-F ^c	9.8	11.8	11.1	8.8	10.6	10.2	7.0	8.7	8.7
Duration of MJS (min)	-6.9	-37.8	-64.9	-6.3	-35.3	-55.7	-5.3	-31.3	-40.2

^aPain VAS scores range from 0 (no pain) to 100 (worst pain).

^bHAQ-DI scores range from 0 (no disability) to 3 (completely disabled).

^cFACIT-F scores range from 0 (worst fatigue) to 52 (no fatigue).

Abbreviations: ADA, adalimumab; BARI, baricitinib; CDAI, Clinical Disease Activity Index; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; MJS, morning joint stiffness; PBO, placebo; PRO, patient-reported outcomes; VAS, visual analog scale.

Conclusion: Estimates of treatment differences suggest that patients treated with BARI 4mg may experience greater improvements in pain, physical function, and MJS duration than patients treated with PBO or ADA regardless of their disease activity status reached after 12 weeks of treatment. Using this approach, improvements in fatigue with BARI 4mg may be greater than with PBO and similar to ADA after 12 weeks.

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Acknowledgements: The authors would like to acknowledge Catherine Lynch, with Eli Lilly and Company, for medical writing and project management support.

Disclosure of Interests: Peter C. Taylor Consultant of: AbbVie, Biogen, Galapagos, Gilead, GlaxoSmithKline, Janssen, Eli Lilly, BMS, Pfizer, Roche, Celltrion, Sanofi, Nordic Pharma, Fresenius and UCB, Grant/research support from: Celgene, Galapagos, Gilead, Eli Lilly, Ricardo Blanco Speakers bureau: Abbvie, Pfizer, Roche, BMS, Janssen, Eli Lilly and MSD, Consultant of: Abbvie, Pfizer, Roche, BMS, Janssen, Eli Lilly and MSD, Grant/research support from: Abbvie, MSD, and Roche, Kei Ikeda Speakers bureau: Eli Lilly, Abbvie, Mitsubishi-Tanabe, Novartis, Paid instructor for: Abbvie, Grant/research support from: Mitsubishi-Tanabe, Bochoa Jia Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, Yun-Fei Chen Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, Chad Walls Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, Ewa Haladyj Employee of: Eli Lilly and Company, Bruno Fautrel Speakers bureau: Eli Lilly, Consultant of: AbbVie, Biogen, Bristol-Myers Squibb, Celgene, Janssen Pharmaceuticals, Eli Lilly and Company, Medac, MSD, NORDIC Pharma, Novartis, Pfizer Inc., Roche, Sanofi-Aventis, SOBI, UCB, Grant/research support from: AbbVie, Eli Lilly and Company, MSD, Pfizer Inc

DOI: 10.1136/annrheumdis-2021-eular.182

POS0650

PREDICTORS OF DURABLE CLINICAL RESPONSE TO TOFACITINIB 11 MG ONCE DAILY WITH OR WITHOUT METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS: POST HOC ANALYSIS OF DATA FROM A PHASE 3a/4 METHOTREXATE WITHDRAWAL STUDY

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TX, United States of America; ³Pfizer Japan Inc, Inflammation and Immunology, Tokyo, Japan; ⁴Pfizer Inc, Inflammation and Immunology, Collegeville, PA, United States of America; ⁵Pfizer SLU, Inflammation and Immunology, Madrid, Spain; ⁶Medical University of Vienna, Department of Rheumatology, Vienna, Austria

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 ($p \leq 0.10$) covariates in the univariate regression were selected in the model using a stepwise selection process with $p \leq 0.15$ entry and $p \leq 0.05$ 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

Figure. Multivariable regression results for predictors of durable CDAI LDA in patients receiving tofacitinib MR 11 mg QD with MTX or placebo in the double-blind phase of ORAL Shift

^aDurable CDAI LDA was defined as achievement of LDA (CDAI score ≤10) at W24–48. ^bThe Wald chi-squared test p value for that comparison. ^cMean CRP levels at W24 (randomisation) were 25.6% higher in the tofacitinib + MTX group (mean CRP 5.05 mg/L) vs tofacitinib + placebo group (mean CRP 4.02 mg/L). During the double-blind phase, CRP stabilised with tofacitinib + MTX but increased with tofacitinib + placebo. The CRP differences between treatment groups may have impacted the CDAI LDA durability outcome. ^dOther refers to Australia, Korea, Philippines, Mexico and South Africa.

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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Acknowledgements: Study sponsored by Pfizer Inc. Medical writing support was provided by Sarah Piggott, CMC Connect, and funded by Pfizer Inc.

Disclosure of Interests: Kunihiro Yamaoka Speakers bureau: Actelion, Astellas, Chugai, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Mitsubishi Tanabe, Nippon Shinyaku, Pfizer Inc, Takeda, Consultant of: Actelion, Astellas, Chugai, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Mitsubishi Tanabe, Nippon Shinyaku, Pfizer Inc, Takeda, Stanley B. Cohen Consultant of: AbbVie, Eli Lilly, Genentech, Gilead Sciences, Pfizer Inc, Grant/research support from: AbbVie, Eli Lilly, Genentech, Gilead Sciences, Pfizer Inc, Naonobu Sugiyama Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, Harry Shi Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, Jose Luis Rivas Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, Annette Diehl Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, Josef S. Smolen Consultant of: AbbVie, AstraZeneca, Celgene, Celltrion, Chugai, Eli Lilly, Gilead Sciences, ILTOO, Janssen, Novartis-Sandoz, Pfizer Inc, Roche, Samsung, Sanofi, Grant/research support from: AbbVie and AstraZeneca

DOI: 10.1136/annrheumdis-2021-eular.357

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).