# The Effect of Reduced or Withdrawn Etanercept-methotrexate Therapy on Patient-reported Outcomes in Patients with Early Rheumatoid Arthritis

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***ABSTRACT.*** ***Objective.*** An analysis of a clinical trial to assess the effects of treatment reduction and withdrawal on patient-reported outcomes (PRO) in patients with early, moderate to severe rheumatoid arthritis (RA) who achieved 28-joint Disease Activity Score (DAS28) low disease activity (LDA) or remission with etanercept (ETN) plus methotrexate (MTX) therapy.

***Methods.*** During treatment induction, patients received open-label ETN 50 mg weekly plus MTX for 52 weeks. In the reduced-treatment phase, patients with DAS28-erythrocyte sedimentation rate (ESR) ≤ 3.2 at Week 39 and DAS28-ESR < 2.6 at Week 52 in the open-label phase were randomized to double-blind treatment with ETN 25 mg plus MTX, MTX, or placebo (PBO) for 39 weeks (weeks 0–39). In the third phase, patients who achieved DAS28 remission (DAS28-ESR < 2.6) or LDA (2.6 ≤ DAS28-ESR ≤ 3.2) at Week 39 in the double-blind phase had all treatment withdrawn and were observed for an additional 26 weeks (weeks 39–65).

***Results.*** Of the 306 patients enrolled, 193 were randomized in the double-blind phase and 131 participated in the treatment-withdrawal phase. After reduction or withdrawal of ETN 50 mg/MTX, patients reduced to ETN 25 mg/MTX experienced slight, nonsignificant declines in the majority of PRO measures, whereas switching to PBO or MTX alone caused significant declines. Presenteeism and activity impairment scores were significantly better in the ETN reduced-dose group versus MTX monotherapy and PBO at Week 39 ($p \leq 0.05$).

***Conclusion.*** In patients with early RA who achieved remission while receiving full-dose ETN/MTX, continuing combination therapy at a lower dose did not cause a significant worsening of PRO response, but switching to MTX alone or PBO did. ClinicalTrials.gov identifier: NCT00913458. (First Release June 1 2016; J Rheumatol 2016;43:1268–77; doi:10.3899/jrheum.151179)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS ETANERCEPT METHOTREXATE
CLINICAL TRIAL DOSE-RESPONSE RELATIONSHIP

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Significant improvements in efficacy, safety, and health-related quality of life (HRQOL) are well documented with antitumor necrosis factor (anti-TNF) agents in patients with rheumatoid arthritis (RA), revolutionizing care and treatment[1,2]. Targeted treatment goals, such as clinical remission and low disease activity (LDA), are critical in the management of RA, and when achieved in early disease, are associated with greater longterm clinical benefits than when achieved in late disease[3,4,5,6]. Patient-reported outcomes (PRO) are an essential assessment of treatment effects on HRQOL[7,8]. Although most RA studies of PRO are in patients with established disease, remission and decreases in 28-joint Disease Activity Score (DAS28) in early RA are associated with longterm HRQOL improvement, in addition to limiting radiographic damage and physical functioning[5,6,9,10,11].

Because patients with RA are receiving lifetime therapies, lower doses of biologic and disease-modifying antirheumatic drugs (DMARD) may be desirable from both a clinical and economic perspective for patients, physicians, and payers[12,13]. Studies have demonstrated that DMARD dosage

can be lowered or treatment discontinued in patients with RA who have shown a sustained response to therapy[14,15]. A growing number of studies have investigated the therapeutic strategy of reducing the dosage or withdrawing biologic treatment once remission has been obtained, to determine whether patients are able to sustain their response[16,17,18,19,20,21,22,23,24]. However, no studies have investigated the effect of this reduced-dose or stepdown therapeutic strategy in biologics specifically on HRQOL measures.

The Productivity and Remission in a RandomIZed Controlled Trial of Etanercept versus Standard of Care in Early Rheumatoid Arthritis (PRIZE) study was designed to investigate the efficacy of etanercept (ETN) plus methotrexate (MTX) as a first-line disease-modifying treatment in patients with early, moderate to severe RA disease activity, to achieve and sustain clinical remission and productivity outcomes. Our analysis of the PRIZE study assessed whether response to PRO measures could be maintained with one-half of the approved dose of ETN or in the absence of any drug (ETN or MTX) in those who achieved remission with full-dose ETN plus MTX. A change in the risk-benefit balance of the therapy, as well as cost savings to the healthcare system may be extrapolated from these findings.

## MATERIALS AND METHODS

*Patients and study design*. PRIZE (ClinicalTrials.gov: NCT00913458) was a 121-week, multicenter study conducted in 3 phases between October 2009 and December 2012 across 57 sites in Europe. The study design is detailed in Figure 1[16]. The first (induction) phase was an open-label, 52-week, single-arm period in which all eligible patients were treated with ETN 50 mg once weekly (QW) plus MTX (ETN50/MTX). Optimization medication in the form of a corticosteroid boost was used in all patients not achieving low (i.e., score was > 3.2) DAS28-erythrocyte sedimentation rate (ESR) at weeks 13 and 26. After completing the first phase, patients who achieved DAS28-ESR ≤ 3.2 at Week 39 and DAS28-ESR < 2.6 at Week 52 were defined as "responders" and eligible to continue into the double-blind phase. Patients who did not meet the protocol-defined responder definition at Week 39 or 52 were withdrawn from the study.

The second (reduced-treatment) phase was a double-blind, 39-week comparison of drug-reduced treatments in induction-phase responders. Responders were randomized (1:1:1) at weeks 0 to 1 to 3 treatments: ETN 25 mg QW plus MTX (ETN25/MTX), MTX plus placebo (PBO) injection (i.e., MTX monotherapy), or PBO capsules plus PBO injection. In patients randomized to MTX or PBO, the reduced-treatment phase included a 2-week period of ETN tapering: the first week from 50 mg to 25 mg QW, and the second week from 25 mg QW to MTX alone or PBO. Patients randomized to PBO also had a 2- to 4-week, double-blind tapering of MTX, depending on their optimized dose. Responders in the reduced-treatment phase, defined as those who had sustained remission (DAS28-ESR < 2.6) or LDA (2.6 ≤ DAS28-ESR ≤ 3.2) at Week 39, were eligible to continue into the third phase. Corticosteroid boosts in responders were permitted at Week 56 or 64 from study enrollment in those with DAS28-ESR > 3.2. Nonresponders with DAS28-ESR > 3.2 at subsequent visits were withdrawn from the study.

The third (treatment-withdrawal) phase was a 26-week observational period in which responders from all treatment arms in the double-blind phase progressively stopped treatment. Nonresponders were withdrawn at Week 91 (Week 39 of the double-blind period) prior to entry. During the treatment-withdrawal phase, patients administered with ETN25/MTX or MTX monotherapy had a 2- to 4-week period of double-blind MTX tapering (depending on the optimized MTX dose). All patients were observed until end of the study (Week 65 from randomization of the double-blind phase). Other than the allowed corticosteroid boosts at the above visits, patients with disease flare who required additional treatment were withdrawn from the study.

Inclusion and exclusion criteria have been previously described in detail[16]. Eligible patients were aged ≥ 18 years, satisfied the 1987 American College of Rheumatology (ACR) revised criteria for RA, had early RA (symptom onset ≤ 12 mos prior to enrollment), were MTX-naive, and had active disease (DAS28-ESR > 3.2) at the time of enrollment[16,25].

Prior to the start of the study, all patients provided written, informed consent in accordance with all applicable local and country-specific regulations. Institutional review boards or independent ethics committees in each

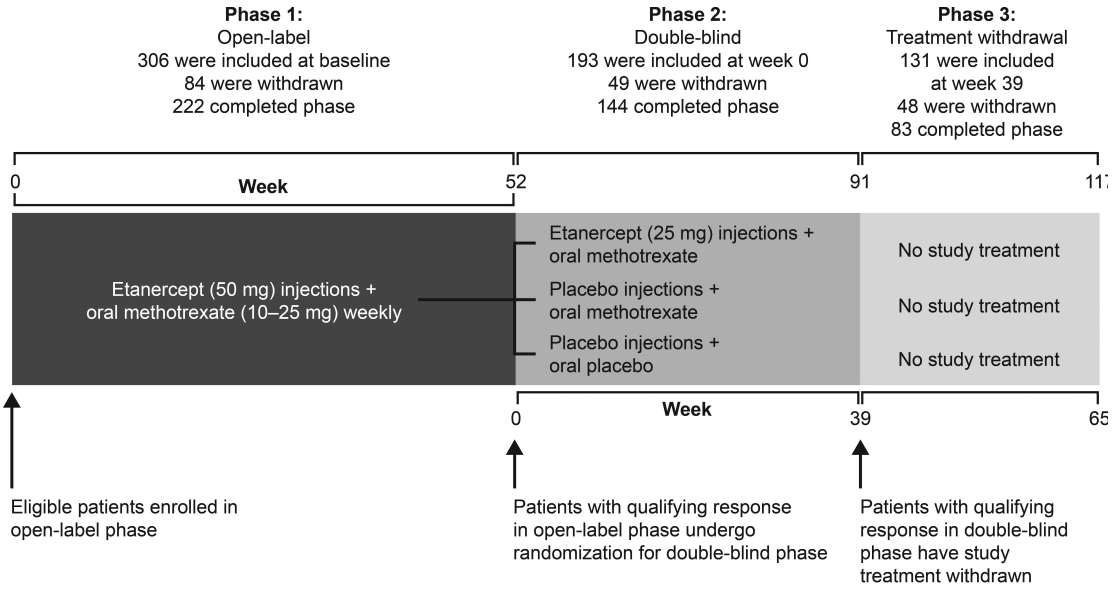


*Figure 1*. Study design. From Emery, *et al*[16], N Engl J Med 2014;371:1781-92; with permission.

region reviewed and approved this study, which was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and all applicable local/country-specific regulations.

*Assessment of PRO*. PRO[26–35] were assessed throughout all 3 phases and are detailed in Table 1[26–35,36,37,38,39,40,41,42,43], with additional details provided in the Appendix.

*Statistical analyses*. PRO analyses were reported using a last observation carried forward (LOCF) approach. Analyses were conducted in the modified intent-to-treat (mITT) population, defined as all patients with at least 1 postrandomization DAS28-ESR evaluation (i.e., the randomized phase 2 population). Descriptive statistics are provided for selected baseline items. For continuous and ordered numeric items, the mean, number of subjects, SD, minimum, maximum, and median values are presented. For categorical items, the number and percent of each level are presented.

Longitudinal models for proportions or continuous data were used to compare treatment groups and to estimate OR or mean differences across timepoints. LOCF values were compared using logistic regression or ANCOVA. Significance tests for change from baseline were based on paired Student t tests using a 2-sided $\alpha = 0.05$. Results of the PRO analysis in the induction phase are reported from weeks 0 to 52, independent of the other 2 phases, with Week 0 of this phase representing the start of the study. Results in the reduced- and withdrawn-treatment phases are emphasized herein and reported continuously as weeks 0 to 65, with Week 0 representing the start of randomization (after Week 52 of the induction phase).

## RESULTS

*Patient characteristics*. Patient disposition for all 3 study phases and key efficacy endpoints have been previously reported[16]. A total of 306 patients were enrolled in the induction phase and received open-label ETN50/MTX. Of these, 198 patients (64.7%) were responders to ETN50/MTX treatment (DAS28-ESR ≤ 3.2 and < 2.6 at weeks 39 and 52, respectively); 193 patients continued into the double-blind phase. During the double-blind phase, 63 patients were randomized to ETN25/MTX and 65 patients each to MTX or PBO. A total of 144 patients completed Week 39 (end of the double-blind phase), with 131 patients considered responders (DAS28-ESR ≤ 3.2). Of these, 131 patients continued into the treatment-withdrawal phase, and 83 completed all 3 phases (ETN25/MTX n = 31, MTX n = 28, PBO n = 24).

Demographic and clinical characteristics of the study participants were well balanced among treatment groups at the start of the double-blind (Week 0) and treatment-free (Week 39) phases[16]. Patients in the double-blind phases had an overall mean (SD) age of 49.4 (14.4) years; 64.8% were women, 94.8% were white, and the mean (SD) duration of symptoms was 6.8 (2.85) months at baseline (induction phase).

*Response in the induction phase*. During the induction phase, all patients received 52 weeks of open-label ETN50/MTX and a high proportion achieved DAS28-ESR remission (< 2.6) and significant improvements in PRO measures. Patients who achieved Patient Acceptable Symptom State improved from 24.8% (Week 0) to 93.6% (Week 52). Mean change (SD) significantly improved from baseline in the EQ-5D utility index [0.33 (0.30)], EQ-5D visual analog scale [VAS; 33.1 (26.1)], Medical Outcomes Study Short Form-36 (SF-36) physical component summary [PCS; 14.4 (8.9)], mental component summary [MCS; 8.1 (10.9)], and Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT-F; 12.9 (12.1), $p < 0.001$]. The proportion of patients with a Work Instability Scale for Rheumatoid Arthritis (RA-WIS) score > 17 (indicating a high risk of work disability) was significantly lower after 1 year of ETN treatment (2.2%) compared with baseline (32.4%, $p < 0.001$). Among patients who were employed, mean change (SD) was significant in the Work Productivity and Activity Impairment Questionnaire–Rheumatoid Arthritis (WPAI-RA) items absenteeism [–12.9 (32.4)], presenteeism [–36.6, (31.5)], and overall work impairment [–37.3 (30.7)], and in all patients, activity impairment [–41.3, (28.6), $p < 0.001$; Appendix].

*Response in the reduced-treatment phase*. PRO were similar among treatment groups at the beginning of this double-blind phase (Week 0), with significant differences noted only between ETN25/MTX and PBO for WPAI-RA items presenteeism and activity impairment, and between MTX and PBO for activity impairment (Table 2). After ETN dose reduction or withdrawal at the end of this phase (Week 39), the ETN25/MTX and MTX groups were significantly different ($p < 0.05$) from PBO in all PRO assessments, with the exception of absenteeism and presenteeism and in the MTX

*Table 1*. Patient-reported outcomes.

| Assessment | Score Range | Clinically Meaningful Change | High Score Indicates | Population Normal |
|---|---|---|---|---|
| PASS[26] | Yes/No | — | Symptoms are more problematic | — |
| EQ-5D utility index[27,28,29] | 0–1 | ≥ 0.05[29] | Better QOL | 0.87[40] |
| EQ-5D VAS[30] | 0–100 mm | — | Better health | 82.5[37,39] |
| SF-36 PCS[31] | 0–100 | 2.5–5 for improvement, 0.8 for deterioration[36] | Better QOL | 50[31,41] |
| SF-36 MCS[31] | 0–100 | 2.5–5 for improvement, 0.8 for deterioration[36] | Better QOL | 50[31,41] |
| FACIT-F[32] | 0–52 | 15.9[42] | Less fatigue | Mean 43.6[33], median 47.0[33] |
| RA-WIS[34,35] | 0–23 | ≥ 5[38] | Risk of work disability: high > 17; moderate 10–17; low < 10[34] | — |
| WPAI-RA[35] | 0–100% | 7%[43] | More impairment | — |

PASS: Patient Acceptable Symptom State; VAS: visual analog scale; SF-36: Medical Outcomes Study Short Form-36; PCS: physical component summary; MCS: mental component summary; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; RA-WIS: Work Instability Scale for Rheumatoid Arthritis; WPAI-RA: Work Productivity and Activity Impairment Questionnaire-Rheumatoid Arthritis; QOL: quality of life.

*Table 2.* PRO assessments in the randomized population in the double-blind and treatment-withdrawal phases (mITT population, LOCF).

| Assessments | Reduced-treatment (Double-blind) Phase | | | | | | Treatment-withdrawal Phase | | |
|---|---|---|---|---|---|---|---|---|---|
| | Week 0, Mean (SD)*, n = 193 | | | Week 39, Mean (SD), (Change from Weeks 0 to 39 [SE])*, n = 193 | | | Week 65, Mean (SD), (Change from Weeks 0 to 65 [SE])*, n = 193 | | |
| | ETN25/MTX, n = 63 | MTX, n = 65 | PBO, n = 65 | ETN25/MTX, n = 63 | MTX, n = 65 | PBO, n = 65 | ETN25, n = 63 | MTX, n = 65 | PBO, n = 65 |
| PASS, % (95% CI) | 93.4 (84.1–98.2) | 98.5 (91.7–100) | 95.3 (86.9–99.0) | 88.9** (78.4–95.4) | 76.9** (64.8–86.5) | 58.5 (45.6–70.6) | 73.0** (60.3–83.4) | 61.5 (48.6–73.3) | 53.8 (41.0–66.3) |
| EQ-5D utility index | 0.86 (0.15) | 0.88 (0.13) | 0.85 (0.15) | 0.84 (0.16)**, (–0.01 [0.03]) | 0.80 (0.20)**, (–0.07 [0.03]) | 0.65 (0.31), (–0.21 [0.03]) | 0.77 (0.24)**, (–0.09 [0.03]) | 0.77 (0.21)**, (–0.10 [0.03]) | 0.61 (0.34), (–0.25 [0.03]) |
| SF-36 PCS | 49.8 (6.4) | 50.1 (6.3) | 48.5 (7.9) | 48.4 (7.7)**, (–1.0 [1.0]) | 46.5 (7.4)**, (–3.3 [1.0]) | 40.8 (10.5), (–7.7 [1.0]) | 44.9 (9.2)**, (–4.5 [1.2]) | 43.9 (8.8), (–5.9 [1.2]) | 39.8 (11.0), (–8.7 [1.2]) |
| SF-36 MCS | 53.0 (7.1) | 53.6 (7.0) | 52.8 (7.9) | 53.0 (6.8)**, (0.1 [1.0]) | 51.7 (8.7)**, (–1.7 [1.0]) | 48.1 (10.5), (–5.0 [1.0]) | 51.5 (8.4)**, (–1.5 [1.1]) | 50.0 (9.6), (–3.4 [1.1]) | 47.3 (10.8), (–5.8 [1.1]) |
| FACIT-F | 44.3 (6.6) | 44.4 (7.3) | 43.2 (8.0) | 43.2 (8.2)**, (–1.1 [1.1]) | 41.4 (9.1)**, (–2.9 [1.1]) | 36.2 (12.1), (–7.3 [1.1]) | 40.8 (9.8)**, (–3.6 [1.3]) | 39.2 (9.5)**, (–5.1 [1.2]) | 35.0 (12.6), (–8.6 [1.2]) |
| RA-WIS | 2.3 (3.6) | 2.6 (4.8) | 3.4 (5.1) | 3.8 (5.2)**, (0.9 [0.7]) | 4.5 (6.0)**, (1.5 [0.7]) | 8.2 (7.7), (4.9 [0.7]) | 5.4 (6.6), (2.5 [0.8]) | 6.2 (6.5), (3.2 [0.8]) | 8.6 (7.7), (5.3 [0.8]) |
| WPAI-RA | | | | | | | | | |
| Absenteeism, %† | 0.2 (1.2) | 0.1 (0.6) | 0.0 (0.0) | 3.8 (16.4), (3.7 [3.7]) | 5.5 (20.9), (5.1 [3.1]) | 10.4 (26.6), (10.5 [4.1]) | 8.0 (24.7), (5.4 [4.4]) | 9.4 (28.0), (9.3 [3.7]) | 10.0 (26.2), (10.5 [4.9]) |
| Presenteeism, %† | 6.2 (9.2)** | 8.9 (15.5) | 14.2 (17.9) | 10.4 (15.5)**‡, (0.2 [3.5]) | 21.3 (25.0), (10.7 [3.1]) | 30.8 (28.0), (19.9 [3.8]) | 17.5 (22.3)**, (7.9 [3.7]) | 22.2 (23.9)**, (11.9 [3.4]) | 35.0 (30.3), (22.7 [4.1) |
| % Overall work impairment† | 5.3 (9.8) | 6.7 (15.0) | 9.2 (12.8) | 10.9 (18.6)**, (4.2 [4.3]) | 20.7 (26.6), (13.2 [3.6]) | 31.4 (29.5), (24.8 [4.9]) | 21.8 (28.7), (14.9 [4.8]) | 21.7 (25.6)**, (14.5 [4.0]) | 33.4 (30.5), (28.1 [5.4]) |
| % Activity impairment | 8.6 (11.0)** | 10.0 (15.9)** | 16.8 (20.0) | 11.2 (15.4)**‡, (–0.6 [3.3]) | 24.4 (26.8)**, (12.4 [3.1]) | 37.3 (30.6), (23.8 [3.2]) | 23.0 (24.5)**, (11.2 [3.6]) | 30.9 (27.4), (19.0 [3.5]) | 42.0 (30.9), (28.5 [3.5]) |

* Values are raw mean (SD) and adjusted mean change (SE) with Week 52 value, treatment, and visit, and interaction of treatment as factors. Week 0 p values are based on 1-way ANOVA only. P values for pairwise treatment comparisons are based on a longitudinal statistical model with factors for Week 0 value, treatment, and visit. ** $p \leq 0.05$ vs PBO arm. † Impairment while working; employed patients only. ‡ $p \leq 0.05$ vs MTX arm. PRO: patient-reported outcomes; mITT: modified intent-to-treat; LOCF: last observation carried forward; ETN25: etanercept 25 mg once weekly; MTX: methotrexate; PBO: placebo; PASS: Patient Acceptable Symptom State; SF-36: Medical Outcomes Study Short Form-36; PCS: physical component summary; MCS: mental component summary; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; RA-WIS: Work Instability Scale for Rheumatoid Arthritis; WPAI-RA: Work Productivity and Activity Impairment Questionnaire-Rheumatoid Arthritis.

group for overall work impairment. In weeks 0–39, patients who received a dose reduction to ETN25/MTX generally maintained the previously achieved PRO response, while those who switched to MTX alone or PBO experienced significant declines (Figure 2).

All WPAI-RA items deteriorated with reduced treatment,

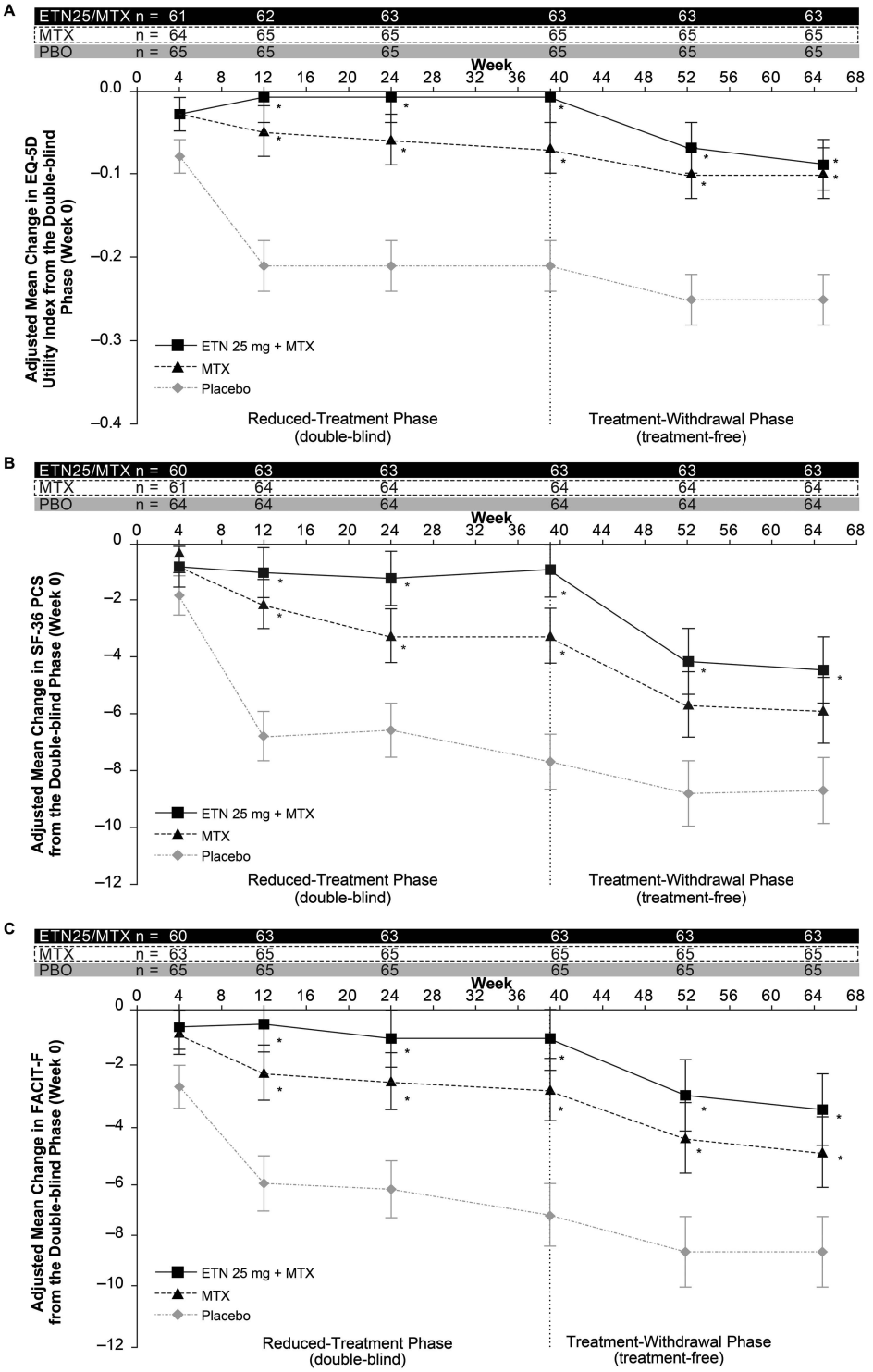


*Figure 2*. Assessments in the double-blind and treatment-withdrawal phases. (A) EQ-5D utility index. (B) SF-36 PCS. (C) FACIT-F. Continuous data based on the double-blind phase (LOCF) in the double-blind and treatment-withdrawal phases (modified intent-to-treat/radiographic intent-to-treat populations). * $p < 0.05$ vs placebo; p values for pairwise treatment comparisons based on a longitudinal statistical model with factors for week 0 value, treatment, and visit. Standard error bars ± 1. SF-36: Medical Outcomes Study Short Form-36; PCS: physical component summary; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; LOCF: last observation carried forward; ETN25: etanercept 25 mg once weekly; MTX: methotrexate; PBO: placebo.

with the exception of activity impairment, which showed a slight improvement at Week 39 (–0.6; Table 2). At Week 39, the MTX and PBO groups showed a greater worsening (i.e., larger increase) than the ETN25/MTX group in all WPAI-RA scores, which were significant versus the MTX and PBO groups for presenteeism and activity impairment, and versus PBO for overall work impairment ($p \leq 0.05$).

At Week 0 of the reduced-treatment phase (after open-label ETN therapy), a large proportion of patients had achieved clinically meaningful improvements in PRO assessments (Table 3)[29,34,36,37,38,39]. Although within-group testing was not performed, after ETN treatment was reduced, the proportion of patients with clinically relevant improvements decreased, with the exception of SF-36 MCS (ETN and MTX groups), with the largest reductions observed in those in the MTX and PBO groups. At Week 39, the percentage of patients achieving minimal clinically important difference (MCID) between the ETN25/MTX and PBO groups was significant for all ($p \leq 0.05$; Table 3).

*Response in treatment-withdrawal phase*. The third phase consisted of an analysis of 193 patients in the mITT population from the double-blind phase, including 131 patients who at Week 39 had DAS28-ESR ≤ 3.2 and 61 patients who were nonresponders or withdrew from the study by Week 39 (by LOCF). At the last on-therapy visit (Week 117), more patients in the ETN25/MTX group had DAS28-ESR remission (< 2.6) than in the MTX or PBO groups (LOCF 44.4%, 29.2%, and 23.1%, respectively; ETN25/MTX vs PBO, $p < 0.05$).

After withdrawal from active treatment (ETN or MTX), improvements in PRO measures significantly declined from weeks 39 to 65 in these treatment arms. Groups were comparable at baseline and Week 4 in the double-blind phase; however, by the treatment-withdrawal phase, patients who had received reduced ETN or switched to MTX had numerically smaller declines in PRO scores compared with PBO. Thus, increased time on combination therapy or MTX alone may have decreased the decline in clinical response seen upon withdrawing treatment. After Week 52, most PRO stabilized in patients randomized to PBO during the double-blind phase, whereas patients withdrawn from ETN25/MTX or MTX monotherapy experienced significant worsening of PRO (Figure 2).

At Week 65, SF-36 MCS and RA-WIS scores were no longer significant between the ETN25/MTX and MTX versus PBO groups or in SF-36 PCS scores between the MTX versus PBO groups. Patients reduced to ETN25/MTX treatment continued to experience a greater maintenance effect in HRQOL and fatigue (similar to the double-blind phase) measured by EQ-5D, SF-36 PCS, and FACIT-F, compared with PBO or MTX alone, which was significant versus PBO ($p \leq 0.05$; Figure 2).

After treatment withdrawal, the proportion of patients who achieved clinically relevant improvements in EQ-5D

*Table 3*. The percentage of patients who achieved clinically relevant improvements in PRO assessments after treatment reduction or withdrawal (mITT population, LOCF). P values based on 2-sided pairwise Fisher's exact tests.

| Variables | Week* | Patients, % | | | Pairwise Comparison, p | | |
|---|---|---|---|---|---|---|---|
| | | ETN25/MTX, n = 63 | MTX, n = 65 | PBO, n = 65 | ETN25/MTX vs MTX/PBO | ETN25/MTX vs PBO/PBO | MTX/PBO vs PBO/PBO |
| EQ-5D utility improvement ≥ 0.05**[29] | 0 | 83.3 | 87.1 | 77.8 | 0.616 | 0.499 | 0.240 |
| | 39 | 76.2 | 73.8 | 53.8 | 0.839 | 0.010 | 0.028 |
| | 65 | 68.3 | 67.7 | 52.3 | 1.000 | 0.073 | 0.107 |
| EQ-5D VAS > 82[37,39] | 0 | 79.7 | 75.8 | 63.9 | 0.666 | 0.069 | 0.172 |
| | 39 | 71.4 | 58.5 | 32.3 | 0.142 | < 0.001 | 0.005 |
| | 65 | 55.6 | 38.5 | 32.3 | 0.076 | 0.012 | 0.582 |
| SF-36 PCS improvement ≥ 5**[36] | 0 | 86.7 | 87.5 | 75.4 | 1.000 | 0.164 | 0.107 |
| | 39 | 79.4 | 76.6 | 42.2 | 0.831 | < 0.001 | < 0.001 |
| | 65 | 58.7 | 62.5 | 34.4 | 0.718 | 0.008 | 0.003 |
| SF-36 MCS improvement ≥ 5**[36] | 0 | 58.3 | 45.3 | 50.8 | 0.156 | 0.467 | 0.593 |
| | 39 | 58.7 | 46.9 | 35.9 | 0.215 | 0.013 | 0.282 |
| | 65 | 60.3 | 39.1 | 39.1 | 0.021 | 0.021 | 1.000 |
| RA-WIS ≤ 9†[34] | 0 | 97.1 | 89.1 | 93.3 | 0.228 | 0.591 | 0.697 |
| | 39 | 86.1 | 84.4 | 62.1 | 1.000 | 0.041 | 0.050 |
| | 65 | 80.6 | 71.1 | 58.6 | 0.438 | 0.062 | 0.319 |

* Weeks 0 to 39 is the double-blind, reduced treatment phase; Weeks 39 to 65, all patients were withdrawn from treatment. ** Improvement from phase I baseline mITT population (LOCF), representing clinically relevant improvement. † Low risk of work disability. PRO: patient-reported outcomes; mITT: modified intent-to-treat; LOCF: last observation carried forward; ETN25: etanercept 25 mg once weekly; MTX: methotrexate; PBO: placebo; VAS: visual analog scale; SF-36: Medical Outcomes Study Short Form-36; PCS: physical component summary; MCS: mental component summary; RA-WIS: Work Instability Scale for Rheumatoid Arthritis.

utility[29], EQ-5D VAS[37,39], and SF-36 PCS[36] decreased in the ETN25/MTX and MTX groups at Week 65, while the proportion in the PBO group largely plateaued. At Week 65, SF-36 MCS was significant between the ETN25/MTX and MTX groups, and EQ-5D VAS, SF-36 PCS, and SF-36 MCS in the ETN25/MTX and MTX groups versus PBO, with EQ-5D utility and PCS significant between MTX versus PBO ($p \leq 0.05$). Within-group changes in proportions were not tested, but the proportion of patients maintaining a low risk of work instability (RA-WIS ≤ 9) appeared to decrease in all groups, with larger decreases observed in the MTX and PBO groups, which were significant between ETN and MTX versus PBO at Week 39 ($p \leq 0.05$). At Week 65, all WPAI-RA items continued to worsen, with the largest increases from Week 0 observed in the PBO group (Table 2). Significant differences in presenteeism and activity impairment between the ETN25/MTX and PBO groups were maintained after treatment withdrawal. The MTX and PBO groups had significant differences in presenteeism and overall work impairment at Week 65 (Table 2).

## DISCUSSION

The possibility of reducing or withdrawing biologic or DMARD treatment in patients with RA after they achieved remission or LDA with induction therapy has been investigated in several clinical trials, to determine whether clinical response can be maintained[16,17,18,20,21,22,23,24]. Results are varied, raising the question as to why some patients maintain clinical response to such a treatment strategy while others do not[13,15,44,45]. Because the current approved dose of ETN for the treatment of adults with RA is 50 mg QW, it is important to establish whether the 25 mg QW dose can be effective as maintenance therapy, particularly in patients with early moderate to severe RA. PRO measures are crucial in determining effective treatment; therefore, it is essential that these measures are taken into consideration when investigating new or alternative treatment strategies[8].

To our knowledge, our analysis of the PRIZE clinical trial, consisting of 3 phases — treatment induction, dose reduction, and treatment withdrawal — is the first to analyze whether anti-TNF therapy response is maintained in PRO measures after reduction or withdrawal of therapy in patients with early, moderate-to-severe RA who had an initial response to therapy[16,18,22]. Patients experienced significant worsening in PRO measures when switched to PBO or MTX monotherapy, while reduction in ETN dose (25 mg QW) resulted in only slight, generally nonsignificant worsening. The trend in PRO worsening was most pronounced when therapy had been completely withdrawn. Further, after withdrawal of all therapy (Week 39), those patients who had received either reduced ETN therapy or MTX alone during the reduced-treatment phase experienced further worsening of PRO through Week 65. In patients who received PBO during this phase, the decline in PRO measures was immediate. During the treatment-reduction and treatment-withdrawal phases, no significant difference was observed between the ETN25/MTX and MTX alone groups, with the exception of the WPAI items presenteeism and activity impairment at Week 39. The proportion of patients achieving clinically relevant benefits during the reduced-treatment phase at Week 39 either remained the same or continued to decline after the withdrawal of all therapy, with the exception of SF-36 MCS.

Few studies published to date have analyzed the maintenance of response on HRQOL and physical functioning[18]. Quinn, *et al* reported that significant differences in Health Assessment Questionnaire (HAQ) and RA quality of life scores were maintained at Year 2 after remission was achieved with 1-year infliximab induction therapy versus PBO/MTX despite no differences in DAS28, ACR response, or radiographic scores[18]. Conversely, Detert, *et al* report that differences between adalimumab (ADA)/MTX and PBO/MTX at Week 48 were not maintained in HAQ and SF-36 scores after ADA therapy was withdrawn at Week 24[22]. Similarly, as previously reported from the PRIZE trial, HAQ ≤ 0.5 was maintained in those with reduced ETN therapy compared with PBO, but was not significant between groups after therapy withdrawal[16].

In general, patients in the PRIZE trial experienced significant worsening in PRO measures when switched to PBO or MTX monotherapy, but experienced only slight, generally nonsignificant worsening after a reduction of the ETN dose (25 mg QW). This is also the first trial to assess the maintenance of response in work-related measures with reduced or withdrawn therapy. Results were typical from the RA-WIS questionnaire in that the ETN25/MTX and MTX monotherapy scores were significant versus PBO at Week 39 after reduced or withdrawn treatment, and significance among the 3 groups was not maintained at Week 65 after all treatment was withdrawn. Results were similar throughout the study in the proportion of those who achieved a low risk of work disability (RA-WIS ≤ 9). Interestingly, results from the 4 WPAI-RA items were uncharacteristic, with a slight improvement in activity impairment and a worsening of absenteeism, presenteeism, and overall work impairment in the reduced-treatment ETN25/MTX group at Week 39, which was significant versus PBO for presenteeism, work, and activity impairment and versus MTX for presenteeism and activity impairment. Overall, worsening of WPAI-RA items was more pronounced with PBO and MTX treatments than with a reduced ETN dosage; however, these groups had a higher percentage of presenteeism, overall work impairment, and activity impairment at randomization. Significance in presenteeism and activity impairment was maintained between the ETN and MTX groups at Week 65 after treatment withdrawal and between MTX and PBO for presenteeism and work impairment. Interpretations of the WPAI-RA results are somewhat limited without an established MCID value.

Limitations to the PRIZE trial include using a population of patients with early RA who had primarily received no previous treatments for RA, which may not be generalized to those with later, previously treated disease. Treatment-naive patients with early RA are also unlikely to receive ETN as first-line therapy in clinical practice. In addition, the MTX only and PBO groups experienced a declining sample size because of lack of efficacy after randomization at Week 0, with the decline continuing in all groups after treatment withdrawal at Week 39. The limitations of the 39-week, reduced-treatment and 26-week, treatment-withdrawal phases prevent further extrapolation of results beyond these timepoints.

Results indicate that after remission or LDA is achieved in patients with early, moderate to severe RA disease, clinically relevant improvements in PRO measures may be maintained in some patients by reducing ETN therapy. Reducing therapy, even temporarily, may help alleviate concerns about longterm side effects and satisfy patient preferences for shorter treatment duration and/or lower treatment frequencies without sacrificing the patient's HRQOL. However, consistent monitoring would be needed for the possibility of retreatment because evidence is insufficient to determine which patients may benefit from reduced or treatment interruption strategies. In addition, the potential economies on cost of therapy should be weighed against potential worsening of work productivity despite stability of other disease and HRQOL measures. The needs of the individual patient versus those of the cohort should also not be overlooked in the pursuit of the most cost-effective treatment strategy in early RA.

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**APPENDIX.** PRO assessments in the open-label phase (mITT population, LOCF).

| PRO | Induction (Open-label) Phase | |
|---|---|---|
| | Week 0, Mean (SD)* | Week 52, Mean (SD)*, [Change from Week 0 to 52 (SE)] |
| | ETN 50 mg/MTX, n = 306 | ETN 50 mg/MTX, n = 306 |
| PASS, % (95% CI) | 24.8 (20.1–30.1) | 93.6 (89.6–96.5)** |
| EQ-5D utility index | 0.47 (0.31) | 0.85 (0.16)† (0.33 [0.30]) |
| EQ-5D VAS | 50.9 (22.6) | 84.9 (18.8)†, (33.1 [26.1]) |
| SF-36 PCS | 33.6 (8.0) | 48.7 (7.1)†, (14.4 [8.9]) |
| SF-36 MCS | 42.9 (10.9) | 52.6 (7.9)†, (8.1 [10.9]) |
| FACIT-F | 29.1 (12.6) | 43.2 (8.0)†, (12.9 [12.1) |
| RA-WIS | 13.5 (6.1) | 3.1 (4.9)†, (–10.0 [6.3]) |
| WPAI-RA | | |
| Absenteeism, % work time missed** | 19.8 (36.0) | 1.2 (9.5)†, (–12.9 [32.4]) |
| Presenteeism, % impairment while working** | 49.4 (27.8) | 11.1 (17.2)†, (–36.6 [31.5]) |
| Overall work impairment, %** | 50.1 (29.1) | 9.3 (17.0)†, (–37.3 [30.7]) |
| Activity impairment, % | 57.2 (24.3) | 13.0 (17.4)†, (–41.3 [28.6]) |

* Unless otherwise indicated. ** Employed patients only. † $p < 0.001$ versus baseline. PRO: patient-reported outcomes; mITT: modified intent-to-treat; LOCF: last observation carried forward; ETN: etanercept; MTX: methotrexate; PASS: Patient Acceptable Symptom State; VAS: visual analog scale; SF-36: Medical Outcomes Study Short Form-36; PCS: physical component summary; MCS: mental component summary; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; RA-WIS: Work Instability Scale for Rheumatoid Arthritis; WPAI-RA: Work Productivity and Activity Impairment Questionnaire-Rheumatoid Arthritis.