Certolizumab pegol for rheumatoid arthritis: effective in combination with methotrexate or as monotherapy

TNF plays an important role in several disease states, including rheumatoid arthritis. Biologic agents that specifically target TNF have revolutionized the treatment of rheumatoid arthritis. Traditional anti-TNF agents have provided significant clinical benefit. However, patient responses to these agents in clinical practice may be variable and additional agents are needed. Certolizumab pegol is the only PEGylated anti-TNF that is now approved for the treatment of patients with rheumatoid arthritis. This article summarizes the published efficacy, safety and patient-reported health outcome results for certolizumab pegol in the treatment of patients with active rheumatoid arthritis who have experienced an inadequate response to treatment with DMARDs, including methotrexate.

KEYWORDS: certolizumab pegol ■ methotrexate ■ monotherapy ■ RAPID ■ rheumatoid arthritis ■ TNF-α

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Rheumatoid arthritis (RA) is estimated to affect 5 million people worldwide [1] with 0.3–1% of the population in industrialized countries suffering from RA [2]. The development of RA is associated with increasing age and female gender, with the prevalence among women being approximately two-times greater than in men [3].

Although the etiology of RA remains unclear, the inflammation and joint damage associated with the disease are known to be partially mediated by TNF [4–6]. The development of biologic agents that target specific elements of the inflammation cascade, particularly TNF inhibitors, has therefore, revolutionized the management of RA. Clinical trials have focused on improvements in signs and symptoms and physical function, as well as the inhibition of structural damage [7–10]. Clinical guidelines from the American College of Rheumatology (ACR) recommend that these therapies are used in combination with methotrexate (MTX) for the best results, in patients with early RA who have high disease activity with features of a poor prognosis and who have not previously received DMARDs, and in patients with established disease with features of a poor prognosis who have had an inadequate response to nonbiologic DMARDs, including MTX [11].

The demonstration that DMARDs are more effective if used early rather than later in disease progression, has led to crucial changes in RA management goals. In the EU, the European League Against Rheumatism recommends disease remission as the main treatment goal for RA in order to prevent structural damage and long-term disability, with biologic therapy in combination with MTX providing superior clinical and radiological efficacy over monotherapy [12]. However, individual patient responses to biologic therapies are variable and achieving remission depends on the initial level of disease activity. Some patients never achieve a response and for those who respond initially, efficacy to one or all of the available agents may decline. Furthermore, tolerability issues may necessitate the need to switch agents or discontinue treatment [13,14].

Overview of the market

■ Biologic therapies & unmet needs

There are three traditional TNF inhibitors for use in RA: infliximab (Remicade®; Centocor, Inc., PA, USA), adalimumab (Humira®; Abbott, IL, USA) and etanercept (Enbrel®; Amgen, CA, USA and Wyeth, NJ, USA). Although they have not been compared in head-to-head trials, all three have shown similar efficacy in randomized, controlled clinical trials in RA, as monotherapy (adalimumab and etanercept) or, more effectively, in combination with MTX [15]. Infliximab is a chimeric monoclonal antibody, adalimumab is a human monoclonal antibody and etanercept is a soluble receptor construct [16]. The difference in the structure of these agents contributes to their different pharmacokinetics and safety profiles [10,17–20]. In addition, abatacept (Orencia®; Bristol-Myers Squibb, NY, USA), a T-cell costimulation antagonist, rituximab (Rituxan®/MabThera®; Genentech, CA, USA, Biogen Idec, Inc., MA, USA), a B-cell depleting

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agent, and anakinra (Kineret®; Amgen), an IL-1 receptor antagonist, are available for use in RA. However, rituximab is only approved for use after the failure of TNF inhibitors and anakinra is approved for patients who have failed one or more DMARD. Not all patients achieve a response to or tolerate these agents and any initial response or tolerability, to one or all of the therapies, may be lost over time. There is, therefore, a need for additional RA therapies.

New biologics for RA

Certolizumab pegol (Cimzia®; UCB, Brussels, Belgium) is a humanized, PEGylated anti-TNF Fab′ fragment that is approved in the USA for the treatment of patients with Crohn's disease and moderately to severely active RA [21]. Golimumab (Simponi™, Centocor, Inc., PA, USA), which like adalimumab is a human monoclonal anti-TNF antibody [22], was also recently approved for the treatment of RA, and tocilizumab, a humanized monoclonal antibody that targets the IL-6 receptor, is in late development [23].

Introduction to certolizumab pegol

Certolizumab pegol is the only PEGylated, Fc-free anti-TNF approved for the treatment of RA. It consists of a humanized Fab′ fragment fused to a 40-kDa poly(ethylene glycol) (PEG) moiety; the attachment of PEG to the Fab′ fragment increases its half-life, allowing a minimum dosing interval of 2 weeks.

Preclinical characteristics

Like the traditional TNF inhibitors, certolizumab pegol effectively neutralizes soluble and membrane TNF-α [24] and potently inhibits TNF-α signaling via both the p55 and p75 receptors *in vitro* [25]. However, by contrast to adalimumab and infliximab, certolizumab pegol does not contain an Fc region. The lack of an Fc portion may avoid potential Fc-mediated effects, such as complement (CDC)- or antibody (ADCC)-dependent cell-mediated cytotoxicity; indeed, *in vitro* studies found that certolizumab pegol did not mediate CDC and ADCC while adalimumab and infliximab did [24]. Furthermore, certolizumab pegol, unlike adalimumab and infliximab, did not cause apoptosis of activated peripheral blood lymphocytes or monocytes *in vitro*; certolizumab pegol also inhibited cytokine production with greater potency than the other TNF inhibitors [24]. In addition, and of potential relevance for RA, certolizumab pegol was shown to have enhanced penetration and retention in inflamed tissues compared with noninflamed tissues in animal models [26].

Studies in rat models have shown that the PEG derived from certolizumab pegol is distributed to all of the major organs, but does not cross the blood–brain barrier. It has a plasma half-life of approximately 2 weeks and the distribution is not influenced by target site binding [27]. In animal models, excretion of the PEG primarily occurs by the renal route; and after cleavage of the Fab′ fragment from the 40 kDa PEG, the PEG is then excreted with no further metabolism. Mean urinary and fecal excretion was 83% after 84 days of administration, with extrapolation to a final total of more than 90% [27]. There is no evidence of accumulation. Data from mouse models indicate that the biliary route may account for 1% of the 40 kDa PEG dose excretion, but this remains to be confirmed [28].

Clinical efficacy

The efficacy and safety of certolizumab pegol in combination with MTX or as monotherapy has been investigated in adult patients with active RA. The results of the published pivotal studies are summarized below.

Phase II trials

In a Phase II, double-blind, ascending dose group study, 36 patients with active RA were randomized to receive placebo or certolizumab pegol at 1, 5 or 20 mg/kg as a single infusion [29]. Patients had received an average of five DMARDs or experimental therapies prior to study entry and the mean duration of RA was 13 years. Certolizumab pegol demonstrated significant efficacy with 66.7 or 58.3% of patients who received certolizumab pegol achieving an ACR20 response after 4 or 8 weeks of treatment, respectively, compared with 16.7% of patients in the placebo group (Table 1).

Phase III trials

Study designs & patient characteristics

Certolizumab pegol in combination with MTX

The efficacy and safety of certolizumab pegol was evaluated in combination with MTX in patients with active RA. The RA prevention of structural damage (RAPID) 1 [30] and 2 [31] trials were double-blind, placebo-controlled, randomized trials of 52 and 24 weeks' duration, respectively, which examined the efficacy of two dose regimens of certolizumab pegol as add-on therapy to MTX in improving the signs and symptoms

Table 1. Clinical efficacy of certolizumab pegol in Phase II clinical trials.

Treatment	ACR20		ACR50	
	Week 4	*Week 8*	*Week 4*	*Week 8*
Placebo (n = 12)	16.7%	16.7%	0%	0%
CZP (n = 24)*	66.7%	58.3%	25%	25%
p-value‡	**0.012**	**0.032**	**0.079**	**0.079**

**Combined CZP group; the CZP 1 mg/kg group, CZP 5 mg/kg group and CZP 20 mg/kg group contained eight patients each.*
‡Combined CZP treatment effect versus placebo. Comparison of the pooled active groups versus placebo was made using a two-tailed closed testing procedure at a significance level of 5%. For detailed analyses, refer to [29].
ACR: American College of Rheumatology; CZP: Certolizumab pegol.

of RA and preventing radiographic progression. Eligible patients (aged ≥18 years with a diagnosis of adult-onset RA) were randomized 2:2:1 to receive subcutaneous certolizumab pegol (400 mg at weeks 0, 2 and 4, followed by 200 or 400 mg every 2 weeks) plus MTX, or placebo plus MTX. Oral corticosteroids (≤10 mg/day prednisone equivalent) and nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors were permitted provided the doses were stable within 28 and 14 days of baseline, respectively, and remained stable during the study.

Two formulations of certolizumab pegol were investigated; a lyophilized formulation of certolizumab pegol was used in RAPID 1 and a liquid formulation was used in RAPID 2. All patients were maintained on a stable dose of MTX (≥10 mg/week) for the duration of the studies. In consideration of disease severity, patients who were ACR20 nonresponders at both weeks 12 and 14 were to be withdrawn from RAPID 1 or 2 and allowed to enter an open-label extension study of certolizumab pegol plus MTX at week 16.

In total, 982 and 619 patients were randomized to treatment in RAPID 1 and 2, respectively; patient demographics and disease characteristics in both studies were comparable (Table 2). The ACR20 response rate at week 24 was a co-primary end point of RAPID 1 and the primary study end point in RAPID 2. Change from baseline in the modified total sharp score (mTSS) at week 52 was the second co-primary end point of RAPID 1. Major secondary end points in both studies included measures of radiographic progression at week 24, physical function and patient-reported outcomes.

Certolizumab pegol monotherapy

The efficacy and safety of certolizumab pegol as monotherapy was also evaluated for the treatment of RA in the 24-week, randomized, double-blind, placebo-controlled efficacy and safety of certolizumab pegol – 4 weekly dosage in rheumatoid arthritis (FAST4WARD) study in adult patients with active RA who had failed at least one prior DMARD [32]. Patients enrolled in this trial were aged 18–75 years with adult-onset active RA and were randomized to receive a lyophilized formulation of subcutaneous certolizumab pegol 400 mg (n = 111) or placebo (sorbitol; n = 109) at baseline and every 4 weeks (patient demographics are shown in Table 2). In FAST4WARD, 82% of randomized patients had prior exposure to MTX and patients were allowed to receive concurrent oral corticosteroids (prednisone equivalent ≤10 mg/day, stable for at least 4 weeks prior to enrolment and during the study); other corticosteroids were prohibited. As with the RAPID studies, the primary end point of the FAST4WARD study was the ACR20 response rate at week 24; secondary end points included ACR50/70 responses, ACR component scores, patient-reported outcomes (including physical function, health-related quality of life, pain and fatigue) and safety.

Clinical results

Effects on signs & symptoms of RA

Certolizumab pegol, when dosed either in combination with MTX or as monotherapy, significantly reduced the signs and symptoms of RA (Figure 1).

In the RAPID 1 and 2 trials, differences in ACR20 responses for patients receiving certolizumab pegol plus MTX were significantly higher than those for patients receiving placebo plus MTX (Figure 1A). At week 24 in RAPID 1, ACR20 response rates were 58.8% with certolizumab pegol 200 mg and 60.8% with certolizumab pegol 400 mg given every 2 weeks versus 13.6% with placebo. Differences in ACR50 and ACR70 responses were significantly higher than placebo at week 24 in the RAPID 1 trial (Figure 1A). Similar ACR20, ACR50 and ACR70 response rates were observed in the RAPID 2 trial (Figure 1A).

In the FAST4WARD study, monotherapy with certolizumab pegol 400 mg every 4 weeks yielded an ACR20 response rate for the modified intention-to-treat population of 45.5 versus 9.3%

Table 2. Demographic and disease characteristics of the Phase III studies.

Baseline characteristics	RAPID 1 (n = 982)	RAPID 2 (n = 619)	FAST4WARD (n = 220)
Age in years, mean (SD)	52.0 (11.6)	51.9 (11.5)	53.8 (12.2)
Female, %	83.2	81.6	83.6
Disease duration in years, mean (SD)	6.1 (4.3)	6.2 (4.2)	9.5 (8.9)
RF-positive (≥14 IU/ml), %	81.8	76.9	100
MTX dose (mg/week), mean	13.6	12.5	n/a
Number of previous DMARDs, mean	1.3*	1.2*	2.0
Tender joint count, mean (SD)	30.7 (12.9)	30.2 (14.0)	29.0 (13.1)
Swollen joint count, mean (SD)	21.5 (9.8)	21.0 (9.8)	20.5 (9.7)
HAQ-DI, mean (SD)	1.7 (0.6)	1.6 (0.6)	1.5 (0.6)
CRP mg/l, geometric mean (CV)	14.7 (144.2)	13.6 (180.9)	11.5 (233.1)
DAS28(ESR), mean (SD)	6.9 (0.8)	6.8 (0.8)	6.3 (1.0)

*Number of previous DMARDs excluding MTX.
CRP: C-reactive protein; CV: Coefficient of variation; DAS28(ESR): Disease activity score-28 (erythrocyte sedimentation rate); HAQ-DI: Health assessment questionnaire – disability index; MTX: Methotrexate; n/a: Not applicable; RF: Rheumatoid factor; SD: Standard deviation.

for the placebo group at week 24 ($p < 0.001$). ACR50 and ACR70 responses for patients treated with certolizumab pegol monotherapy were also significantly higher compared with placebo (Figure 1B).

Response to certolizumab pegol was rapid when dosed in combination with MTX in RAPID 1 and 2 or as monotherapy in FAST4WARD. In all trials, the ACR20 response was significantly greater at week 1 with certolizumab pegol (with MTX or alone) than with placebo (with MTX or alone), and the differences in ACR20 responses remained significant through the end of all studies (week 52 in RAPID 1 and week 24 in RAPID 2 and FAST4WARD) (Figure 2). Patients receiving certolizumab pegol experienced significantly greater percentage improvements in all ACR core components relative to those treated

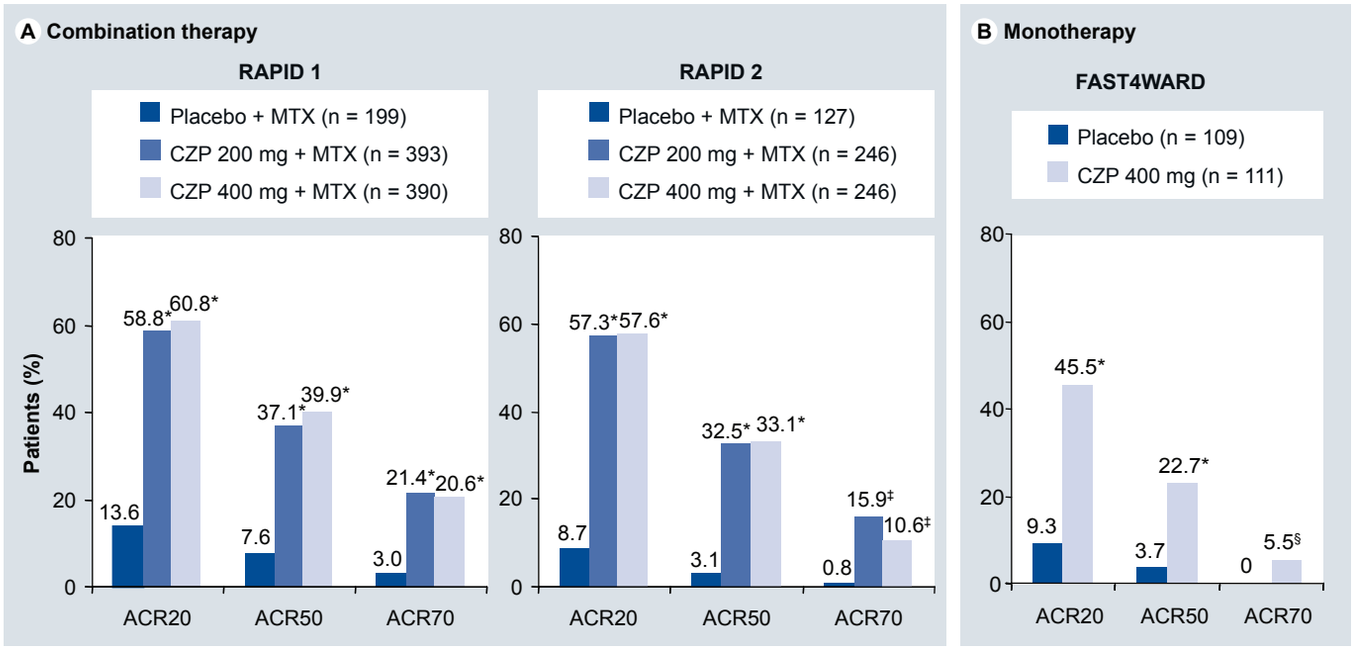

Figure 1. ACR response rates at week 24 in patients treated with certolizumab pegol. Meaningful improvements were observed in ACR20/50/70 responses in patients treated with **(A)** CZP plus MTX or **(B)** CZP monotherapy. Treatment comparisons of ACR20/50/70 responses between the CZP group(s) and placebo were calculated using logistic regression with treatment and geographic region as factors in the RAPID trials or a Cochran–Mantel–Haenszel test stratified by country in the FAST4WARD trial. For detailed analyses, refer to the primary publications [30–32].
*$p < 0.001$; ‡$p \leq 0.01$; §$p \leq 0.05$.
ACR: American College of Rheumatology; CZP: Certolizumab pegol; MTX: Methotrexate.
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with placebo (TABLE 3). These improvements were observed as early as week 1 and were sustained throughout all trials (TABLE 3). In the RAPID trials, improvements were similar in the certolizumab pegol 200 or 400 mg plus MTX groups.

Inhibition of progression of structural damage

The ability of certolizumab pegol plus MTX to inhibit the progression of structural joint damage was investigated in RAPID 1 and 2. In both trials, the progression of structural joint damage was significantly inhibited by certolizumab pegol plus MTX (FIGURE 3). After 52 weeks of therapy in RAPID 1, the changes from baseline in mTSS, erosion scores (ES) and joint space narrowing (JSN) scores were significantly lower in patients receiving certolizumab pegol plus MTX compared with patients receiving placebo plus MTX (FIGURE 3A). Changes in mTSS, ES and JSN scores were also significantly smaller with certolizumab pegol plus MTX versus placebo plus MTX when assessed after 24 weeks in the RAPID 2 trial (FIGURE 3B). In the RAPID 2 trial, a negative 95% CI of the change in mTSS was observed in the certolizumab pegol 400-mg group suggesting that some repair may have occurred [31]. In both trials, results of the primary analysis, which was based on linear extrapolation, were confirmed by multiple sensitivity analyses, including last observation carried forward analysis, observed data analysis and analysis on log-transformed data.

Inhibition of the progression of structural damage was observed in both trials as early as 16 weeks of treatment. A *post-hoc* analysis performed at week 16 on the group of patients who withdrew due to lack of ACR20 response at weeks 12 and 14 showed inhibition of structural damage in patients treated with certolizumab pegol (FIGURES 3C AND 3D). In RAPID 1, mean changes (± standard deviation [SD]) from baseline to week 16 were lower with certolizumab pegol plus MTX (pooled analysis on certolizumab pegol 400- and 200-mg groups) compared with placebo plus MTX for mTSS (0.2 ± 2.2 vs 1.0 ± 2.5; FIGURE 3C), ES (0.1 ± 1.1 vs 0.5 ± 1.4) and JSN (0.2 ± 1.7 vs 0.4 ± 1.5). Rank analysis showed these reductions to be statistically significant ($p \leq 0.05$). Similar results were observed in the RAPID 2 trial (FIGURE 3D).

Health outcomes

In addition to significantly improving the signs and symptoms of RA and inhibiting the progression of structural joint damage, certolizumab pegol plus MTX or certolizumab pegol monotherapy significantly improved all evaluated aspects of patients' quality of life, including physical function, pain, fatigue, and work and home productivity.

Improvements in physical function

Physical function was assessed using the health assessment questionnaire – disability index (HAQ-DI). Patients treated with either dose of

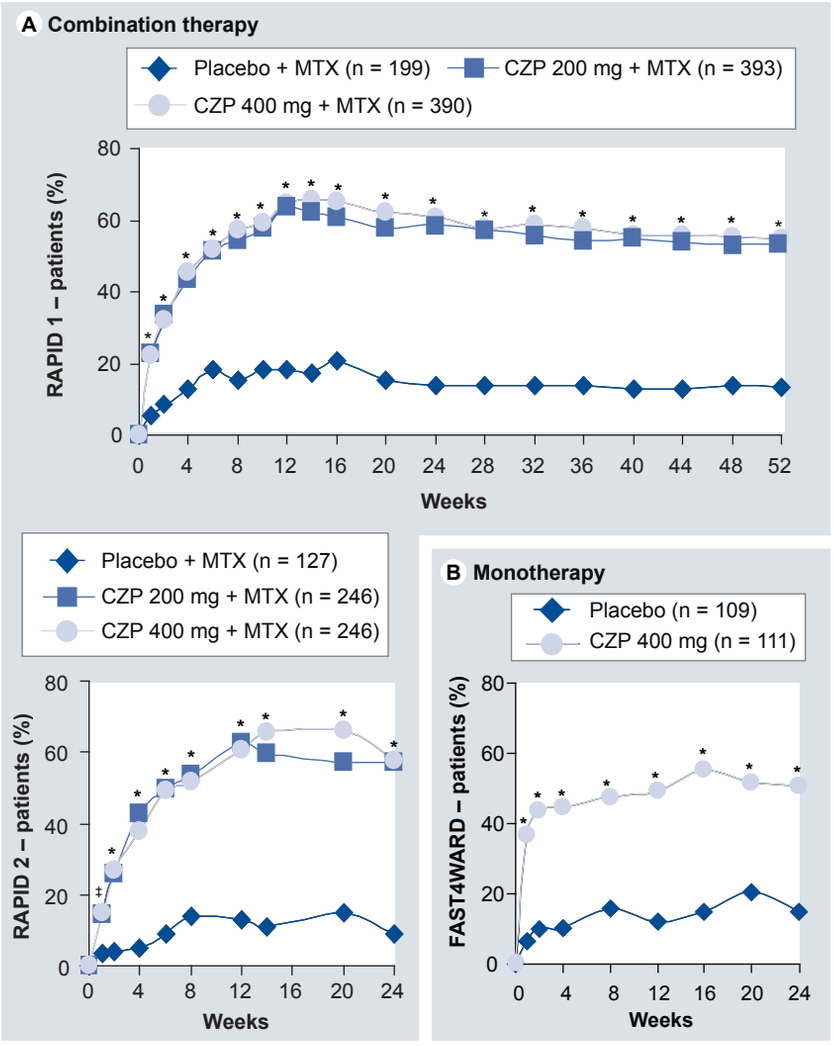

Figure 2. ACR20 response rates over time in patients treated with certolizumab pegol. ACR20 responses were statistically significant in CZP-treated patients compared with placebo-treated patients by week 1 and throughout the **(A)** RAPID 1 ($p < 0.001$ vs placebo plus MTX) and RAPID 2 ($p < 0.001$ vs placebo plus MTX) and **(B)** FAST4WARD ($p \leq 0.01$ vs placebo) studies. Treatment comparisons of ACR20 responses between the CZP group(s) and placebo were calculated using logistic regression with treatment and geographic region as factors in the RAPID trials or a Cochran–Mantel–Haenszel test stratified by country in the FAST4WARD trial. For detailed analyses, refer to [30–32].
*$p < 0.001$; ‡$p \leq 0.01$ versus placebo.
ACR: American College of Rheumatology CZP: Certolizumab pegol; MTX: Methotrexate.
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Table 3. Effect of certolizumab pegol on core components of ACR response.

Study	Week	Treatment regimen	Patients (n)	Percentage change from baseline					
				TJC[*]	*SJC*[*]	*PhGA*[*]	*PtGA*[*]	*Pain*[*]	*HAQ*[*]	*CRP*[‡]
RAPID 1	1	Placebo + MTX	199	-6.7	-4.5	-3.3	-2.9	-1.0	-2.4	1
		CZP 200 mg + MTX	393	-18.9	-18.2	-19.0	-12.9	-20.6	-13.5	-65
	52	Placebo + MTX	199	-10.1	-10.6	-12.8	-7.6	-6.6	-5.6	-13
		CZP 200 mg + MTX	393	-61.6	-65.8	-55.6	-43.8	-43.2	-35.1	-54
RAPID 2	1	Placebo + MTX	127	-3.5	-3.3	-2.5	-3.0	5.4	0.2	-5
		CZP 200 mg + MTX	246	-13.8	-18.2	17.3	-14.3	-16.5	-12.5	-74
	24	Placebo + MTX	127	-10.5	-13.3	-12.0	5.8	8.3	-3.7	-8
		CZP 200 mg + MTX	246	-54.8	-64.2	-52.3	-34.2	-35.9	-31.8	-59
FAST4WARD	1	Placebo	109	-5.5	-12.0	-2.5	1.4	1.2	0.9	10
		CZP 400 mg	111	-29.6	-27.1	-18.6	-13.4	-22.8	-13.6	-70
	24	Placebo	109	-13.3	-23.4	-1.5	6.4	41.5	8.6	20
		CZP 400 mg	111	-44.0	-40.6	-27.4	-15.7	-23.7	-21.5	-40

Intention-to-treat population in RAPID; modified intention-to-treat population in FAST4WARD.
[*]Percentage change from baseline (mean); [‡]Geometric means of ratio to baseline -1 (in %).
CRP: C-reactive protein; CZP: Certolizumab pegol; HAQ: Health assessment questionnaire; MTX: Methotrexate; PhGA: Physician's global assessment; PtGA: Patient's global assessment; Pain: Patient's assessment of pain; SJC: Swollen joint count; TJC: Tender joint count.

certolizumab pegol plus MTX in RAPID 1 or 2 reported significant improvements in physical function compared with placebo plus MTX as early as week 1 (Table 3). These improvements were maintained throughout both studies (week 52 of RAPID 1 and week 24 of RAPID 2) (Table 3 & Figure 4A). In addition, significantly more patients treated with certolizumab pegol plus MTX reported clinically meaningful improvements in physical function as indicated by the HAQ-DI minimum clinically important difference (MCID) from week 1 to the end of the study (Figure 4A): 47 or 57% of patients treated with certolizumab pegol 200 mg plus MTX in RAPID 1 or 2, respectively, achieved the MCID at study end (weeks 52 or 24, respectively) compared with 13 or 11% of patients treated with placebo plus MTX.

Patients treated with certolizumab pegol monotherapy in FAST4WARD also had statistically significant improvements versus placebo in all eight HAQ-DI domains by week 1 and throughout the study for the majority of assessments. At the end of the study, the mean change from baseline in HAQ-DI was -0.36 for certolizumab pegol versus 0.13 for placebo ($p < 0.001$, Figure 4B). Furthermore, a significantly higher proportion of patients receiving certolizumab pegol (49–61%) reported clinically meaningful improvements in their physical function (HAQ-DI MCID) than those receiving placebo (12–27%) throughout the entire study period (weeks 1–24; $p < 0.001$).

Improvements in health-related quality of life

Health-related quality of life (HRQoL) was assessed using the short form 36-item health survey (SF-36). In RAPID 1, the physical and mental component summary scores and all eight SF-36 domain scores were significantly improved following certolizumab pegol plus MTX treatment at weeks 24 and 52 irrespective of the dose regimen ($p < 0.001$). Significantly greater improvements from baseline in all scores were also observed at each visit with certolizumab pegol plus MTX than placebo plus MTX. In FAST4WARD, certolizumab pegol monotherapy also led to improvements in all domains and in the physical and mental component summary scores ($p < 0.001$) at week 24. Significantly more certolizumab pegol-treated patients experienced HRQoL MCIDs (in all eight domains and in the physical and mental component summary scores) than those receiving placebo at week 24 ($p \leq 0.01$).

Reduction in pain & fatigue

Certolizumab pegol plus MTX provided rapid and durable relief from pain and fatigue in the RAPID 1 and 2 studies, with statistically significant improvements in both pain (visual analogue scale [VAS]; FIGURE 4C) and fatigue assessment scale (FAS) scores (FIGURE 4E) reported as early as week 1, which were sustained to the end of the studies. In the FAST4WARD study, daily pain assessments were performed over the first week using a modified brief pain inventory, where patients were asked to rate their 'worst pain in the last 24 h', 'average pain in the last 24 h' and 'pain right now'. Patients experienced significant pain relief within 2 days of receiving certolizumab pegol monotherapy compared with placebo ($p \leq 0.05$). After the first week, pain assessments were performed using the pain VAS. Significant and clinically meaningful differences in reductions (mean change from baseline) in arthritis pain (VAS) scores in the certolizumab pegol arm relative to placebo were observed by week 1 (-16.7 vs -5.2, respectively) and were sustained throughout the study up to

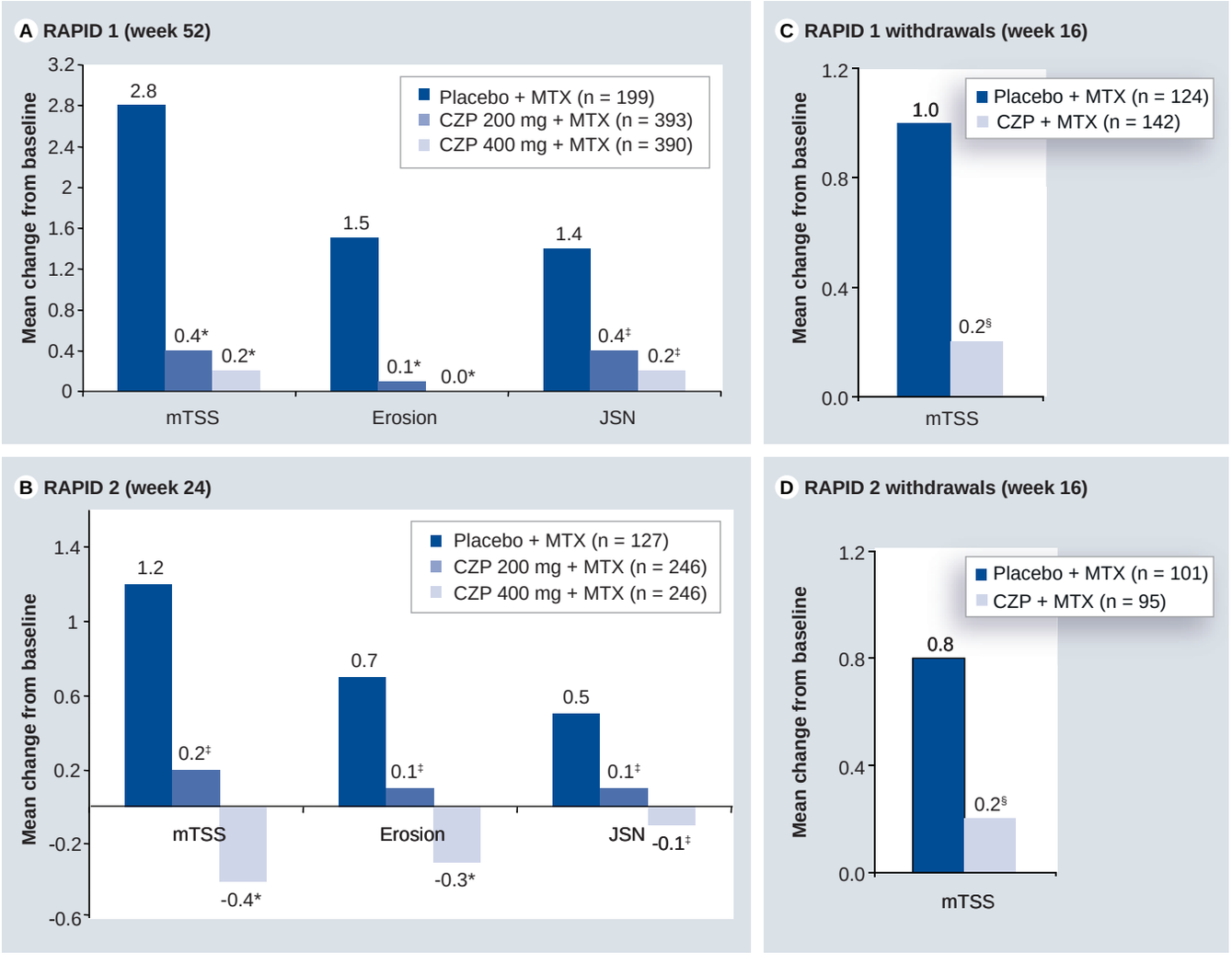

Figure 3. Effect of certolizumab pegol plus MTX on radiographic progression of structural joint damage. Changes from baseline in mTSS, erosion score and JSN score were significantly smaller with CZP plus MTX versus placebo in **(A)** RAPID 1 and **(B)** RAPID 2 studies after 52 or 24 weeks of treatment, respectively. In a *post-hoc* analysis of patients who withdrew at week 16 due to lack of ACR20 response at weeks 12 and 14, changes in mTSS were significantly smaller in patients treated with CZP plus MTX (both dose groups combined) versus placebo plus MTX in **(C)** RAPID 1 and **(D)** RAPID 2 studies ($p \leq 0.05$ vs placebo plus MTX). In both studies, treatment comparisons were made using analysis of covariance on the ranks with treatment and geographic region as factors and the ranked baseline mTSS as the covariate. For detailed analyses, refer to [30,31].
*Significantly different from placebo, $p < 0.001$; ‡Significantly different from placebo, $p \leq 0.01$; §$p \leq 0.05$ versus placebo.
CZP: Certolizumab pegol; JSN: Joint space narrowing; mTSS: Modified total sharp score; MTX: Methotrexate; RAPID: Rheumatoid arthritis prevention of structural damage.
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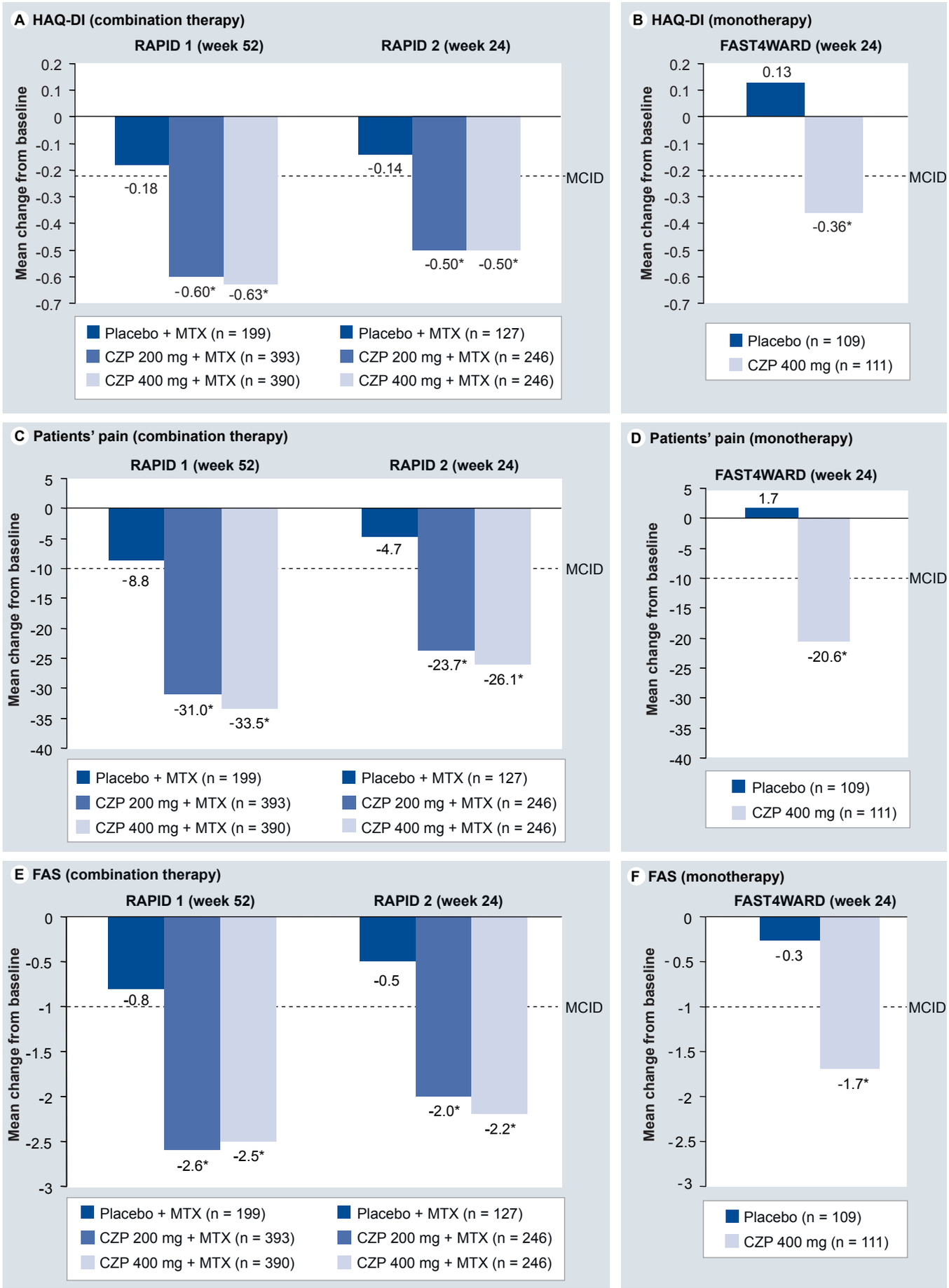
A HAQ-DI (combination therapy)
RAPID 1 (week 52)
RAPID 2 (week 24)
Mean change from baseline
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.18
-0.60*
-0.63*
-0.14
-0.50*
-0.50*
MCID
Placebo + MTX (n = 199)
CZP 200 mg + MTX (n = 393)
CZP 400 mg + MTX (n = 390)
Placebo + MTX (n = 127)
CZP 200 mg + MTX (n = 246)
CZP 400 mg + MTX (n = 246)
B HAQ-DI (monotherapy)
FAST4WARD (week 24)
Mean change from baseline
0.13
-0.36*
MCID
Placebo (n = 109)
CZP 400 mg (n = 111)
C Patients' pain (combination therapy)
RAPID 1 (week 52)
RAPID 2 (week 24)
Mean change from baseline
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-8.8
-31.0*
-33.5*
-4.7
-23.7*
-26.1*
MCID
Placebo + MTX (n = 199)
CZP 200 mg + MTX (n = 393)
CZP 400 mg + MTX (n = 390)
Placebo + MTX (n = 127)
CZP 200 mg + MTX (n = 246)
CZP 400 mg + MTX (n = 246)
D Patients' pain (monotherapy)
FAST4WARD (week 24)
Mean change from baseline
1.7
-20.6*
MCID
Placebo (n = 109)
CZP 400 mg (n = 111)
E FAS (combination therapy)
RAPID 1 (week 52)
RAPID 2 (week 24)
Mean change from baseline
0
-0.5
-1
-1.5
-2
-2.5
-3
-0.8
-2.6*
-2.5*
-0.5
-2.0*
-2.2*
MCID
Placebo + MTX (n = 199)
CZP 200 mg + MTX (n = 393)
CZP 400 mg + MTX (n = 390)
Placebo + MTX (n = 127)
CZP 200 mg + MTX (n = 246)
CZP 400 mg + MTX (n = 246)
F FAS (monotherapy)
FAST4WARD (week 24)
Mean change from baseline
-0.3
-1.7*
MCID
Placebo (n = 109)
CZP 400 mg (n = 111)

Figure 4 (see facing page). Effects of certolizumab pegol on physical function, pain and fatigue at end of study. Greater mean improvements in HAQ-DI scores at end of study were observed in patients treated with CZP **(A)** in combination with MTX or **(B)** as monotherapy compared with placebo. Greater mean improvements from baseline in patients' assessment of pain (VAS) (mITT population) at end of study were observed in patients treated with CZP **(C)** in combination with MTX or **(D)** as monotherapy compared with placebo. Similarly, patients treated with CZP **(E)** in combination with MTX or **(F)** as monotherapy had greater mean improvements from baseline in FAS (mITT population) compared with patients treated with placebo. In the RAPID and FAST4WARD trials, mean change from baseline in HAQ-DI, patients' assessment of pain and FAS were performed using analysis of covariance, with treatment and geographic region as factors and baseline value as the covariate. For detailed analyses, please refer to [30].
*$p < 0.001$ versus placebo.
CZP: Certolizumab pegol; FAST4WARD: Efficacy and safety of certolizumab pegol – 4 weekly dosage in rheumatoid arthritis; HAQ-DI: Health assessment questionnaire – disability index; MCID: Minimum clinically important difference; mITT: Modified intent-to-treat; MTX: Methotrexate; RAPID: Rheumatoid arthritis prevention of structural damage; VAS: Visual analog scale.
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week 24 (-20.6 vs 1.7, respectively) ($p < 0.001$; FIGURE 4D). Statistically significant and clinically meaningful improvements FAS scores were achieved as early as week 1 with certolizumab pegol compared with placebo and were sustained throughout the 24-week study: mean change from baseline in FAS was -1.7 for certolizumab pegol compared with -0.3 for placebo at week 24 ($p < 0.001$; FIGURE 4F).

Improvements in work & household productivity

In the RAPID trials, the validated work productivity survey (WPS-RA) questionnaire [33] was used to measure RA-related productivity at work and home as well as social and leisure time. The WPS-RA was administered every 4 weeks starting at baseline.

Certolizumab pegol reduced the impact of RA on household productivity and improved the ability of patients with RA to carry out family, social and leisure activities [34]. By week 24, patients treated with certolizumab pegol 200 mg plus MTX in RAPID 1 or 2 gained 4.7 or 4.2 full days of household activities per month from baseline, respectively, compared with only 1.5 or 0.2 days for patients in the placebo group ($p \leq 0.01$). Patients treated with certolizumab pegol 200 mg plus MTX also reported fewer limitations in performing their household duties as demonstrated by an increase in household productivity of 5.7 or 6.1 days per month from baseline compared with only 2.9 or 1.4 days for patients in the placebo group ($p \leq 0.01$). Similar gains in full days of household duties and days with increased productivity were reported by patients treated with certolizumab pegol 400 mg plus MTX.

Treatment also improved the performance at work of subjects with active RA, as shown by the reduction in presenteeism (reduced productivity when at work) and absenteeism (absence from work) and the decrease in the RA interference on their work productivity [35]. By week 24, patients treated with certolizumab pegol 200 mg plus MTX gained a monthly average of 1.6 or 2.1 work days from baseline in RAPID 1 or 2, respectively, compared with a gain of only 0.1 or 0.6 days by patients in the placebo group. Patients treated with certolizumab pegol 200 mg plus MTX also reported fewer limitations at work due to RA, as seen by an increase of 4.6 or 6.1 productive work days per month from baseline compared with 1.0 or a decrease of 1.5 days in the placebo group ($p < 0.01$).

Safety & tolerability

Certolizumab pegol was generally well-tolerated when administered in combination with MTX or as monotherapy (TABLE 4).

Certolizumab pegol in combination with MTX

Because of the protocol-mandated withdrawals at week 16 and 2:1 patient randomization for the certolizumab pegol groups vs placebo in RAPID 1 and 2, mean exposure to study treatment was markedly longer in the pooled certolizumab pegol groups than in the placebo group. The incidence rates of treatment-emergent adverse events (TEAEs) were therefore adjusted to account for differences in study drug exposure.

The majority of adverse events (AEs) were mild-to-moderate in intensity. Discontinuation due to AEs was low in all groups (TABLE 4). The most frequent AEs leading to withdrawal were infections and infestations (22 patients), skin and subcutaneous tissue disorders (7 patients), general disorders and administration site conditions (7 patients) and cardiac disorders (6 patients).

All TEAEs leading to death were considered unlikely to be related or unrelated to the study drug. In RAPID 1, AEs led to death in seven patients: one in the placebo group (myocardial infarction), two in the certolizumab pegol 200-mg group (one each from hepatic neoplasm

and cardiac arrest) and four in the certolizumab pegol 400-mg group (one each from cerebrovascular accident, myocardial infarction, cardiac arrest, and one from atrial fibrillation and fatigue). In RAPID 2, AEs led to death in two patients: one in the certolizumab pegol 200-mg group (acute myocardial infarction and cerebrovascular accident) and one in the certolizumab pegol 400-mg group (femur fracture and shock).

Infection rates were also similar across all arms (TABLE 4). The most frequently reported infections in all groups were urinary tract infections (19.4, 10.6 and 11.6 per 100 patient-years in the placebo, certolizumab pegol 200- and 400-mg groups, respectively) and upper respiratory tract infections (including nasopharyngitis) (17.5, 29.1 and 26.7 per 100 patient-years in the placebo, certolizumab pegol 200- and 400-mg groups, respectively). Serious infections were observed more frequently in the certolizumab pegol plus MTX treatment groups (6.0 and 7.1 per 100 patient-years in the certolizumab pegol 200- and 400-mg groups, respectively) than in the placebo plus MTX group (1.5 per 100 patient-years). The most frequently reported serious infections in the certolizumab pegol 200- and 400-mg plus MTX treatment groups were TB, pneumonia and erysipelas (new cases per 100 patient-years: 1.2 and 1.2; 0.7 and 1.0; 0.2 and 1.2, respectively). All TB cases occurred in countries with high incidence rates of TB (including five cases in Russia) and none were reported in patients from North America.

The rates of malignancies (heterogeneous in type) were similar across all treatment arms (1.5, 2.0 and 1.2 per 100 patient-years in the placebo, certolizumab pegol 200- and 400-mg groups, respectively). In RAPID 1, malignant neoplasms were observed in 12 patients: one thyroid neoplasm in the placebo group (1.1 per 100 patient-years), seven in the certolizumab pegol 200-mg group (2.3 per 100 patient-years; three basal cell carcinomas including one that metastasized to the brain, one adrenal adenoma, one hepatic neoplasm, one esophageal carcinoma and one uterine cancer) and four in the certolizumab pegol 400-mg group (1.3 per 100 patient-years; two tongue neoplasms, one extranodal marginal zone B-cell lymphoma and one papilloma). In RAPID 2, one case of malignant neoplasm was reported in each of the placebo (bladder cancer), certolizumab pegol 200-mg (testis cancer) and certolizumab pegol 400-mg (colon cancer) groups. There were no clinically significant differences in the incidence of cardiac disorders between the three treatment groups. The incidence of injection-site pain with either dose of certolizumab pegol plus MTX was low in both studies (<3 new cases per 100 patient-years, compared with none in the placebo plus MTX group).

Certolizumab pegol monotherapy

In FAST4WARD, most AEs were mild or moderate. AEs leading to withdrawal were reported in two (1.8%) placebo-treated patients

Table 4. Selected AEs from certolizumab pegol Phase III clinical trials.

Adverse events	RAPID 1 and 2 pooled populations rate per 100 patient-years (n)			FAST4WARD number of patients (%)	
	Placebo + MTX (n = 324)	*CZP 200 mg + MTX (n = 640)*	*CZP 400 mg + MTX (n = 635)*	*Placebo (n = 109)*	*CZP 400 mg (n = 111)*
Exposure (patient years)	132.0	406.7	419.5	–	–
Any TEAE	246.4	239.1	221.1	63 (57.8)	84 (75.7)
Mild intensity	155.5	162.3	156.4	43 (39.4)	62 (55.9)
Moderate intensity	96.7	79.0	75.6	40 (36.7)	52 (46.8)
Severe intensity	14.2	12.5	12.9	11 (10.1)	8 (7.2)
Related to study drug	66.9	78.1	74.4	24 (22.0)	27 (24.3)
Serious AE	11.9 (15)	16.3 (63)	16.6 (66)	3 (2.8)	8 (7.2)
AE leading to withdrawal	3.8 (5)	7.2 (29)	7.0 (29)	2 (1.8)	5 (4.5)
AE leading to death	0.8 (1)	0.7 (3)	1.2 (5)	0 (0)	0 (0)
Infections	73.2 (78)	80.9 (240)	76.7 (237)	16 (14.7)	33 (29.7)
Serious infections	1.5 (2)	6.0 (24)	7.1 (29)	0 (0)	2 (1.8)
TB	0 (0)	1.2 (5)	1.2 (5)	0 (0)	0 (0)
Malignancies	1.5 (2)	2.0 (8)	1.2 (5)	0 (0)	2 (1.8)
Cardiac disorders	5.3 (7)	4.7 (19)	4.8 (20)	2 (1.8)	0 (0)

AE: Adverse events; CZP: Certolizumab pegol; FAST4WARD: Efficacy and safety of certolizumab pegol – 4 weekly dosage in rheumatoid arthritis; MTX: Methotrexate; RAPID: Rheumatoid arthritis prevention of structural damage; TEAE: Treatment-emergent adverse event.
Adapted from [32].

(nausea and pneumonitis) and in five (4.5%) certolizumab pegol-treated patients (bacterial arthritis, salmonella arthritis, increased blood creatinine/increased blood urea, ischemic stroke and menorrhagia). No deaths were reported. Serious AEs were reported in three patients (2.8%) in the placebo group and eight patients (7.2%) in the certolizumab pegol group (9 vs 18 events per 100 patient-years, respectively). In the placebo group, these comprised one case (0.9%) each of vomiting, chronic renal failure and pneumonitis. In the certolizumab pegol group, they consisted of two cases (1.8%) of aggravated RA and one case (0.9%) each of bacterial arthritis, mastitis, benign parathyroid tumor, postural dizziness, ischemic stroke and menorrhagia.

The incidence of serious infections was low (0% with placebo and 1.8% with certolizumab pegol), and there were no reported cases of TB or opportunistic infections. The incidence of tumors was also low, with no reported cases in the placebo group and two (1.8%) in the certolizumab pegol group (one case of uterine fibroids and one of benign parathyroid tumor). No malignancies, including lymphoma, or cases of demyelinating disease were reported. Injection-site pain was reported in 1.8% of placebo-treated patients, while no patients treated with certolizumab pegol reported it.

Regulatory affairs

Certolizumab pegol is commercially available in the USA and is approved by the US FDA for the treatment of adult patients with moderately to severely active RA and for reducing the signs and symptoms of moderately to severely active Crohn's disease in adult patients who have had an inadequate response to conventional therapy [21]. It is also approved in Switzerland for the treatment of patients with Crohn's disease.

Conclusion

Certolizumab pegol is the only PEGylated anti-TNF approved for the treatment of RA. Clinical studies with certolizumab pegol have shown that the drug provides a rapid improvement in the signs and symptoms of RA and physical function, both in combination with MTX and as monotherapy. Results from the RAPID 1 trial showed that these responses were durable and were maintained over at least 1 year. Certolizumab pegol inhibited the progression of structural damage as early as week 16 in ACR20 nonresponders. Furthermore, certolizumab pegol significantly improved multiple aspects of patients' HRQoL, including physical function, pain, fatigue, and productivity both at work and home. The clinical trials presented here also demonstrate that certolizumab pegol is well-tolerated with low incidences of treatment discontinuations due to AEs and injection-site pain or reactions when administered in combination with MTX for up to 1 year or as monotherapy for 6 months. These results are promising, and longer-term experience, especially related to safety analyses of the open-label extension trials patient registries, will provide additional information on the real-life safety profile of certolizumab pegol.

In conclusion, certolizumab pegol has demonstrated consistent, rapid and sustained clinical efficacy in the treatment of RA either in combination with MTX or as monotherapy across clinical and patient-reported outcome measures, and is an effective, well-tolerated option for the treatment of RA.

Future perspective

The introduction of the TNF inhibitors represented a major advance in the treatment of RA, allowing inhibition of disease progression, and even remission, to be realistic goals of therapy. However, some patients do not benefit from, or are unable to tolerate, the agents that are currently available, or they may lose their initial response or tolerability to one or more of the agents. Therefore, the addition of new agents that extend the treatment armamentarium for patients with RA is welcome. As a PEGylated, Fc-free molecule, certolizumab pegol represents a new class of anti-TNF agents, and like infliximab and adalimumab, it has proven efficacy in Crohn's disease, for which it is already approved in the USA. However, unlike infliximab and adalimumab, certolizumab pegol lacks an Fc region, so it may avoid potential Fc-mediated effects such as CDC or ADCC, which has been observed *in vitro* [24]. In addition, the PEGylation of certolizumab pegol may minimize AEs, such as injection-site pain/reaction, may aid in maintaining effective plasma concentrations, and may enhance its penetration and retention in inflamed tissues compared with noninflamed tissues, as has been observed in an animal model [26]. Elevated drug concentrations at the site of disease may be of particular importance for the effective treatment of RA and may underlie both the rapidity of response and the extent of response observed with certolizumab pegol treatment.

The traditional TNF inhibitors all have similar efficacy in relieving the signs and symptoms of RA, and in inhibiting the progression of radiographic joint damage. What is likely to become important in clinical trials of novel agents is more attention to the speed of response. Clinical trials have traditionally assessed efficacy at 3, 6 or 12 months. However, certolizumab pegol has been shown to improve RA signs and symptoms as early as week 1 of treatment and inhibits the progression of structural joint damage as early as week 16 [30–32]. The inclusion of HRQoL outcomes in clinical trials, which are increasingly important from the patient perspective, will also become more common. These outcomes include physical disability, pain, fatigue, and home and work productivity.

Cost and reimbursement of the biologic therapies will remain an issue. However, RA remains a serious chronic condition that leads to significant morbidity and even accelerated mortality in patients. The joint damage and functional disability associated with the disease have negative economic consequences not only for the patients, but also for their families and employers, and thus wider society [36]. Although the overall cost of biologic therapies is higher than traditional DMARDs, they result in more quality-adjusted life-years [37] and their economic impact beyond immediate healthcare costs should be taken into account more frequently in the future.

In conclusion, as the field of biologic therapy for RA develops, new therapies are likely to become available that may have a more rapid onset of action and can significantly improve all aspects of patients' quality of life, allowing them to return to their former levels of productivity at work and home.

Financial & competing interests disclosure

Dr Mease has received consulting fees from UCB. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Editorial support was provided by L Wychowski, PhD, and K Munro, PhD, of PAREXEL and was funded by UCB, Inc. No other writing assistance was utilized in the production of this manuscript.

Executive summary

Overview of the market

- TNF inhibitors have revolutionized the management of rheumatoid arthritis (RA).
- Not all patients with RA achieve or maintain a response to one or more of the currently available TNF inhibitors.
- Patients with RA may also be unable to tolerate, or lose tolerance to, available treatments.
- Therefore, there is a need for more treatments for RA.

Introduction to certolizumab pegol

- Certolizumab pegol is the only PEGylated anti-TNF approved for the treatment of RA.
- Certolizumab pegol preferentially concentrates in inflamed tissues compared with normal tissues in animal models, and has a plasma half-life of approximately 2 weeks.
- Poly (ethylene glycol) (PEG) excretion occurs primarily by the renal route after cleavage of the Fab´ fragment from the PEG.

Clinical efficacy

- Certolizumab pegol, in combination with methotrexate (MTX) or as monotherapy, provides significant improvements in the signs and symptoms of disease with benefits in all ACR core components seen as early as week 1 compared with placebo. The RAPID 1 trial showed that the benefits of certolizumab pegol in combination with MTX were sustained up to at least 1 year.
- Significant inhibition of the progression of structural joint damage was seen with certolizumab pegol as early as week 16 of treatment.
- Significant improvements in physical function and rapid reductions in pain and fatigue were also reported by patients receiving certolizumab pegol, with a rapid onset of action that was sustained.

Safety & tolerability

- Certolizumab pegol, in combination with MTX or as monotherapy, had an acceptable safety profile.
- Rates of treatment-emergent adverse events leading to discontinuation and incidence of injection-site pain were low.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Stakeholder Insight: Rheumatoid arthritis, biologics battle up the treatment algorithm. *Data Monitor* 1–181, 7 September (2006).

2 Woolf AD, Pfleger B: Burden of major musculoskeletal conditions. *Bull. World Health Organ.* 81(9), 646–656 (2003).

3 Helmick CG, Felson DT, Lawrence RC *et al.*: Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. *Arthritis Rhuem.* 58, 15–25 (2008).

4 Feldmann M, Brennan FM, Maini RN: Role of cytokines in rheumatoid arthritis. *Annu. Rev. Immunol.* 14(1), 397–440 (1996).

5 Maini RN, Elliott MJ, Brennan FM *et al.*: Monoclonal anti-TNF α antibody as a probe of pathogenesis and therapy of rheumatoid disease. *Immunol. Rev.* 144, 195–223 (1995).

6 Redlich K, Schett G, Steiner G, Hayer S, Wagner EF, Smolen JS: Rheumatoid arthritis therapy after tumor necrosis factor and interleukin-1 blockade. *Arthritis Rheum.* 48(12), 3308–3319 (2003).

7 Furst DE, Breedveld FC, Kalden JR *et al.*: Updated consensus statement on biological agents, specifically tumour necrosis factor α (TNF α) blocking agents and interleukin-1 receptor antagonist (IL-1RA), for the treatment of rheumatic diseases. *Ann. Rheum. Dis.* 64(Suppl. 4), iv2–iv14 (2005).

8 Maini R, St Clair EW, Breedveld F *et al.*: Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 354(9194), 1932–1939 (1999).

▪ **Phase III trial of infliximab plus methotrexate (MTX) in patients with active rheumatoid arthritis (RA) who had received MTX for at least 3 months.**

9 Weinblatt ME, Kremer JM, Bankhurst AD *et al.*: A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N. Engl. J. Med.* 340(4), 253–259 (1999).

10 Weinblatt ME, Keystone EC, Furst DE *et al.*: Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum.* 48(1), 35–45 (2003).

▪ **Randomized, placebo-controlled study investigating the safety and efficacy of adalimumab plus MTX in patients with active RA despite MTX treatment.**

11 Saag KG, Teng GG, Patkar NM *et al.*: American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 59(6), 762–784 (2008).

12 Combe B, Landewé R, Lukas C *et al.*: EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann. Rheum. Dis.* 66, 34–45 (2007).

13 van Vollenhoven R, Harju A, Brannemark S *et al.*: Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor α blockers can make sense. *Ann. Rheum. Dis.* 62, 1195–1198 (2003).

14 Hyrich KL, Lunt M, Watson KD *et al.*: Outcomes after switching from one anti-tumor necrosis factor α agent to a second anti-tumor necrosis factor α agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum.* 56, 13–20 (2007).

15 Alonso-Ruiz A, Pijoan JI, Ansuategui E, Urkaregi A, Calabozo M, Quintana A: Tumor necrosis factor α drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. *BMC Musculoskelet. Disord.* 9, 52 (2008).

16 Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP: Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol. Ther.* 117(2), 244–279 (2008).

17 Moreland LW, Schiff MH, Baumgartner SW *et al.*: Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. *Ann. Intern. Med.* 130(6), 478–486 (1999).

▪ **Randomized study investigating the efficacy of etanercept in patients with active RA who had an inadequate response to DMARDs.**

18 Maini RN, Breedveld FC, Kalden JR *et al.*: Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum.* 50(4), 1051–1065 (2004).

19 Genovese MC, Bathon JM, Martin RW *et al.*: Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum.* 46(6), 1443–1450 (2002).

20 Keystone EC, Kavanaugh AF, Sharp JT *et al.*: Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum.* 50(5), 1400–1411 (2004).

21 Cimzia® (certolizumab pegol): Prescribing Information. UCB, Inc. Smyrna, GA, USA (2008).

22 Kay J, Matteson EL, Dasgupta B *et al.*: Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum.* 58(4), 964–975 (2008).

23 Emery P, Keystone E, Tony HP *et al.*: IL-6 Receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-TNF biologics: results from a 24-week multicentre Randomised Placebo Controlled Trial. *Ann. Rheum. Dis.* 67, 1516–1523 (2008).

▪ **Randomized, placebo-controlled trial investigating the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy.**

24 Nesbitt A, Fossati G, Bergin M *et al.*: Mechanism of action of certolizumab pegol (CDP870): *in vitro* comparison with other anti-tumor necrosis factor α agents. *Inflamm. Bowel Dis.* 13(11), 1323–1332 (2007).

25 Gramlick G, Fossati G, Nesbitt A *et al.*: Neutralization of soluble and membrane tumor necrosis factor-α by infliximab, adalimumab, or certolizumab pegol using P55 or P75 TNF-α receptor-specific bioassays. *Gastroenterology* 130(Suppl. 2), A697 (2006).

26 Nesbitt A, Fossati G, Brown D, Henry A, Palframan R, Stephens S: Effect of structure of conventional anti-TNFs and certolizumab pegol on mode of action in rheumatoid arthritis. *Ann. Rheum. Dis.* 66, 296 (2007).

27 Parton T, King L, van Asperen J, Heywood S, Nesbitt A: Investigation of the distribution and elimination of the PEG component of certolizumab pegol in rats. *J. Crohn's Colitis Suppl.* 2, 26 (2008).

28 Yamaoka T, Tabata Y, Ikada Y: Distribution and tissue uptake of poly(ethylene glycol) with different molecular weights after intravenous administration to mice. *J. Pharm. Sci.* 83, 601–606 (1994).

29 Choy EHS, Hazleman B, Smith M *et al.*: Efficacy of a novel PEGylated humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: a phase II double-blinded, randomised, dose-escalating trial. *Rheumatology.* 41, 1133–1137 (2002).

30 Keystone E, van der Heijde D, Mason D *et al.*: Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis. *Arthritis Rheum.* 58, 3319–3329 (2008).

▪▪ **A 52-week, Phase III study demonstrating safety and efficacy of certolizumab pegol plus MTX in RA.**

31 Smolen J, Landewé RB, Mease P *et al.*: Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: The RAPID 2 Study. *Ann. Rheum. Dis.* 68(6), 797–804 (2009).

▪▪ **A 24-week, Phase III study demonstrating safety and efficacy of certolizumab pegol plus MTX in RA.**

32 Fleischmann R, Vencovsky J, van Vollenhoven RF *et al.*: Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST 4WARD study. *Ann. Rheum. Dis.* 68(6), 805–811 (2009).

▪▪ **Randomized, placebo-controlled study demonstrating safety and efficacy of certolizumab pegol monotherapy in RA.**

33 Osterhaus J, Purcaru O, Richard L: Discriminant validity, responsiveness and reliability of the rheumatoid arthritis-specific work productivity survey (WPS-RA). *Arthritis Res. Ther.* 11(3), R73 (2009).

34 Emery P, Smolen J, Kavanaugh A, Richard L, Purcaru O: Combination therapy with certolizumab pegol plus methotrexate improves household productivity and daily activities in patients with active rheumatoid arthritis. *Arthritis Rheum*. 58(Suppl.), 977 (2008).

35 Smolen J, Emery P, Kavanaugh A, Richard L, Purcaru O: Certolizumab pegol with methotrexate improves performance at work in patients with active rheumatoid arthritis. *Arthritis Rheum*. 58(Suppl.), 978 (2008).

36 Mader R, Keystone E: Optimizing treatment with biologics. *J. Rheumatol.* 80(Suppl.), 16–24 (2007).

37 Kavanaugh A: Economic consequences of established rheumatoid arthritis and its treatment. *Best Pract. Res. Clin. Rheumatol.* 21(5), 929–942 (2007).