Research Article

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Etanercept in moderate rheumatoid arthritis: PRESERVE study results from central/eastern Europe, Latin America and Asia

Aims: We compared etanercept 50 mg once weekly (ETN50)/methotrexate versus etanercept 25 mg (ETN25)/methotrexate or biologic-free methotrexate after response to ETN50/methotrexate in moderate rheumatoid arthitis patients from central/eastern Europe, Latin America and Asia. **Methods:** In a 36-week induction phase, methotrexate-resistant patients received ETN50/methotrexate. In a 52-week, double-blind phase, patients who achieved sustained Disease Activity Score in 28 joints low disease activity (LDA) were randomized to ETN50/methotrexate, ETN25/methotrexate or methotrexate. **Results:** Sustained Disease Activity Score in 28 joints LDA was achieved in 85% at week 36. LDA was achieved in 83, 81 and 50% with ETN50/methotrexate, ETN25/methotrexate and methotrexate and remission in 66, 61 and 31%, respectively, at week 88 ($p < 0.0001$). **Conclusion:** Etanercept/methotrexate therapy for 36 weeks effectively induced response in this moderate rheumatoid arthritis subpopulation. Conventional- and reduced-dose etanercept/methotrexate was significantly more effective over the subsequent 52 weeks than biologic-free therapy.

Keywords: biologic • efficacy • etanercept • low disease activity • methotrexate • moderate rheumatoid arthritis • remission

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Early in the course of the disease, active inflammation may lead to irreversible joint damage and functional disability in patients with rheumatoid arthritis (RA) [1–3]. The degree of joint damage is linked to the level of disease activity at the time of therapy initiation and its progression over the treatment duration [1,4–5]; therefore, the extent of disease activity reduction is associated with the level of functional disability improvement [1–2,6–7]. The primary goal of treatment of RA is to achieve long-term clinical remission or substantial reduction of disease activity to reduce these risks [8].

Biologic therapies such as anti-TNF agents have allowed disease remission and low disease activity to become increasingly achievable goals in patients with RA. Although studies have shown that patients with lower disease activity may experience progressive joint destruction and significant disability [7,9–10], treatment outcomes in patients with moderately active RA, who represent a large segment of the overall RA population [11–13], have not been well studied. Moreover, controlled studies of biologic agents have primarily evaluated the effects of treatment in North American and western European study populations. Given their large, distinctive populations, central and eastern Europe, Latin American and Asia represent unique geographical regions in terms of treatment of RA and access to biologic therapies. Biologic agents were introduced to central and eastern Europe, Latin America and Asia after their introduction in North America and western Europe and are generally administered less frequently in these regions to treat RA. Local treatment guidelines vary widely in these regions, but biologic use is often limited to patients with highly active disease despite previous treatment with several disease-modifying antirheumatic drug (DMARD) regimens,

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primarily owing to the high cost of biologic therapies relative to traditional DMARDs, such as methotrexate (MTX). Induction–maintenance–withdrawal strategies, calling for biologic dose adjustment or withdrawal after the targeted treatment response is achieved, are of particular interest in these regions and worldwide [14]. However, primarily observational data on such strategies have been reported in the literature to date [15–17].

The multinational, randomized, controlled PRESERVE trial (a prospective randomized etanercept study to evaluate reduced dose etanercept MTX vs full dose etanercept + MTX vs MTX alone for efficacy and radiographic end points in a moderate RA population) was designed to assess the induction of clinical response with biologic conventional-dose therapy (etanercept) on background MTX in adults with moderately active RA despite previous treatment with MTX, with subsequent evaluation of the maintenance of clinical, functional and radiographic outcomes with etanercept conventional or reduced doses or with etanercept withdrawal (i.e., biologic-free), when continuing MTX therapy. Results from the overall PRESERVE study population indicated that in patients with moderately active RA who achieved sustained low disease activity with conventional-dose etanercept/MTX therapy at 36 weeks, both the conventional- and reduced-dose combination regimens were superior to the biologic-free regimen across clinical, functional and structural outcomes at 88 weeks [18]. In this subanalysis, we explored outcomes observed in both the induction and maintenance periods of the PRESERVE study in a subpopulation of patients with moderately active RA from selected countries in central and eastern Europe, Latin America and Asia.

Methods

Patients & study design

The complete methodology of the PRESERVE study has been published elsewhere [18]. In brief, this two-period, multicenter investigation evaluated the effects of combination etanercept plus MTX therapy in patients with moderately active RA despite optimal stable doses of oral MTX, who were enrolled at 80 centers in Europe (Austria, Belgium, UK, France, Germany, Italy, The Netherlands, Spain, Sweden, Czech Republic, Hungary, Serbia, Montenegro, Poland and Russia), Latin America (Chile, Colombia and Mexico), Asia (Korea and Taiwan) and Australia, between 6 March 2008 and 9 September 2009. The subanalyses presented here included patients from central and eastern Europe (Czech Republic, Hungary, Poland, Russia and Serbia), Latin America (Chile, Colombia and Mexico) and Asia (Taiwan).

The main eligibility requirements for period 1 (open-label) included age 18–70 years and moderately active RA disease activity (Disease Activity Score based on a 28-joint count [DAS28] >3.2 and ≤5.1) at screening and baseline visits. In the investigators' opinion, all patients were receiving optimal oral doses of MTX once weekly; stable MTX doses of 15–25 mg/week for the treatment of RA, as tolerated, were required for ≥8 weeks at screening. Patients were excluded from period 1 if they had received: etanercept or any other biologic treatment; any DMARD except MTX within 28 days of baseline; or concurrent treatment with more than one NSAID at baseline. Patients also were ineligible if they: used prednisone (or equivalent) at a dose >10 mg/day or changed within 14 days of screening; used intra-articular, intravenous, intramuscular or subcutaneous glucocorticoid within 28 days of screening; received live vaccine within 28 days of baseline; or had active or recent (<2 years) tuberculosis (TB) infection (patients with latent TB infection were included only if local guidelines for prophylactic therapy were followed and if treatment of TB preceded etanercept therapy).

Patients were eligible for randomization to period 2 (double-blind) if they completed the first 36 weeks of period 1 and achieved sustained DAS28 (based on erythrocyte sedimentation rate) low disease activity, defined as an average DAS28 ≤3.2 points from weeks 12–36 and DAS28 ≤3.2 points at week 36. Patients were excluded from period 2 if they had received: an NSAID dose that changed within 14 days of randomization; prednisone (or equivalent) dose >10 mg/day or that changed within 14 days of randomization; or an MTX dose that changed within 8 weeks of randomization (except a reduced dose owing to adverse events).

All patients provided written informed consent before any study-related procedures were performed. This study was conducted according to the International Conference on Harmonization guidelines for Good Clinical Practice and the ethical principles that have their origins in the Declaration of Helsinki and was approved by the independent ethics committee or institutional review board at each participating center. This study is registered on ClinicalTrials.gov, number NCT00565409 [19].

Treatment

In period 1, all patients received etanercept 50 mg once weekly plus MTX (ETN50/MTX) for 36 weeks. Patients continued on the same screening dose of MTX as previously administered. At the investigator's discretion, the initial MTX dose was titrated up to a maximum of 25 mg/week until week 28. In patients who experienced intolerance to MTX, MTX administration

was withheld for up to two doses and/or reduced by 2.5 or 5.0 mg/week until tolerated. To remain in the study, patients had to receive MTX ≥10 mg/week.

Patients in period 2 were randomized (1:1:1 ratio) to one of three treatment groups: ETN50/MTX; reduced-dose etanercept 25 mg once weekly plus MTX (ETN25/MTX); or etanercept-matching placebo once weekly plus MTX (i.e., MTX monotherapy) for the subsequent 52 weeks. MTX administration was maintained at the same dose as the last 8 weeks of period 1.

Assessments

Efficacy evaluations included the proportions of patients achieving low disease activity based on DAS28 (≤3.2) [20] and Simplified Disease Activity Index (SDAI) (≤11) [21,22]; remission based on DAS28 (<2.6) [20], SDAI (≤3.3) [21,22] and the ACR/European League Against Rheumatism (EULAR) Boolean-based definition (i.e., tender joint count ≤1 and swollen joint count ≤1, C-reactive protein ≤1 mg/dl and patient global assessment ≤1 [0–10 scale]) [23]; and ACR 20/50/70 responses [24]. Patient-reported outcomes assessments included the Health Assessment Questionnaire (HAQ) total score (0–3, lower scores denote less functional disability and scores ≤0.50 represent normal; changes ≥0.22 considered clinically meaningful) [25,26]; the European Quality of Life 5-Dimensions (EQ-5D) utility index (0–1, higher scores denote better quality of life; changes ≥0.05 considered clinically meaningful) [27,28]; an assessment of pain (visual analog scale [VAS]; 0–100, minimum to maximum pain); a global assessment of overall arthritis activity (0–10, least to most activity); the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue questionnaire (0–52, higher scores denote less fatigue; changes ≥3.0 considered minimally clinically important) [29–31]; the Medical Outcomes Study (MOS) Sleep Scale, including measures of sleep adequacy and shortness of breath or headache and the Sleep Problems Index I (0–100, lower scores denote better sleep) [32]; the Brief Pain Inventory (BPI), including measures of interference (0–10, no interference to complete interference) and severity (0–10, no pain to worst pain; ≥30% improvement from worst pain considered clinically meaningful) [33]; and the Work Productivity and Activity Impairment (WPAI) questionnaire, including measures of activity impairment, impairment while working, overall work impairment and work time missed owing to RA (0–100%, lower percentages denote less work impairment) [34].

Statistical analyses

The same statistical analyses were conducted for the subpopulation reported here as for the overall study population [18]. All subpopulation analyses were performed using the modified intention-to-treat (mITT) efficacy population. In period 1, the mITT and safety populations included all patients who received at least one dose of study drug. In period 2, the mITT population comprised all patients who received at least one dose of study drug and at least one postrandomization DAS28 evaluation. The safety population in period 2 included all patients who received at least one dose of study drug.

For the subpopulation analyses, demographic and baseline disease characteristics were summarized with descriptive statistics and analyzed with one-way analysis of variance for continuous parameters and χ^2 tests for categorical parameters. In period 2, analyses of proportions were analyzed for all pairwise treatment differences using the χ^2 test, stratified by geographic region and DAS28 low disease activity/remission status at week 36. The DAS28 low disease activity/remission strata were removed only for DAS28 analyses.

DAS28 low disease activity at week 88 was analyzed in the subpopulation using the Cochran–Mantel–Haenszel test of general association; a modified nonresponder imputation analysis was performed, in which patients who discontinued early owing to lack of efficacy were imputed as nonresponders for all time points and all other patients were analyzed using the last observation carried forward method. All other postbaseline analyses were based on the last observation carried forward approach. Continuous end points were analyzed in analysis of covariance models using the week 36 baseline values of end points as covariates, treatment, geographic region and week 36 DAS28 low disease activity/remission (except for DAS28).

Results

Demographics/disposition

Subpopulation analyses in period 1 (n = 491) and period 2 (n = 388) included patients enrolled (in periods 1 and 2, respectively) from Czech Republic (n = 47 and 36), Hungary (n = 31 and 23), Poland (n = 67 and 51), Russia (n = 100 and 86), Serbia (n = 57 and 47), Chile (n = 58 and 53), Colombia (n = 51 and 39), Mexico (n = 76 and 49) and Taiwan (n = 4 and 4). Baseline demographic features and disease-state characteristics were similar among the ETN50/MTX, ETN25/MTX and biologic-free MTX treatment groups (Table 1).

Clinical outcomes

In period 1, 85 and 68% of patients achieved DAS28 low disease activity and DAS28 remission, respectively, after 36 weeks of treatment with ETN50/MTX. Additional outcomes at week 36 are shown in Table 2.

In the period 2 mITT population, a significantly higher proportion (83%) of patients in the

Table 1. Demographic and disease characteristics in the PRESERVE subpopulation at baseline (week 0) in the open-label and randomized, double-blind periods.

Characteristic	Open-label period	Randomized, double-blind period		
	ETN50/MTX	ETN50/MTX	ETN25/MTX	MTX
Demographics	n = 491	n = 127	n = 134	n = 127
Mean age, (years)	46.6 (11.7)	46.2 (11.8)	44.9 (11.9)	47.3 (12.0)
Female, n (%)	434 (88.4)	114* (89.8)	106 (79.1)	117* (92.1)
White, n (%)	379 (77.2)	102 (80.3)	102 (76.1)	100 (78.7)
Disease characteristics				
Disease duration (years)	7.0 (6.2)	6.7 (5.8)	6.9 (6.9)	7.2 (6.0)
Rheumatoid factor positive, n (%)	378 (77.0)	94 (74.0)	104 (77.6)	99 (78.0)
aCCP antibody positive, n (%)	406 (82.7)	103 (81.1)	112 (83.6)	106 (83.5)
CRP (mg/l)	13.2 (17.4)	11.9* (12.4)	15.1 (20.0)	9.0* (8.4)
ESR (mm/h)	23.3 (12.9)	23.1 (12.5)	23.8 (14.4)	20.8 (9.8)
DAS28	4.4 (0.4)	4.4 (0.4)	4.4 (0.4)	4.3 (0.4)
SDAI	18.4 (4.9)	17.8 (4.3)	18.8 (4.6)	17.9 (4.9)
Swollen joint count, 28 joints, prorated†	3.5 (2.3)	3.3 (2.2)	3.5 (2.2)	3.5 (2.3)
Tender joint count, 28 joints, prorated†	5.1 (2.6)	4.9 (2.5)	5.2 (2.5)	5.2 (2.5)
Patient-reported characteristics				
HAQ total score (0–3)	1.2 (0.6)	1.1 (0.6)	1.2 (0.6)	1.1 (0.5)
EQ-5D utility index (0–1)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.1)
Pain VAS (0–100 mm)	43.5 (16.1)	43.6 (17.3)	41.4 (14.4)	43.1 (14.0)
Patient global assessment (0–10)	4.6 (1.6)	4.6 (1.7)	4.7 (1.6)	4.4 (1.5)
FACIT-Fatigue total score (0–52)	33.6 (9.0)	33.1 (9.6)	34.6 (8.2)	34.6 (8.5)
MOS sleep adequacy (0–100)	57.8 (25.0)	56.0 (24.8)	60.9 (25.1)	58.0 (23.8)
MOS shortness of breath or headache (0–100)	20.2 (21.8)	18.9 (21.1)	19.0 (22.1)	20.4 (20.0)
MOS Sleep Problems I index (0–100)	34.4 (17.5)	35.0 (17.8)	33.2 (16.9)	33.1 (16.2)
BPI interference (0–10)	3.8 (1.9)	3.9 (2.0)	3.7 (2.0)	3.6 (1.6)
BPI severity (0–10)	3.9 (1.5)	3.9 (1.5)	4.0 (1.5)	3.7 (1.3)
WPAI domains	n = 488	n = 125	n = 134	n = 127
WPAI, % activity impairment	42.2 (19.2)	42.3 (20.0)	41.7 (18.9)	40.0 (17.6)

All values are mean (standard deviation), unless otherwise noted.
†For joint counts with missing swollen or tender joint measurements (not <80%), total swollen or tender joint counts were prorated by multiplying by a factor of 28 divided by the number of nonmissing swollen or tender joints.
*$p < 0.01$; ETN50/MTX and MTX vs ETN25/MTX.
aCCP: Anti-cyclic citrullinated peptide; BPI: Brief Pain Inventory; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; ESR: Erythrocyte sedimentation rate; ETN25/MTX: Etanercept 25 mg/methotrexate; ETN50/MTX: Etanercept 50 mg/methotrexate; EQ-5D: European Quality of Life 5-Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ: Health Assessment Questionnaire; MOS: Medical Outcomes Study; MTX: Methotrexate; SDAI: Simplified Disease Activity Index; VAS: Visual analog scale; WPAI: Work Productivity and Activity Impairment Questionnaire.

Table 1. Demographic and disease characteristics in the PRESERVE subpopulation at baseline (week 0) in the open-label and randomized, double-blind periods (cont.).

Characteristic	Open-label period	Randomized, double-blind period		
	ETN50/MTX	ETN50/MTX	ETN25/MTX	MTX
	n = 212	n = 50	n = 64	n = 59
WPAI, % impairment while working	34.4 (19.4)	34.6 (21.3)	35.2 (19.0)	32.9 (17.9)
WPAI, % overall work impairment	38.6 (22.6)	39.1 (24.9)	38.3 (21.4)	36.0 (19.5)
WPAI,% work time missed	11.2 (25.1)	14.0 (27.6)	7.6 (19.0)	9.7 (24.2)

All values are mean (standard deviation), unless otherwise noted.
†For joint counts with missing swollen or tender joint measurements (not <80%), total swollen or tender joint counts were prorated by multiplying by a factor of 28 divided by the number of nonmissing swollen or tender joints.
*p < 0.01; ETN50/MTX and MTX vs ETN25/MTX.
aCCP: Anti-cyclic citrullinated peptide; BPI: Brief Pain Inventory; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; ESR: Erythrocyte sedimentation rate; ETN25/MTX: Etanercept 25 mg/methotrexate; ETN50/MTX: Etanercept 50 mg/methotrexate; EQ-5D: European Quality of Life 5-Dimensions; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ: Health Assessment Questionnaire; MOS: Medical Outcomes Study; MTX: Methotrexate; SDAI: Simplified Disease Activity Index; VAS: Visual analog scale; WPAI: Work Productivity and Activity Impairment Questionnaire.

ETN50/MTX group achieved DAS28 low disease activity at week 88 compared with those in the biologic-free MTX group (50%; $p < 0.0001$; Table 3). Similarly, significantly more (81%) patients receiving ETN25/MTX attained DAS28 low disease activity at week 88 compared with patients receiving MTX without etanercept ($p < 0.0001$).

Stable rates of remission based on DAS28, ACR/EULAR Boolean and SDAI criteria were seen over time in patients maintaining etanercept at conventional or reduced doses, whereas rapid loss of remission was observed in patients who received the biologic-free MTX regimen (Figure 1; $p < 0.05$, week 40; $p < 0.001$, all other time points, vs MTX). At week 88, SDAI low disease activity and ACR 20/50/70 responses also were achieved by significantly higher percentages of patients receiving the two ETN/MTX regimens versus patients receiving the biologic-free regimen ($p < 0.001$; Table 3).

Statistically significant differences were observed in mean changes in DAS28 and SDAI from period 2 baseline to week 88 favoring the ETN/MTX regimens over the biologic-free MTX regimen (Figure 2). Patients who maintained etanercept at conventional or reduced doses continued to have mean values in the low disease activity range or lower (DAS28 <3.2 or SDAI ≤11), whereas patients receiving biologic-free therapy had mean scores that rose to or exceeded the moderate disease activity threshold by week 88 (Figure 2).

No significant treatment differences were observed between the conventional- and reduced-dose ETN/MTX regimens in any week 88 clinical outcomes.

Patient-reported outcomes

Etanercept plus MTX therapy (conventional or reduced doses) was associated with significantly less adjusted mean change in HAQ total score and EQ-5D from weeks 36–88 compared with biologic-free MTX therapy ($p \leq 0.001$ and $p < 0.05$, respectively; Figure 3), indicating less deterioration in function and overall health status with continued use of etanercept. At week 88, significantly higher proportions of patients receiving the etanercept plus MTX regimens achieved a normal HAQ total score compared with patients receiving the biologic-free regimen ($p < 0.05$).

Significant differences favoring the ETN50/MTX and ETN25/MTX regimens over the biologic-free regimen also were observed in the pain VAS ($p \leq 0.001$), patient global assessment ($p < 0.001$), MOS sleep adequacy and Sleep Problems indices ($p < 0.05$ for both) and BPI interference and severity ($p < 0.05$ for both; Table 3). Significantly less change in FACIT score was also seen in the ETN50/MTX group compared with the biologic-free MTX group ($p < 0.05$).

Patients in the ETN50/MTX and ETN25/MTX groups had significantly less change in the percentage of activity impairment owing to RA (measured using WPAI) than patients in the biologic-free MTX group at week 88 ($p < 0.05$; Table 3). A significant between-group difference was observed in the change in overall work impairment owing to RA favoring the conventional-dose etanercept plus MTX regimen versus reduced-dose etanercept plus MTX ($p < 0.05$); however, no significant differences were observed between the conventional- and reduced-dose regimens in any other patient-reported outcomes.

Safety

Individual safety analysis by region was not performed because the study was designed for whole population

Table 2. Summary of treatment efficacy in the PRESERVE subpopulation in the open-label period.

Clinical/functional/work productivity end points*	ETN50/MTX (week 36)
Total, n (%)	491
DAS28 LDA (≤3.2), % patients (95% CI)	85 (82.0–88.5)
DAS28 remission (<2.6), % patients (95% CI)	68 (63.7–72.2)
SDAI LDA (≤11), % patients (95% CI)	88 (84.7–90.7)
SDAI remission (≤3.3), % patients (95% CI)	30 (26.1–34.4)
ACR 20/50/70 responses, % patients (95% CI)	80 (75.8–83.1)/68 (64.0–72.4)/34 (29.6–38.1)
ACR/EULAR Boolean remission, % patients (95% CI)	41 (36.4–45.3)
Normal HAQ (≤0.5), % patients (95% CI)	60 (55.8–64.6)
Mean (SD) clinical assessments	
DAS28	2.4 (1.0)
SDAI	6.1 (6.0)
Mean (SD) patient-reported outcomes*	
HAQ total score (0-3)	0.5 (0.5)
EQ-5D utility index (0-1)	0.8 (0.2)
Pain VAS (0–100 mm)	16.0 (18.0)
Patient global assessment (0–10)	2.1 (1.9)
FACIT total score (0–52)	42.3 (8.5)
MOS sleep adequacy (0–100)	76.4 (23.5)
MOS shortness of breath or headache (0–100)	12.7 (20.4)
MOS Sleep Problems I index (0–100)	19.9 (17.4)
BPI interference	1.4 (1.7)
BPI severity	1.7 (1.7)
Mean (SD) WPAI domains*	
Total, n (%)	488
WPAI, % activity impairment	18.5 (19.1)
Total, n (%)	212
WPAI, % impairment while working	14.1 (16.2)
WPAI, % overall work impairment	15.6 (18.0)
WPAI, % work time missed	3.3 (13.3)

Modified intention-to-treat population (open-label period, n = 834); clinical assessments (except DAS28 LDA) and HAQ (Cochran–Mantel–Haenszel test of general association): LOCF; DAS28 LDA (week 88): modified nonresponder imputation (patients who discontinued early owing to lack of efficacy were imputed as nonresponders for all time points; all others analyzed using LOCF).
*$p < 0.0001$, all week 36 findings vs baseline.
BPI: Brief Pain Inventory; DAS28: Disease Activity Score in 28 joints; ETN: Etanercept; ETN50/MTX: Etanercept 50 mg/methotrexate; EULAR: European League Against Rheumatism; EQ-5D: European Quality of Life 5-Dimensions: FACIT: Functional Assessment of Chronic Illness Therapy; HAQ: Health Assessment Questionnaire; LDA: Low disease activity; LOCF: Last observation carried forward; MOS: Medical Outcomes Study; MTX: Methotrexate; OR: Odds ratio; SD: Standard deviation; SDAI: Simplified Disease Activity Index; SE: Standard error of the mean; VAS: Visual analog scale; WPAI: Work Productivity and Activity Impairment Questionnaire.

balanced randomization. No new safety signals were detected during the 88-week trial in the overall safety population (ETN50/MTX, n = 202; ETN25/MTX, n = 202; MTX, n = 200) [18]. In period 1, serious adverse events were reported in 4.6% of patients; the most frequent were pneumonia (n = 5 [0.6%]) and cellulitis, acute pyelonephritis and basal cell carcinoma (n = 2 [0.2%] each). There were two (0.2% of patients) pneumonia-related deaths in Mexico during the 2009 H1N1 influenza outbreak. Serious infections were reported in 14 (1.7%) patients. In period 2, significant differences in the safety profiles were not observed among the three treatment groups. Serious adverse events were reported in 5.8% of patients. There were two deaths in the ETN50/MTX group, owing to pulmonary embolism and septicemia. Serious

Table 3. Summary of treatment efficacy in the PRESERVE subpopulation in the randomized double-blind period.

Outcome	ETN50/MTX		ETN25/MTX		MTX	
	Week 36	Week 88	Week 36	Week 88	Week 36	Week 88
Clinical/functional state end points, % patients (OR, ETN vs MTX [95% CI])						
Total (n)	127		134		127	
DAS28 LDA (≤3.2)	98	83* (4.6 [2.6–8.2])	99	81* (4.1 [2.3–7.2])	100	50
DAS28 remission (<2.6)	84	66* (4.3 [2.5–7.3])	81	61* (3.7 [2.2–6.3])	79	31
SDAI LDA (≤11)	95	86* (3.3 [1.8–6.2])	99	84** (3.0 [1.7–5.5])	95	64
SDAI remission (≤3.3)	42	39* (3.1 [1.7–5.8])	35	36** (2.6 [1.4–4.9])	30	16
ACR/EULAR Boolean remission	51	37* (3.9 [2.1–7.5])	45	38* (4.1 [2.2–7.8])	49	13
ACR 20/50/70 responses	88/80/45	75**/63*/37*(2.6 [1.5–4.4]/3.7 [2.2–6.3]/3.3 [1.8–6.2])	90/78/39	78*/60*/37* (3.2 [1.9–5.5]/3.4 [2.0,5.7]/3.3 [1.8–6.2])	90/79/39	53/31/14
Normal HAQ (≤0.5)	65	58*** (1.7 [1.1–2.9])	69	56*** (1.7 [1.0–2.7])	69	43
Clinical activity assessments						
DAS28:						
– Mean (SD)	2.0 (0.6)	2.4 (1.0)	2.1 (0.6)	2.5 (1.1)	2.1 (0.6)	3.3 (1.3)
– Adjusted mean change (SE)	–	0.3* (0.1)	–	0.4* (0.1)	–	1.2 (0.1)
SDAI						
– Mean (SD)	4.2 (3.2)	5.6 (5.8)	4.3 (2.7)	6.3 (6.6)	4.6 (2.9)	11.2 (9.8)
– Adjusted mean change (SE)	–	1.4* (0.7)	–	2.0* (0.7)	–	6.7 (0.7)
Patient-reported outcomes						
Total (n)	125		134		127	
HAQ total score (0–3):						
– Mean (SD)	0.5 (0.5)	0.6 (0.5)	0.4 (0.5)	0.5 (0.5)	0.4 (0.4)	0.8 (0.6)
– Adjusted mean change (SE)	–	0.07* (0.04)	–	0·10** (0.04)	–	0.32 (0.04)
EQ-5D utility index (0–1):						
– Mean (SD)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.7 (0.2)
– Adjusted mean change (SE)	–	-0.05*** (0.02)	–	-0.05*** (0.02)	–	-0.10 (0.02)

Modified intention-to-treat population (double-blind period, n = 599); clinical assessments (except DAS28 LDA) and HAQ (Cochran–Mantel–Haenszel test of general association): LOCF; DAS28 LDA (week 88): modified nonresponder imputation (patients who discontinued early owing to lack of efficacy were imputed as nonresponders for all time points; all others analyzed using LOCF). All analyses are stratified by geographic region and week 36 DAS28 LDA/remission (except DAS28 analyses) in the double-blind period. Mean changes for continuous end points are adjusted in ANCOVA models for double-blind period baseline, treatment and geographic region. Proportions were analyzed for treatment differences with χ^2-tests.
*p < 0.0001, ETN50/MTX or ETN25/MTX vs MTX, from ANCOVA model; **p < 0.001, ETN50/MTX or ETN25/MTX vs MTX, from ANCOVA model; ***p < 0.05, ETN50/MTX or ETN25/MTX vs MTX, from ANCOVA model; ****p < 0.05, ETN50/MTX vs ETN25/MTX.
ANCOVA: Analysis of covariance; BPI: Brief Pain Inventory; CI: Confidence interval; DAS28: Disease Activity Score in 28 joints; ETN: Etanercept; ETN25/MTX: Etanercept 25 mg/methotrexate; ETN50/MTX: Etanercept 50 mg/methotrexate; EULAR: European League Against Rheumatism;EQ-5D: European Quality of Life 5-Dimensions: FACIT: Functional Assessment of Chronic Illness Therapy; HAQ: Health Assessment Questionnaire; LDA: Low disease activity; LOCF: Last observation carried forward; MOS: Medical Outcomes Study; MTX: Biologic-free methotrexate; OR: Odds ratio; SD: Standard deviation; SDAI: Simplified Disease Activity Index; SE: Standard error of the mean; VAS: Visual analog scale; WPAI: Work Productivity and Activity Impairment Questionnaire.

Table 3. Summary of treatment efficacy in the PRESERVE subpopulation in the randomized double-blind period (cont.).

Outcome	ETN50/MTX		ETN25/MTX		MTX	
	Week 36	Week 88	Week 36	Week 88	Week 36	Week 88
Pain VAS (0–100 mm):						
– Mean (SD)	11.7 (15.2)	16.0 (18.6)	11.5 (13.0)	17.4 (18.1)	13.1 (14.7)	26.9 (21.7)
– Adjusted mean change (SE)	–	3.6* (1.7)	–	5.2** (1.6)	–	14.1 (1.7)
Patient global assessment (0–10):						
– Mean (SD)	1.7 (1.7)	2.1 (2.0)	1.5 (1.3)	2.2 (1.9)	1.8 (1.6)	3.1 (2.1)
– Adjusted mean change (SE)	–	0.4* (0.2)	–	0.5** (0.2)	–	1.4 (0.2)
FACIT total score (0–52):						
– Mean (SD)	42.1 (9.2)	40.4 (8.9)	44.8 (6.3)	41.7 (8.1)	43.4 (7.3)	39.2 (9.3)
– Adjusted mean change (SE)	–	-1.7*** (0.7)	–	-2.4 (0.7)	–	-4.0 (0.7)
MOS sleep adequacy (0–100):						
– Mean (SD)	76.3 (23.7)	71.4 (22.6)	82.0 (20.2)	75.8 (21.9)	77.3 (21.7)	66.3 (25.0)
– Adjusted mean change (SE)	–	-5.7*** (2.0)	–	-3.9*** (1.9)	–	-11.6 (2.0)
MOS shortness of breath or headache (0–100):						
– Mean (SD)	10.0 (16.1)	14.7 (20.4)	8.8 (18.4)	13.6 (19.1)	13.4 (20.7)	17.0 (20.0)
– Adjusted mean change (SE)	–	3.2 (1.9)	–	2.2 (1.8)	–	5.0 (1.9)
MOS Sleep Problems I index (0–100):						
– Mean (SD)	20.5 (18.0)	24.6 (17.5)	14.8 (13.7)	21.5 (15.6)	19.2 (16.1)	27.3 (17.7)
– Adjusted mean change (SE)	–	4.5*** (1.4)	–	4.5*** (1.4)	–	8.5 (1.4)
BPI interference (0–10):						
– Mean (SD)	1.2 (1.8)	1.6 (1.8)	1.1 (1.3)	1.5 (1.6)	1.1 (1.4)	2.1 (2.0)
– Adjusted mean change (SE)	–	0.3*** (0.2)	–	0.4*** (0.2)	–	1.0 (0.2)
BPI severity (0–10):						
– Mean (SD)	1.5 (1.6)	1.8 (1.7)	1.4 (1.3)	1.8 (1.6)	1.4 (1.3)	2.5 (1.8)
– Adjusted mean change (SE)	–	0.4*** (0.2)	–	0.4*** (0.1)	–	1.0 (0.1)

Modified intention-to-treat population (double-blind period, n = 599); clinical assessments (except DAS28 LDA) and HAQ (Cochran–Mantel–Haenszel test of general association): LOCF; DAS28 LDA (week 88): modified nonresponder imputation (patients who discontinued early owing to lack of efficacy were imputed as nonresponders for all time points; all others analyzed using LOCF). All analyses are stratified by geographic region and week 36 DAS28 LDA/remission (except DAS28 analyses) in the double-blind period. Mean changes for continuous end points are adjusted in ANCOVA models for double-blind period baseline, treatment and geographic region. Proportions were analyzed for treatment differences with χ^2-tests.

*p < 0.0001, ETN50/MTX or ETN25/MTX vs MTX, from ANCOVA model; **p < 0.001, ETN50/MTX or ETN25/MTX vs MTX, from ANCOVA model; ***p < 0.05, ETN50/MTX or ETN25/MTX vs MTX, from ANCOVA model; ****p < 0.05, ETN50/MTX vs ETN25/MTX.

ANCOVA: Analysis of covariance; BPI: Brief Pain Inventory; CI: Confidence interval; DAS28: Disease Activity Score in 28 joints; ETN: Etanercept; ETN25/MTX: Etanercept 25 mg/methotrexate; ETN50/MTX: Etanercept 50 mg/methotrexate; EULAR: European League Against Rheumatism;EQ-5D: European Quality of Life 5-Dimensions: FACIT: Functional Assessment of Chronic Illness Therapy; HAQ: Health Assessment Questionnaire; LDA: Low disease activity; LOCF: Last observation carried forward; MOS: Medical Outcomes Study; MTX: Biologic-free methotrexate; OR: Odds ratio; SD: Standard deviation; SDAI: Simplified Disease Activity Index; SE: Standard error of the mean; VAS: Visual analog scale; WPAI: Work Productivity and Activity Impairment Questionnaire.

Table 3. Summary of treatment efficacy in the PRESERVE subpopulation in the randomized double-blind period (cont.).

Outcome	ETN50/MTX		ETN25/MTX		MTX	
	Week 36	Week 88	Week 36	Week 88	Week 36	Week 88
WPAI domains						
Total (n)	125		134		127	
WPAI, % activity impairment:						
– Mean (SD)	15.7 (18.3)	20.2 (21.4)	15.5 (17.0)	19.4 (19.7)	16.4 (17.4)	26.9 (22.9)
– Adjusted mean change (SE)	–	4.4*** (1.8)	–	3.7*** (1.7)	–	10.7 (1.8)
Total (n)	50		64		59	
WPAI, impairment while working due to problem:						
– Mean (SD)	12.5 (16.7)	12.5 (13.8)	13.1 (14.7)	15.4 (16.7)	11.3 (12.6)	16.8 (16.4)
– Adjusted mean change (SE)	–	1.5 (1.9)	–	4.7 (1.7)	–	5.7 (1.7)
WPAI, % overall work impairment:						
– Mean (SD)	15.2 (20.0)	14.7 (17.2)	14.3 (15.9)	19.7 (21.3)	12.3 (14.3)	18.7 (20.1)
– Adjusted mean change (SE)	–	0.2**** (2.4)	–	7.4 (2.2)	–	6.5 (2.2)
WPAI, % work time missed:						
– Mean (SD)	5.6 (17.4)	4.7 (16.5)	2.3 (11.0)	8.4 (22.4)	2.9 (13.5)	6.8 (20.9)
– Adjusted mean change (SE)	–	1.6 (3.0)	–	6.2 (2.6)	–	5.1 (2.6)

Modified intention-to-treat population (double-blind period, n = 599); clinical assessments (except DAS28 LDA) and HAQ (Cochran–Mantel–Haenszel test of general association): LOCF; DAS28 LDA (week 88): modified nonresponder imputation (patients who discontinued early owing to lack of efficacy were imputed as nonresponders for all time points; all others analyzed using LOCF). All analyses are stratified by geographic region and week 36 DAS28 LDA/remission (except DAS28 analyses) in the double-blind period. Mean changes for continuous end points are adjusted in ANCOVA models for double-blind period baseline, treatment and geographic region. Proportions were analyzed for treatment differences with χ^2-tests.

*p < 0.0001, ETN50/MTX or ETN25/MTX vs MTX, from ANCOVA model; **p < 0.001, ETN50/MTX or ETN25/MTX vs MTX, from ANCOVA model; ***p < 0.05, ETN50/MTX or ETN25/MTX vs MTX, from ANCOVA model; ****p < 0.05, ETN50/MTX vs ETN25/MTX.

ANCOVA: Analysis of covariance; BPI: Brief Pain Inventory; CI: Confidence interval; DAS28: Disease Activity Score in 28 joints; ETN: Etanercept; ETN25/MTX: Etanercept 25 mg/methotrexate; ETN50/MTX: Etanercept 50 mg/methotrexate; EULAR: European League Against Rheumatism;EQ-5D: European Quality of Life 5-Dimensions: FACIT: Functional Assessment of Chronic Illness Therapy; HAQ: Health Assessment Questionnaire; LDA: Low disease activity; LOCF: Last observation carried forward; MOS: Medical Outcomes Study; MTX: Biologic-free methotrexate; OR: Odds ratio; SD: Standard deviation; SDAI: Simplified Disease Activity Index; SE: Standard error of the mean; VAS: Visual analog scale; WPAI: Work Productivity and Activity Impairment Questionnaire.

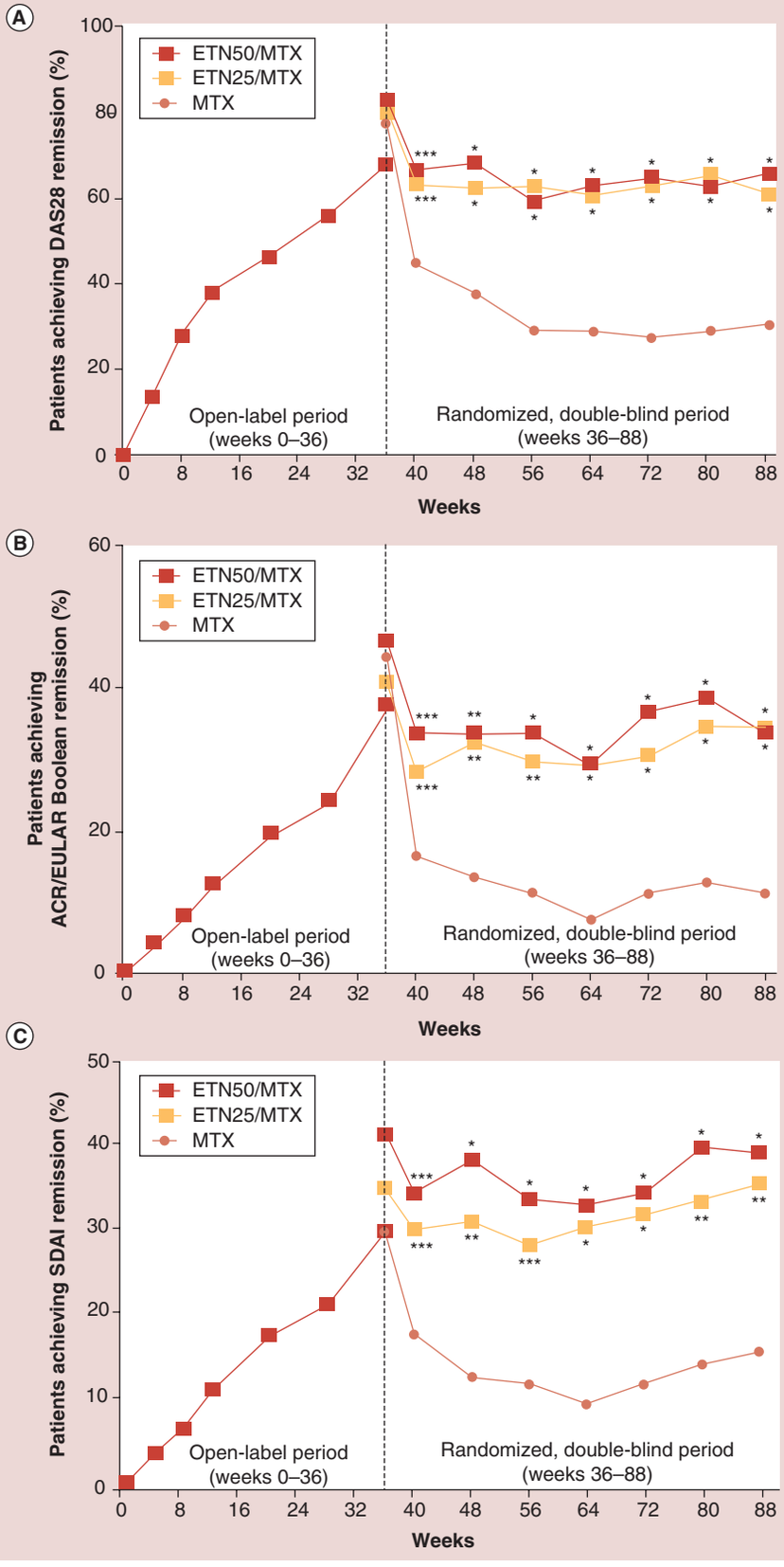
A
Patients achieving DAS28 remission (%)
ETN50/MTX
ETN25/MTX
MTX
Open-label period (weeks 0–36)
Randomized, double-blind period (weeks 36–88)
Weeks
B
Patients achieving ACR/EULAR Boolean remission (%)
ETN50/MTX
ETN25/MTX
MTX
Open-label period (weeks 0–36)
Randomized, double-blind period (weeks 36–88)
Weeks
C
Patients achieving SDAI remission (%)
ETN50/MTX
ETN25/MTX
MTX
Open-label period (weeks 0–36)
Randomized, double-blind period (weeks 36–88)
Weeks

Figure 1. Remission in the PRESERVE subpopulation (see facing page). Patients achieving **(A)** DAS28, **(B)** ACR/EULAR Boolean and **(C)** ACR/EULAR index (SDAI) remission over 88 weeks. Period 1 (i.e., weeks 0–36) results based on period 1 mITT population; period 2 (i.e., weeks 40–88) results based on period 2 mITT population. *p < 0.0001, ETN50/MTX and ETN25/MTX vs MTX alone; **p < 0.001, ETN50/MTX and ETN25/MTX vs MTX alone; ***p < 0.05, ETN50/MTX and ETN25/MTX vs MTX alone (Cochran–Mantel–Haenszel tests of general association); stratified by geographic region and week 36 DAS28 low disease activity/remission (except DAS28 analyses) in the double-blind period 2.
ACR: American College of Rheumatology; DAS28: Disease Activity Score in 28 joints; ETN25/MTX: Etanercept 25 mg/methotrexate; ETN50/MTX: Etanercept 50 mg/methotrexate; EULAR: European League Against Rheumatism; mITT: Modified intention-to-treat; MTX: Methotrexate; SDAI: Simplified Disease Activity Index.

infections were reported in six (1.0%) patients in the ETN50/MTX (n = 3) and biologic-free MTX (n = 3) groups.

Discussion

This subanalysis of the PRESERVE trial addresses several novel aspects of treatment of RA: evaluation of a moderately active RA population despite MTX therapy in countries outside of the frequently studied North America and western Europe; induction of low disease activity with conventional-dose combination etanercept plus MTX therapy; and evaluation of the maintenance of response with continued treatment with conventional-dose etanercept therapy, with reduced-dose etanercept therapy (ETN25/MTX) or with the withdrawal of etanercept while maintaining biologic-free MTX therapy. Patients with moderately active RA from central and eastern European, Latin American and Asian populations comprised approximately 60% of the overall PRESERVE study population [18]. This regional subpopulation was generally similar to the overall PRESERVE population in terms of demographic and disease characteristics; the duration of disease was 6.9 years and mean DAS28 was 4.4 in both populations at baseline.

This subpopulation analysis demonstrated that treatment with etanercept plus MTX is very effective in patients with RA who reside in these regions. Similar outcomes were observed in the regional subset as in the total population of the PRESERVE study [18]. As in the overall population, the proportion of patients in the regional subpopulation achieving DAS28 low disease activity at week 88 (the primary end point) was significantly higher in the conventional- or reduced-dose etanercept plus MTX groups compared with the biologic-free MTX group after sustained low disease activity was achieved with the conventional-dose etanercept regimen at week 36. The subpopulation results also indicated that patients receiving either etanercept plus MTX combination regimen were statistically significantly more likely to achieve other major clinical end points, including DAS remission, ACR/EULAR Boolean- and index-based remission, ACR responses and normal HAQ versus patients receiving the biologic-free MTX regimen. In the regional subpopulation, significant between-treatment differences favoring the etanercept plus MTX regimens over the biologic-free MTX regimen also were observed in most of the patient-reported outcomes, including HAQ total and EQ-5D scores, pain VAS, patient global assessment, MOS sleep adequacy and Sleep Problems I indices, BPI interference and severity and WPAI percentage activity impairment. Significantly less mean change in FACIT score was seen with the ETN50/MTX regimen than with the biologic-free MTX regimen, indicating less deterioration, although no significant difference was found between the ETN25/MTX and biologic-free MTX regimens.

Most patients included in the double-blind phase (period 2) of the PRESERVE study had attained sustained low disease activity. Reduction of the etanercept dose was associated with continuation of good response, which was generally similar to that observed with the conventional dose. Patients who continued the full dose in period 2 had slightly better response across most assessments compared with patients who received the reduced dose. The trial was not sufficiently powered to detect significant differences between the two etanercept dose regimens. However, statistical testing was performed, detecting a significant difference between regimens for only one parameter (i.e., change in overall work impairment on the WPAI) and the differences between the regimens did not appear to be clinically meaningful. The results suggest that patients who achieve a good response to a biologic anti-TNF agent may maintain that response with a reduced dose of the agent, at a substantially reduced cost. In contrast, while a portion of the patients in the biologic-free group did respond and maintained their response, half of the patients lost low disease activity. The latter finding suggests that even once a response is sustained, its maintenance may require continued biologic therapy, at least in this population of patients with established RA. Overall, the efficacy and safety results for etanercept in the PRESERVE study are consistent with findings recently reviewed in the literature [35,36].

In addition to the PRESERVE study's insufficient power to detect differences between the conventional- and reduced-dose etanercept plus MTX groups, other

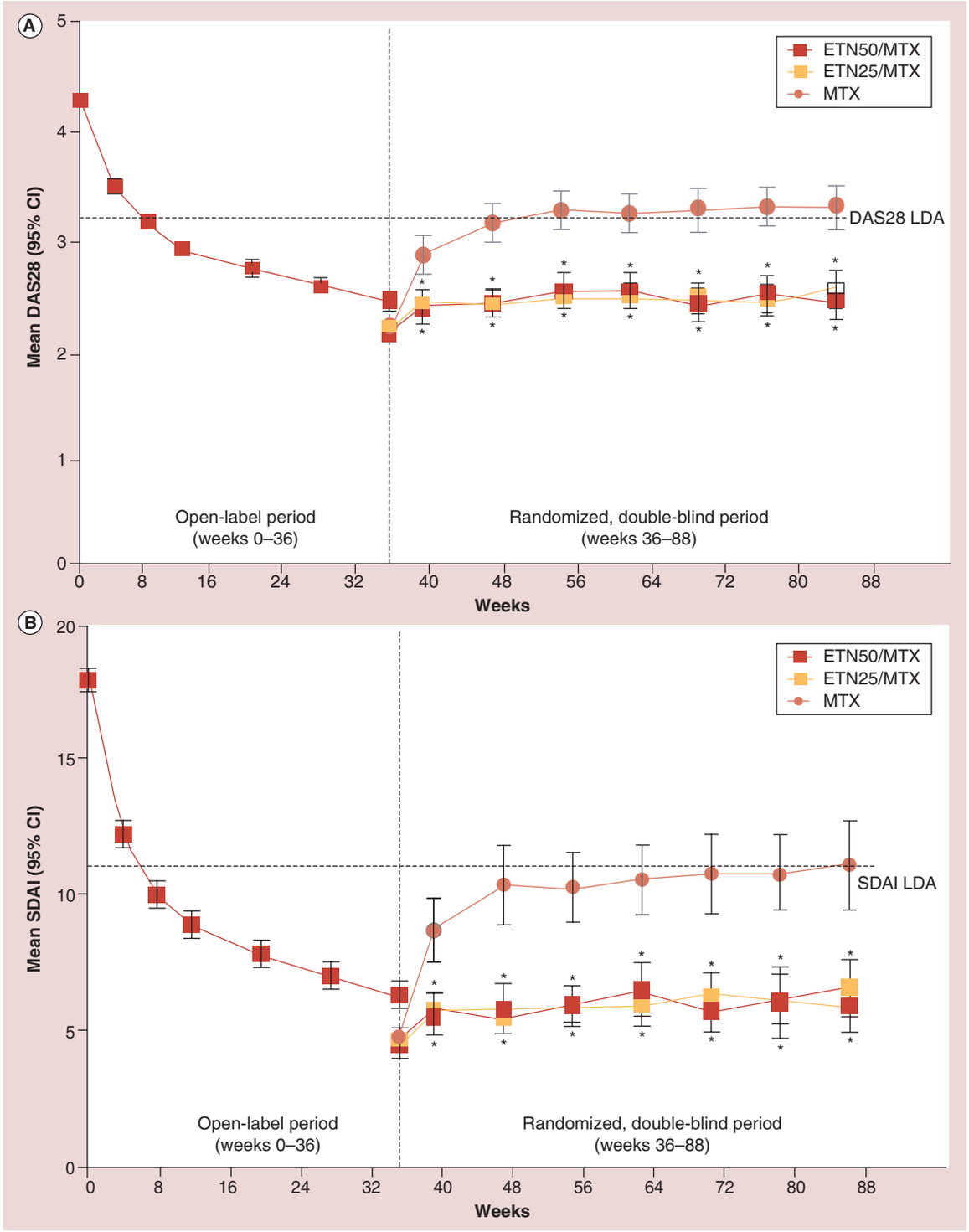

Figure 2. Mean DAS28 and SDAI (and 95% CI) over 88 weeks in the PRESERVE subpopulation. (A) DAS28 and **(B)** SDAI. Period 1 (i.e., weeks 0–36) results based on period 1 mITT population; period 2 (i.e., weeks 40–88) results based on period 2 mITT population.
*p < 0.0001, ETN50/MTX and ETN25/MTX vs MTX alone. *F*-tests from ANCOVA models, adjusted for week 36 baseline, geographic region and week 36 DAS28 low disease activity/remission.
ANCOVA: Analysis of covariance; DAS28: Disease Activity Score in 28 joints; ETN25/MTX: Etanercept 25 mg/methotrexate; ETN50/MTX: Etanercept 50 mg/methotrexate; LDA: Low disease activity; mITT: Modified intention-to-treat; MTX: Methotrexate; SDAI: Simplified Disease Activity Index.

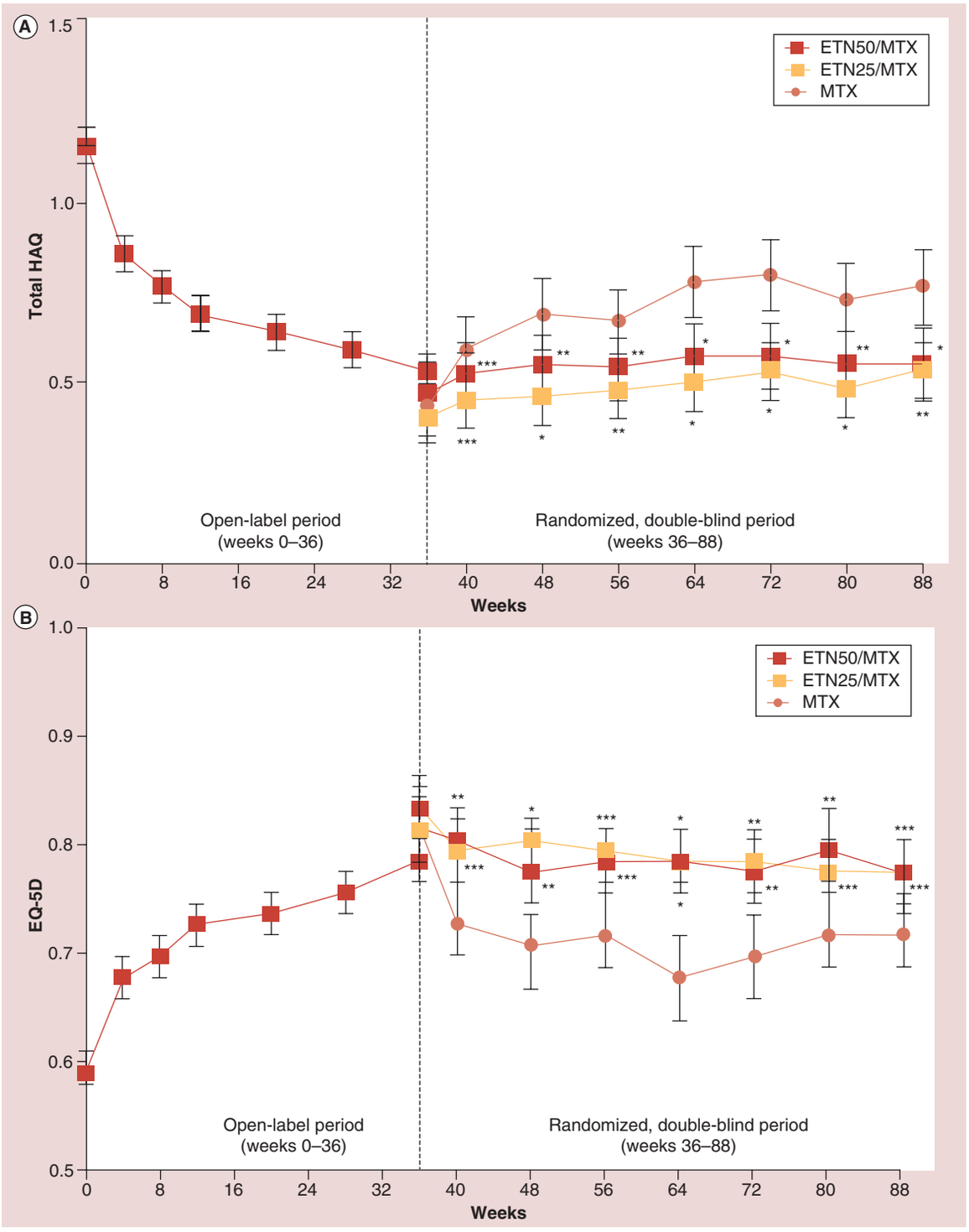

Figure 3. Mean HAQ Total and EQ-5D (and 95% CI) over 88 weeks in the PRESERVE subpopulation. (A) HAQ Total and **(B)** EQ-5D. Period 1 (i.e., weeks 0–36) results based on period 1 mITT population; period 2 (i.e., weeks 40–88) results based on mITT population.
*p < 0.0001, ETN50/MTX and ETN25/MTX vs MTX alone; **p < 0.001, ETN50/MTX and ETN25/MTX vs MTX alone; ***p < 0.05, ETN50/MTX and ETN25/MTX vs MTX alone. *F*-tests from ANCOVA models, adjusted for week 36 baseline, geographic region and week 36 DAS28 low disease activity/remission.
ANCOVA: Analysis of covariance; ETN25/MTX: Etanercept 25 mg/methotrexate; ETN50/MTX: Etanercept 50 mg/methotrexate; EQ-5D: EuroQol 5-Dimensions; HAQ: Health Assessment Questionnaire; mITT: Modified intention-to-treat; MTX: Methotrexate.

limitations of the study include the open-label design of the initial induction period. At week 40 (the first visit after randomization), a decrease in DAS28 response across all treatment groups was noted; the largest decrease was observed in the biologic-free MTX group. Although this phenomenon may have been related to the period 2 eligibility requirement of DAS28 low disease activity at week 36 artificially increasing response at week 36, other explanations include natural variability or fluctuation in disease state, regression to the mean or conversion from the open-label study design to a blinded randomized design. Findings from this 36-week period may not be extrapolated to patients in the clinical setting who achieve low disease activity or remission in shorter or longer time frames, just as findings from the 52-week double-blind period may not be extrapolated to patients continuing therapy beyond 88 weeks of observation. In addition, because the PRESERVE study included only patients with moderately active RA disease activity despite prior MTX therapy, results are not applicable to patients with early or more severe disease. Finally, the impact of longer-term treatment and re-treatment was not addressed in this study, as no attempts were made to recapture low disease activity by reintroducing etanercept at either the conventional or reduced dose in patients who had lost low disease activity after withdrawal of etanercept.

In conclusion, in this cross-continental subpopulation of the PRESERVE study, combination therapy with etanercept plus MTX was effective induction therapy for the improvement of clinical symptoms, function and patient-reported outcomes in patients with moderately active RA disease activity despite prior MTX therapy. Although the conventional-dose combination regimen induced low disease activity in more than 80% of patients in the initial 36-week study period, this response was lost in half of the patients receiving the biologic-free MTX regimen in the subsequent 52-week randomized period. The conventional- and reduced-dose combination regimens with etanercept were superior to the biologic-free regimen with regard to the impact on most clinical, functional (i.e., HAQ) and patient-reported outcomes after induction of low disease activity. At the end of the study, similar clinical, functional and patient-reported outcomes

Executive summary

Background

- Most biologic clinical studies have focused on patients with severe rheumatoid arthritis (RA) in Western Europe and North America.
- The PRESERVE study was the first study conducted in adults with RA to examine the induction of treatment response with a full-dose regimen of a biologic agent (etanercept) plus methotrexate, followed by response maintenance with full- or reduced-dose combination therapy or biologic-free methotrexate.
- In this subanalysis of the PRESERVE study, clinical and patient-reported outcomes for both the induction and maintenance periods were analyzed in a subpopulation of patients with moderately active RA from central and eastern Europe, Latin America and Asia.

Methods

- In the 36-week induction phase, patients with an inadequate response to methotrexate (active RA, Disease Activity Score in 28 joints [DAS28] [erythrocyte sedimentation rate] >3.2, ≤5.1) were administered etanercept 50 mg/methotrexate.
- In the 52-week double-blind phase, induction-phase patients who achieved sustained DAS28 low disease activity or lower (at week 36; on average, weeks 12–36) were randomized to etanercept 50 mg/methotrexate, etanercept 25 mg/methotrexate, or methotrexate monotherapy.

Results

- Sustained DAS28 low disease activity was achieved in 85% of patients at week 36.
- A greater percentage had low disease activity at week 88 with the 50 mg (83%) and 25 mg (81%) combinations vs methotrexate (50%; $p < 0.0001$); DAS28 remission rates were 66, 61 and 31%, respectively ($p < 0.0001$ vs methotrexate).
- Similar significant between-group differences were observed for other clinical/patient-reported outcomes at week 88, favoring combination regimens.

Discussion

- Consistent with results from the overall PRESERVE study population, in this analysis of a geographically diverse subpopulation, full-dose etanercept/methotrexate therapy was effective in inducing sustained response in moderately active RA patients at 36 weeks, and both the full- and reduced-dose combination regimens were superior to the biologic-free regimen across clinical and patient-reported outcomes at 88 weeks.
- Maintenance therapy with the full- or reduced-dose etanercept/methotrexate regimen was needed because the initial benefits of combination therapy were lost in many patients subsequently treated with methotrexate monotherapy.

were seen in patients who received the full- and reduced-dose etanercept regimens, suggesting that biologic dose reduction may be possible in many patients without loss of response at considerably lower cost.

Author contribution

All the authors approved the entirety of the submitted material and contributed actively to the study.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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