

Two Dosing Regimens of Certolizumab Pegol in Patients With Active Rheumatoid Arthritis

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Objective. To investigate clinical efficacy and safety of 2 certolizumab pegol (CZP) maintenance dosing regimens plus methotrexate (MTX) in active rheumatoid arthritis (RA) patients achieving the American College of Rheumatology 20% improvement criteria (ACR20) after the CZP 200 mg every 2 weeks open-label run-in period.

Methods. DOSEFLEX (dosing flexibility) was a double-blind, placebo-controlled randomized study with an open-label run-in phase. During the run-in phase, all patients received CZP 400 mg (weeks 0, 2, and 4) and 200 mg every 2 weeks to week 16. Week 16 ACR20 responders were randomized 1:1:1 at week 18 to CZP 200 mg every 2 weeks, 400 mg every 4 weeks, or placebo.

Results. A total of 209 (of 333) patients were randomized at week 18 (CZP: 200 mg, n = 70; 400 mg, n = 70; placebo, n = 69). Groups had similar baseline characteristics (week 0). Week 34 ACR20 response rates were comparable between the CZP 200 mg every 2 weeks and the 400 mg every 4 weeks groups (67.1% versus 65.2%), which was significantly higher than placebo (44.9%; $P = 0.009$ and $P = 0.017$). ACR50/70 and remission criteria were met more frequently in CZP groups than placebo at week 34, with similar responses between anti-tumor necrosis factor-experienced and naive patients. Improvements from baseline Disease Activity Score in 28 joints using the erythrocyte sedimentation rate and Health Assessment Questionnaire disability index scores were maintained in CZP groups from week 16 to 34 while worsening on placebo. Adverse event (AE) rates in the double-blind phase were 62.9% versus 60.9% versus 62.3%; serious AE rates were 7.1% versus 2.9% versus 0.0% (CZP 200 mg, 400 mg, and placebo groups).

Conclusion. In active RA patients with an incomplete MTX response, CZP 200 mg every 2 weeks and 400 mg every 4 weeks were comparable and better than placebo for maintaining clinical response to week 4 following a 16-week, open-label run-in phase.

INTRODUCTION

Anti-tumor necrosis factor (anti-TNF) agents represent a major improvement in rheumatoid arthritis (RA) treatment (1–3). Although efficacy and safety remain the primary

factors in selecting treatments, convenience of administration is also an important consideration. Patient surveys report that subcutaneous therapies are the preferred choice as they can be administered at home. Furthermore, re-

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Significance & Innovations

- The study design used here to investigate the efficacy of maintenance dose regimens has not been specifically tested previously in adult rheumatoid arthritis patients. It examines maintenance of response both in anti-tumor necrosis factor (anti-TNF)-naïve patients and in anti-TNF secondary incomplete responders after an open label run-in phase. It also examines dose differences in those circumstances and compares results to placebo on methotrexate (MTX) background. The placebo group allows some understanding of duration of response after the initial open-label period. A similar design could be used to answer questions on dosing flexibility and duration of response on withdrawal for other drugs.
- This study showed that certolizumab pegol (CZP) both 200 mg every 2 weeks and 400 mg every 4 weeks dosing regimens are effective in maintaining a clinical and functional response in combination with MTX in patients with an incomplete response to MTX alone, once an initial response has been achieved.
- Specifically, this study also demonstrated that both maintenance doses of CZP are efficacious in patients who were anti-TNF naïve and those who initially responded to previous anti-TNF treatment but who later discontinued due to loss of efficacy or other reasons. This result may allow patients to have more flexibility in maintenance dosing treatment.

search has shown a preference for therapies that can be administered as infrequently as possible (4,5).

Certolizumab pegol (CZP) is a PEGylated, Fc-free anti-TNF agent approved in Europe and the US for the treatment of adult patients with moderate to severe active RA (6). The current recommended dose for CZP therapy is a loading dose of 400 mg at weeks 0, 2, and 4, followed by a maintenance dose of 200 mg CZP every 2 weeks (7,8). The maintenance dosing regimen of CZP 400 mg every 4 weeks is approved in the US and Europe, providing dosing flexibility and the convenience of less frequent dosing for some patients. Clinical trials have compared the safety and efficacy of CZP dosing regimens of 200 mg every 2 weeks and 400 mg every 2 weeks versus placebo (7,9), and CZP 400 mg every 4 weeks has also demonstrated efficacy, both in combination with methotrexate (MTX) (10) and as monotherapy (11). This is the first study to date to compare the maintenance therapy regimens.

Limited data from clinical trials exist on the efficacy of second and subsequent biologic therapy in patients who require a switch from their initial anti-TNF agent (12). In this study, the impact on treatment by prior anti-TNF use is also considered.

PATIENTS AND METHODS

Patients. Eligible patients were age ≥ 18 years, with a diagnosis of adult-onset RA (6 months–15 years); all had moderate to severe active RA insufficiently controlled by MTX. Patients must have had active disease, defined by ≥ 6 tender joints, ≥ 4 swollen joints (of 28 joints), ≥ 10 mg/dl C-reactive protein level and/or 28 mm/hour erythrocyte sedimentation rate (ESR), and be rheumatoid factor or anti-cyclic citrullinated peptide antibody positive. All had ≥ 3 months MTX treatment (10–25 mg/week) with a stable dose for ≥ 2 months prior to the baseline visit.

Patients who failed to respond to previous anti-TNF treatment were excluded. Anti-TNF responders who later discontinued that drug due to loss of efficacy or other reasons were eligible, provided that previous biologic therapy was stopped ≥ 3 months before baseline, except for etanercept or anakinra (1 month). Concomitant treatment was allowed with analgesics, nonsteroidal antiinflammatory drugs/cyclooxygenase 2 inhibitors and corticosteroids (prednisone or equivalent, ≤ 10 mg/day). Corticosteroid doses could be reduced according to local guidelines; dose increases were not permitted. Exclusion criteria included diagnosis of any other inflammatory arthritis, secondary noninflammatory arthritis, history of chronic infections, serious infections, lymphoproliferative disorder, malignancy or demyelinating disease, history of or currently active tuberculosis (TB), a positive chest radiograph for TB or a positive purified protein derivative (PPD) skin test (≥ 5 mm) or close contact with individuals with active TB. Patients positive for PPD could be included if active TB was ruled out and they were adequately treated for latent TB (e.g., isonicotinic acid hydrazide therapy for 9 months [with vitamin B6]), with treatment initiated ≥ 1 month prior to study drug administration. Classical exclusion criteria for anti-TNF therapy were also applied.

Study design. This was a phase IIIb multicenter study with an open-label run-in period, followed by a double-blind, placebo-controlled randomized period (Figure 1A). The study protocol was approved by an independent ethics committee or institutional review board at each center across the US, France, and Canada and carried out in accordance with the Declaration of Helsinki. During the open-label run-in phase, all patients received a CZP loading dose followed by 200 mg CZP every 2 weeks up to week 16 as add on to background MTX therapy. Patients were classified according to the American College of Rheumatology 20% improvement criteria (ACR20) (13) response at week 16; at week 18 ACR20 nonresponders were withdrawn and responders were randomized 1:1:1 to either 200 mg CZP every 2 weeks, 400 mg CZP every 4 weeks, or placebo during the double-blind phase, up to week 34. Unblinded staff prepared and administered study medication but had no other involvement in the study. US or Canadian patients who experienced disease flares between week 18 and 34 (defined as patients who had a swollen joint count and tender joint count equal to or worse than baseline) or who completed week 34 could enroll in an open-label safety study (NCT00753454). At the

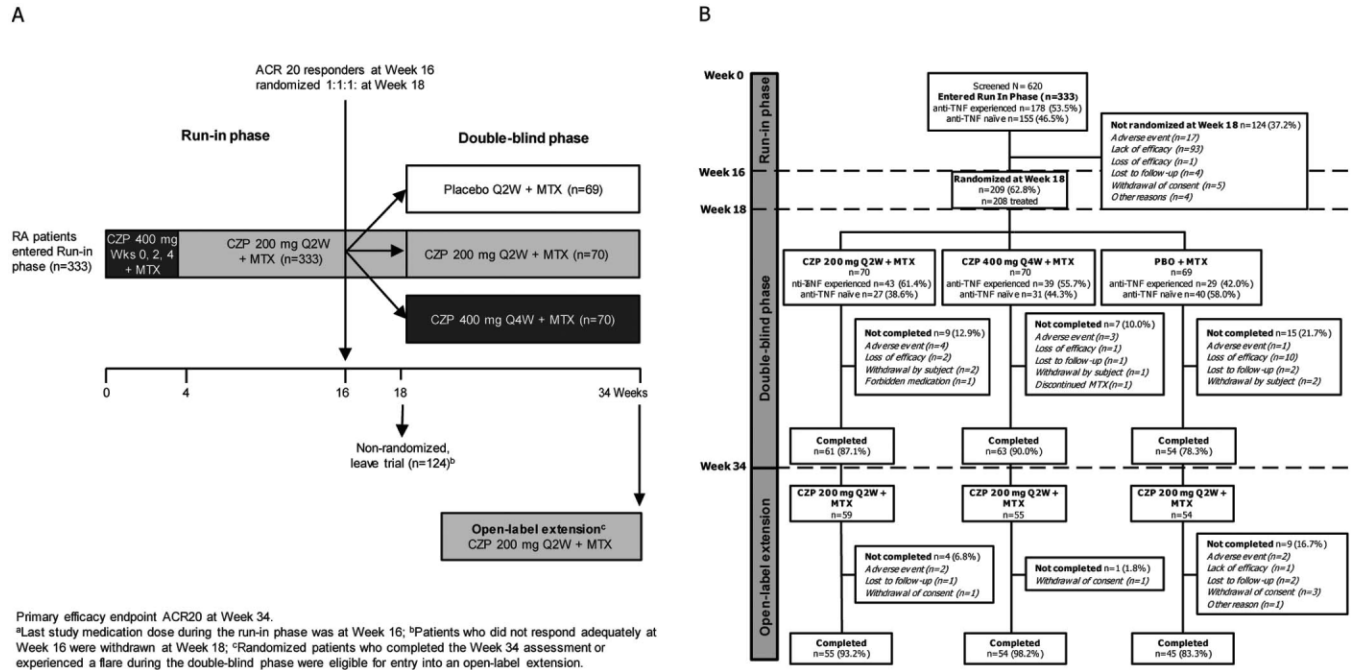


Figure 1. DOSEFLEX (dosing flexibility) study design (A) and patient disposition in the DOSEFLEX study (B). ACR = American College of Rheumatology; Q2W = every 2 weeks; MTX = methotrexate; RA = rheumatoid arthritis; CZP = certolizumab pegol; Q4W = every 4 weeks; anti-TNF = anti-tumor necrosis factor; PBO = placebo.

start of the open-label safety study, to maintain the blinding, all patients received 400 mg CZP at weeks 0, 2, and 4, followed by 200 mg CZP every 2 weeks thereafter.

Efficacy and safety evaluations. The primary objective was clinical efficacy by ACR20 response criteria at the end of the double-blind phase (week 34). ACR20 responders at week 18 were assessed for maintenance of clinical response over an additional 16 weeks (week 34). Secondary efficacy end points were: 1) ACR20, ACR50, and ACR70 response rates at week 4, 8, 12, 16, 18, and 20, then every 4 weeks until week 34; 2) the Clinical Disease Activity Index (CDAI), the Simplified Disease Activity Index (SDAI), the Disease Activity Score in 28 joints using the ESR (DAS28-ESR) remission (defined as ≤ 2.8 , ≤ 3.3 , and < 2.6 , respectively), and change from baseline (week 0) in CDAI, SDAI, DAS28-ESR, and Health Assessment Questionnaire (HAQ) disability index (DI) at week 16 and 34; and 3) patient’s assessment of arthritis pain and patient’s global assessment of disease activity (both assessed on a 100-mm visual analog scale), fatigue (measured on a 10-point fatigue assessment scale), and Short Form 36 (SF-36) domains and physical component (PCS) and mental component (MCS) summaries at week 34. Safety assessments, performed over the entire study period, included measurement of vital signs and laboratory parameters, recording of adverse events (AEs), serious AEs (SAEs), injection-site reactions, serious infections, and monitoring for signs or symptoms of TB.

Statistical analysis. Assuming a 50% response rate in the placebo group and 80% in the CZP-treated arms, 67 patients were needed per treatment arm to achieve $\geq 90\%$

power to show a statistically significant difference in ACR20 response rate at week 34, using a 2-sided Fisher’s exact test with a significance level of 0.025. The sample size was based upon the Bonferroni method, which conservatively sets the alpha level at 2.5% to account for 2 primary comparisons.

Baseline demographics and disease characteristics were summarized for the enrolled patients, defined as those who entered the run-in phase, as well as those entering the double-blind phase. Efficacy analyses on week 16 outcomes were conducted on patients who took ≥ 1 dose of study medication during the run-in phase. Efficacy analyses on the randomized population were carried out on the full analysis set, defined as the treated, randomized patients during the double-blind phase.

Safety analyses were performed on the enrolled set (all patients who entered the run-in phase) and on the safety set (all patients who were treated in the double-blind phase) for the overall study period (run-in phase, double-blind phase, and open-label extension).

Analyses by prior anti-TNF therapy at baseline up to week 34 were post hoc, and statistical comparisons were not undertaken due to the exploratory nature of the analyses.

Missing data were imputed using nonresponder imputation for ACR responses and CDAI, SDAI, and DAS28-ESR remission rates, and last observation carried forward for other outcomes. ACR20, ACR50, and ACR70 responder rates and DAS28, CDAI, and SDAI remission rates were analyzed using a logistic regression model, including terms for treatment. Each comparison of active versus placebo arm was compared at the 2.5% level, and odds ratios (ORs) were estimated and presented with 97.5% confi-

Table 1. Patient baseline demographics and disease characteristics*

	Run-in phase†			Double-blind phase‡				
	Overall (n = 333)	Overall prior anti-TNF (n = 178)	Overall prior anti-TNF naive (n = 155)	Randomized set (n = 209)	Nonrandomized set (n = 124)	Placebo + MTX (n = 69)	CZP 200 mg + MTX (n = 70)	CZP 400 mg + MTX (n = 70)
Age, years	54.2 ± 12.8	54.2 ± 12.7	54.2 ± 13.5	53.4 ± 12.7	55.5 ± 12.8	51.5 ± 13.2	55.6 ± 10.7	53.1 ± 13.8
Female, %	76.0	77.0	74.8	78.0	72.6	81.2	70.0	82.9
Disease duration, years	6.4 ± 4.5	7.6 ± 4.4	5.0 ± 4.3	6.3 ± 4.5	6.7 ± 4.6	6.5 ± 4.6	5.9 ± 4.2	6.4 ± 4.7
Concomitant MTX dosage, mg/week	17.6 ± 4.7	17.2 ± 4.7	17.9 ± 4.7	17.4 ± 4.8	17.8 ± 4.6	16.6 ± 4.8	17.5 ± 4.3	18.0 ± 5.2
Corticosteroid use	148 (44.4)	72 (40.4)	76 (49.0)	90 (43.1)	58 (46.8)	32 (46.4)	31 (44.3)	27 (38.6)
Prior anti-TNF use	178 (53.5)	178 (100.0)	0	111 (53.1)	67 (54.0)	29 (42.0)	43 (61.4)	39 (55.7)
RF positive, ≥14 IU/ml	315 (94.6)	167 (93.8)	148 (95.5)	197 (94.3)	118 (95.2)	67 (97.1)	65 (92.9)	65 (92.9)
Anti-CCP antibody positive ≥60 units§	273 (82.0)	145 (83.8)	128 (83.7)	170 (81.3)	103 (83.1)	56 (81.2)	59 (84.3)	55 (78.6)
TJC¶	15.0 ± 6.7	14.7 ± 6.6	15.3 ± 6.7	14.6 ± 6.4	15.6 ± 7.0	16.0 ± 6.4	14.7 ± 6.6	13.1 ± 6.0
SJC¶	11.8 ± 5.7	11.4 ± 5.6	12.4 ± 5.8	11.6 ± 5.3	12.3 ± 6.2	12.0 ± 5.6	10.9 ± 5.2	11.8 ± 5.2
CRP (mg/dl), geometric mean (CV)	12.3 ± 121.2	12.3 ± 128.7	12.2 ± 128.7	12.6 ± 100.2	11.7 ± 141.2	13.1 ± 108.8	13.1 ± 86.7	11.7 ± 101.3
ESR (mm/hour), geometric mean (CV)	38.5 ± 52.9	36.2 ± 58.2	41.3 ± 61.4	36.2 ± 52.8	42.6 ± 51.0	35.5 ± 53.4	36.7 ± 44.5	36.5 ± 59.1
DAS28-ESR	6.4 ± 1.0	6.4 ± 0.9	6.5 ± 1.0	6.3 ± 0.9	6.6 ± 1.0	6.4 ± 1.0	6.4 ± 0.8	6.2 ± 1.0
HAQ DI	1.52 ± 0.64	1.6 ± 0.6	1.5 ± 0.7	1.47 ± 0.61	1.61 ± 0.69	1.42 ± 0.55	1.57 ± 0.65	1.41 ± 0.61
CDAI	38.4 ± 13.4	37.9 ± 13.3	38.9 ± 13.6	37.6 ± 12.9	39.6 ± 14.2	39.8 ± 13.8	36.8 ± 12.1	36.4 ± 12.8
SDAI	40.4 ± 14.2	39.8 ± 13.8	41.1 ± 14.6	39.6 ± 13.5	41.8 ± 15.2	41.8 ± 14.5	38.6 ± 12.4	38.4 ± 13.5

* Values are the mean ± SD or number of patients (percentage) unless indicated otherwise. Anti-TNF = anti-tumor necrosis factor; MTX = methotrexate; CZP = certolizumab pegol; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide; TJC = tender joint count; SJC = swollen joint count; CRP = C-reactive protein; CV = coefficient of variation; ESR = erythrocyte sedimentation rate; DAS28-ESR = Disease Activity Score in 28 joints using the ESR; HAQ DI = Health Assessment Questionnaire disability index; CDAI = Clinical Disease Activity Index; SDAI = Simplified Disease Activity Index.

† Modified enrolled set: all patients CZP 200 mg every 2 weeks + MTX.

‡ Randomized set: placebo + MTX, CZP 200 mg every 2 weeks + MTX, or CZP 400 mg every 4 weeks + MTX.

§ Greater or equal to 60 units.

¶ Twenty-eight-joint count.

dence intervals (97.5% CIs). Changes from baseline in DAS28, CDAI, SDAI, HAQ DI, SF-36 domains, PCS and MCS, pain, and fatigue were analyzed using analysis of covariance models, including treatment as a factor.

RESULTS

Patients. A total of 333 patients entered the run-in phase, of which 209 patients (62.8%) received CZP 200 mg every 2 weeks up to week 16 and then were randomized at week 18 to placebo plus MTX (n = 69), CZP 200 mg every 2 weeks plus MTX (n = 70), and CZP 400 mg every 4 weeks plus MTX (n = 70) (Figure 1B). One patient, randomized to the CZP 400 mg every 4 weeks group, was not treated in the double-blind phase. Of the 124 patients who withdrew from the study during the run-in phase, 94 either did not achieve ACR20 response or lost their initial response, 17 experienced AEs leading to drop out, 5 removed consent, 4 were lost to followup, and 4 dropped out for other reasons (Figure 1B).

In total, 54 placebo patients (78.3%), 61 CZP 200 mg every 2 weeks patients (87.1%), and 63 CZP 400 mg every 4 weeks patients (90.0%) completed the double-blind phase. Overall, baseline characteristics were similar among the 3 double-blind treatment groups (Table 1). However, more patients who were randomized to the CZP treatment arms had prior anti-TNF exposure at baseline compared to placebo patients; patients with prior anti-TNF use at baseline had longer disease duration and lower ESR than those without (Table 1).

Treatment efficacy: week 16 (run-in phase). After open-label administration of CZP 200 mg every 2 weeks, 61.3%, 37.8%, and 16.2% of patients achieved an ACR20, ACR50, and ACR70 response, respectively (Figure 2A). Remission rates for the DAS28-ESR, SDAI, and CDAI at week 16 are shown in Figure 2B, and the change from baseline in disease activity by these measures was -2.3, -24.1, and

-23.3, respectively. The mean change from baseline in the HAQ DI was -0.5.

Treatment efficacy: week 34 (double-blind phase). The ACR20 response at week 34 in the CZP 200 mg every 2 weeks group and the CZP 400 mg every 4 weeks group was significantly greater than in the placebo group ($P = 0.009$ and $P = 0.017$ by logistic regression, respectively) (Figure 3A). Similarly, the ACR50 responses were significantly higher in both the CZP 200 mg every 2 weeks and 400 mg every 4 weeks groups than in the placebo group, with a comparable magnitude of change for both CZP dose regimens. For the ACR70 response, the CZP 400 mg every 4 weeks group was significantly better than the placebo group (Figure 3A), while the CZP 200 mg every 2 weeks group was numerically greater but did not differentiate from placebo ($P = 0.005$ and $P = 0.052$ by logistic regression, respectively).

Improvements in disease activity and physical function at week 34 were greater in patients receiving CZP in the double-blind phase compared to those randomized to switch to placebo (Figure 3B and D). Both disease activity and physical function worsened from week 16 following CZP withdrawal (Figure 3C and D).

For pain and fatigue, least squares mean change from baseline values at week 34 were -34.33 (CZP 200 mg every 2 weeks) and -26.4 (400 mg every 4 weeks), and -3.03 (CZP 200 mg every 2 weeks) and -2.39 (400 mg every 4 weeks), respectively, which was significantly greater than the placebo group (pain: -17.47; $P < 0.001$ for both groups; fatigue: -1.33; $P < 0.001$ and $P = 0.005$, respectively).

The proportion of patients who met the minimum clinically important difference (MCID) for fatigue (1 unit) was numerically larger in both the CZP 200 mg every 2 weeks group (65.7%) and the CZP 400 mg every 4 weeks (58.0%) group than in the placebo group (46.4%). The same was true for pain, where 62.9% of the CZP 200 mg

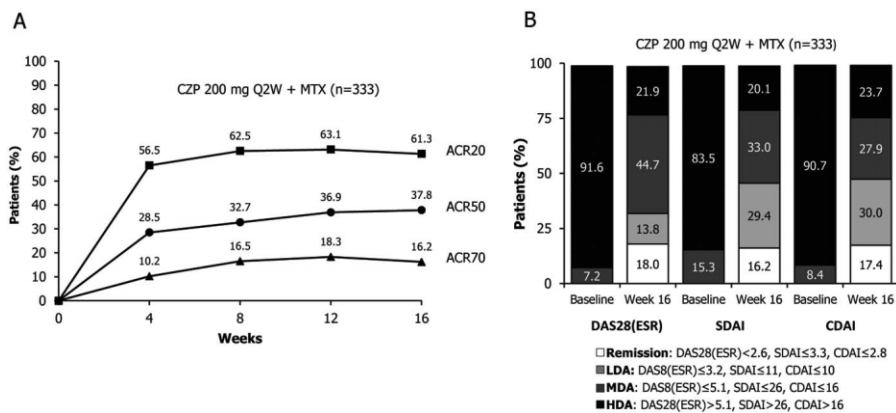


Figure 2. Outcomes at the end of the run-in phase at week 16, where all patients were treated with certolizumab pegol (CZP) 200 mg every 2 weeks (Q2W). **A**, Kinetics of the American College of Rheumatology 20% improvement (ACR20)/ACR50/ACR70 responses (modified enrolled set, nonresponder imputation) and **B**, the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28[ESR]), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) disease activity states (modified enrolled set, last observation carried forward). MTX = methotrexate; LDA = low disease activity; MDA = moderate disease activity; HAD = high disease activity.

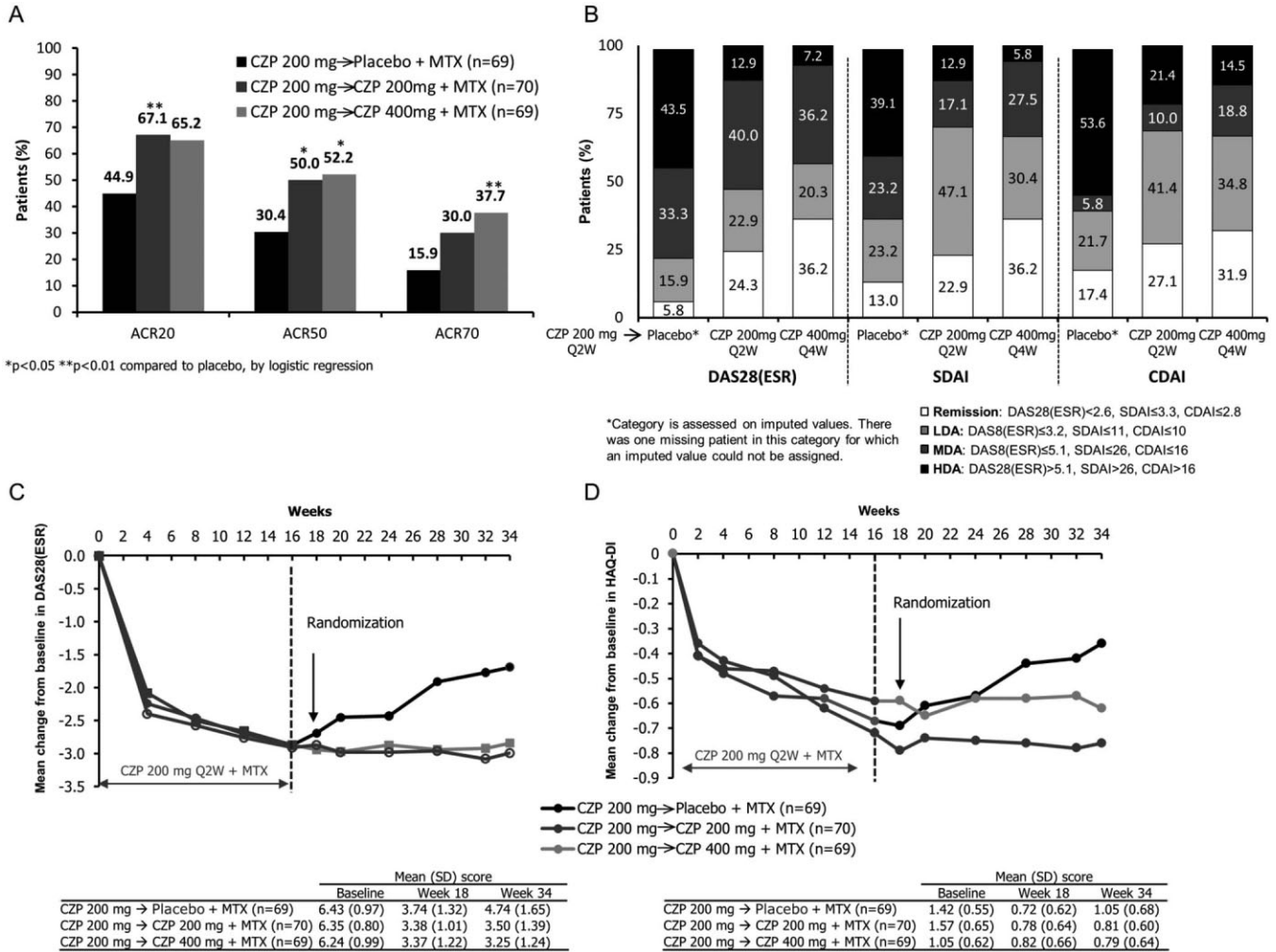


Figure 3. Outcomes at week 34, the end of the double-blind phase. **A**, American College of Rheumatology 20% improvement (ACR20)/ACR50/ACR70 responses at week 34 (nonresponder imputation); **B**, Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28[ESR]), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) disease activity states at week 34 (last observation carried forward [LOCF]); **C**, mean change from baseline in DAS28(ESR) to week 34 (LOCF); **D**, mean change from baseline in Health Assessment Questionnaire disability index (HAQ-DI) to week 34 (LOCF). CZP = certolizumab pegol; MTX = methotrexate; Q2W = every 2 weeks; Q4W = every 4 weeks; LDA = low disease activity; MDA = moderate disease activity; HDA = high disease activity.

every 2 weeks patients and 58.0% of the CZP 400 mg every 4 weeks patients achieved the MCID (10 mm) compared to 49.3% of placebo patients.

Treatment efficacy by prior anti-TNF. At week 16, following treatment with CZP 200 mg every 2 weeks, the ACR response was similar for patients with (n = 178) versus without (n = 155) prior anti-TNF exposure: ACR20: 60.7% versus 61.9%; ACR50: 34.8% versus 41.3%; and ACR70 14.0% versus 18.7%, respectively. Within the randomized set, ACR20, ACR50, and ACR70 responses at week 34 were comparable in both CZP treatment arms regardless of prior anti-TNF experience (Figure 4A). Similar DAS28-ESR, SDAI, and CDAI remission rates were observed in both CZP-treated groups at week 34 (Figure 4B). The proportion of patients with low disease activity was comparable. For patients in the placebo group, response and remission rates at week 34 were numerically lower in prior anti-TNF patients compared to anti-TNF-naïve patients

(Figure 4A and B), although these rates were not tested statistically.

Overall, the change from baseline in DAS28-ESR to week 34 was similar between patients with and without prior anti-TNF exposure at baseline in the placebo (−1.50 versus −1.82), CZP 200 mg every 2 weeks (−2.76 versus −2.97), and CZP 400 mg every 4 weeks groups (−2.77 versus −3.28). DAS28-ESR scores increased in patients in the placebo group from week 16 onwards, whereas in both CZP groups the response was maintained regardless of prior anti-TNF exposure (data not shown). The change from baseline in the HAQ DI to week 34 was similar between patients with and without prior anti-TNF exposure in the placebo (0.29 versus 0.41), CZP 200 mg (0.80 versus 0.69), and CZP 400 mg (0.49 versus 0.79) groups.

Safety. Safety results are reported for all patients who received CZP in the study, and in the run-in, double-blind,

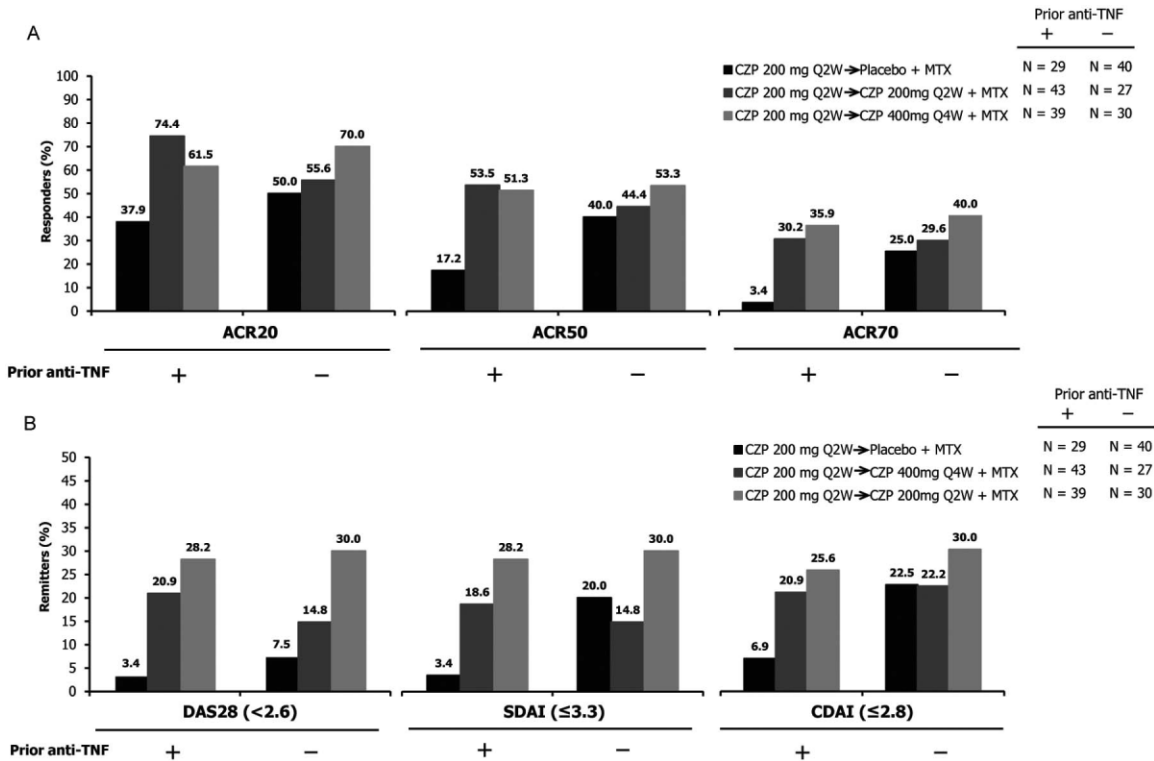


Figure 4. Clinical outcomes at the end of the double-blind phase (week 34), stratified by prior anti-tumor necrosis factor (anti-TNF) exposure. **A**, American College of Rheumatology 20% improvement (ACR20)/ACR50/ACR70 responses at week 34 (nonresponder imputation); **B**, Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28[ESR]), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) disease activity states at week 34 (last observation carried forward). CZP = certolizumab pegol; Q2W = every 2 weeks; MTX = methotrexate; Q4W = every 4 weeks.

and open-label extension phases (Table 2). Taken together, the most common AEs were infections and infestations, (occurring in 54.1% of patients) and the most common of those were upper respiratory tract infections. Injection and infusion site reactions occurred in 11 patients (3.3%) overall. SAEs were reported in 8.7% of patients, with the most frequent being infections and infestations (3.9%), musculoskeletal and connective tissue disorders (1.8%), and cardiac disorders (1.2%). There were no deaths and 1 case each of malignant melanoma and basal cell carcinoma. Standard exclusion criteria for TB in trials of biologic agents were applied, and there were no reported TB cases in any phase.

During the double-blind phase, the rate of AEs for all randomized, treated patients (safety set) was comparable among the 3 treatment groups (Table 2). The most common AEs in the placebo, CZP 200 mg every 2 weeks, and CZP 400 mg every 4 weeks groups were in the systems: infections and infestations, musculoskeletal and connective tissue disorders, gastrointestinal disorders and respiratory, and thoracic and mediastinal disorders. Among these, there were no visual differences, except for the respiratory, thoracic, and mediastinal disorders (e.g., cough) where the placebo group was subject to more AEs. There were no deaths, TB infections, or malignancies reported.

There were no SAEs reported in the placebo group during the double-blind phase as compared to 5 patients

(7.1%) in the CZP 200 mg every 2 weeks group and 2 patients (2.9%) in the CZP 400 mg every 4 weeks group. The most common SAEs were infections and infestations, with 1 case each of oral candidiasis, herpes pharyngitis, pneumonia, and kidney infection in the CZP 200 mg every 2 weeks group. There were no serious infections in the CZP 400 mg every 4 weeks group. There were no instances of injection site pain and only 1 instance of a local injection site rash, reported by an investigator in the CZP 200 mg every 2 weeks group during the double-blind phase.

DISCUSSION

The DOSEFLEX study investigated the efficacy and safety of 2 dosing regimens of CZP (200 mg every 2 weeks and 400 mg every 4 weeks) in maintaining clinical response in active RA patients who had demonstrated an initial response to CZP.

The primary outcome, ACR20 response at week 34, was met by approximately two-thirds of patients in both CZP dosage groups, significantly more than the 45% in the group randomized to placebo following initial CZP treatment. These results were consistent across secondary end points, including the composite disease activity indices and measures of physical function. Interestingly, although DAS28 remission is often considered to be the least strin-

Table 2. Summary of adverse events (AEs) in patients treated in the DOSEFLEX study*

	Double-blind phase†			Overall (run-in, double-blind, and OLE)‡ (n = 333)
	Placebo + MTX (n = 69)	CZP 200 mg + MTX (n = 70)	CZP 400 mg + MTX (n = 69)	
Any AEs§	43 (62.3)/323.6	44 (62.9)/312.1	42 (60.9)/299.9	276 (82.9)/358.2
Infections	24 (34.8)/136.2	20 (28.6)/104.9	25 (36.2)/132.4	180 (54.1)/113.6
Upper respiratory tract infection	10 (14.5)/46.5	5 (7.1)/23.0	8 (11.6)/36.2	68 (20.4)/30.7
Urinary tract infection	7 (10.1)/33.4	5 (7.1)/23.1	6 (8.7)/27.6	41 (12.3)/17.0
Ear infection	0	0	3 (4.3)/13.3	5 (1.5)/1.9
Nasopharyngitis	4 (5.8)/18.4	1 (1.4)/4.4	1 (1.4)/4.4	11 (3.3)/4.3
Sinusitis	0	2 (2.9)/9.0	3 (4.3)/13.1	16 (4.8)/6.3
Musculoskeletal/connective tissue disorders	13 (18.8)/64.2	8 (11.4)/37.6	11 (15.9)/51.4	75 (22.5)/34.6
Arthralgia	2 (2.9)/8.9	1 (1.4)/4.5	5 (7.2)/22.5	17 (5.1)/6.7
Back pain	1 (1.4)/4.4	3 (4.3)/13.5	0	16 (4.8)/6.3
RA aggravation	6 (8.7)/27.7	1 (1.4)/4.4	2 (2.9)/8.9	15 (4.5)/5.9
Pain in extremity	3 (4.3)/13.5	2 (2.9)/8.9	0	10 (3.0)/3.9
Nervous system disorders	1 (1.4)/4.4	5 (7.1)/22.8	4 (5.8)/17.8	43 (12.9)/18.3
Dizziness	1 (1.4)/4.4	3 (4.3)/13.5	0	10 (3.0)/3.9
Headache	0	2 (2.9)/9.0	0	15 (4.5)/5.9
Skin/subcutaneous tissue disorders	5 (7.2)/22.4	5 (7.1)/22.7	5 (7.2)/22.7	54 (16.2)/23.7
Rash	1 (1.4)/4.4	2 (2.9)/8.9	0	15 (4.5)/6.0
Respiratory/thoracic/mediastinal disorders	10 (14.5)/46.9	6 (8.6)/28.0	1 (1.4)/4.4	58 (17.4)/25.1
Cough	3 (4.3)/13.4	0	0	17 (5.1)/6.7
Gastrointestinal disorders	9 (13.0)/41.6	9 (12.9)/43.9	8 (11.6)/37.9	75 (22.5)/33.8
Nausea	1 (1.4)/4.4	3 (4.3)/13.8	0	16 (4.8)/6.3
General disorders/administration site conditions	5 (7.2)/22.8	6 (8.6)/27.8	3 (4.3)/13.3	51 (15.3)/22.0
Pyrexia	1 (1.4)/4.4	4 (5.7)/18.1	0	11 (3.3)/4.3
Serious AEs	0	5 (7.1)/23.1	2 (2.9)/8.8	29 (8.7)/11.5
Serious infections	0	3 (4.3)/13.6	0	13 (3.9)/5.0
Cardiac disorders	0	1 (1.4)/4.5	0	4 (1.2)/1.5
Musculoskeletal/connective tissue disorders	0	2 (2.9)/9.0	1 (1.4)/4.4	6 (1.8)/2.3
Respiratory/thoracic/mediastinal disorders	0	0	0	3 (0.9)/1.1
AE leading to death	0	0	0	0
AE leading to withdrawal¶	8 (11.6)/37.3	12 (17.1)/58.4	6 (8.7)/27.5	85 (25.5)/38.0
AE leading to permanent discontinuation	0	4 (5.7)/18.4	1 (1.4)/4.4	31 (9.3)/12.1

* Values are the number of patients (percentage)/incidence rate per 100 person-years. DOSEFLEX = dosing flexibility; MTX = methotrexate; CZP = certolizumab pegol; OLE = open-label extension; AEs = adverse events; RA = rheumatoid arthritis.
† Safety set (all treated randomized patients, not including the one patient randomized who did not receive any treatment).
‡ Includes all AEs in patients during the run-in phase, all AEs in patients who received CZP in the double-blind phase, and all AEs that started during the OLE.
§ AEs occurring in >3% of patients.
¶ Temporary and permanent discontinuations.

gent of these measures (14), in this study similar numbers of patients achieved DAS28, SDAI, and CDAI remission. Both the maintenance dose of CZP 200 mg every 2 weeks and the increased dosing interval regimen of CZP 400 mg every 4 weeks demonstrated comparable and greater efficacy versus placebo. Provision of such dosing flexibility for CZP-treated RA patients in clinical practice would provide patients and physicians with increased choice and convenience. The utility of such variation in dosing has been shown for both infliximab (2,15,16) and adalimumab (17) in RA, with less frequent dosing schedules resulting in increased rates of compliance and adherence across a range of therapeutic areas (18–20).

Post hoc analyses demonstrated that response to CZP during the run-in phase and the response for the 2 different dosing regimens were similar regardless of prior anti-TNF exposure at baseline. This supports emerging data on the efficacy of CZP in patients with prior anti-TNF exposure from clinical trials (21,22), observational studies

(23,24), and registries (25). These studies have shown robust clinical responses to CZP, irrespective of previous anti-TNF therapy. Studies with other biologic agents have also shown efficacy in RA patients with prior anti-TNF experience (26–29). In such anti-TNF exposed patients, clinical responses tend to decrease in patients who have received more previous anti-TNF therapy (30,31).

The DOSEFLEX study also enabled assessment of the impact of withdrawing therapy in patients who demonstrate an initial ACR20 response to CZP, although this was not a primary objective of the trial. European League Against Rheumatism recommendations suggest withdrawal of biologic disease-modifying antirheumatic drugs (DMARDs) should be considered only in patients with persistent stable remission once glucocorticoids have been tapered (32). The results from the DOSEFLEX study in CZP responders add to the limited evidence base from studies that have assessed withdrawal of biologic agents after prolonged clinical remission (33–36), and provide some evi-

dence that a proportion of patients may be able to have CZP therapy withdrawn while some require continued treatment. At week 34, 44.9% of patients withdrawn from CZP and randomized to the placebo group remained unchanged with respect to ACR20 response and 55.1% worsened, with mean change from baseline in DAS28-ESR score worsening between weeks 18 and 34. Of interest, patients with prior anti-TNF exposure had a greater increase in disease activity compared with those who were anti-TNF naive. Although sample sizes are small and a longer followup period would be needed, this suggests that the prior anti-TNF exposure patients are more refractory and it may therefore be more difficult to withdraw therapy. Further investigation of predictive factors allowing discontinuation of therapy is clearly appropriate. Studies have shown that, in general, it is possible to withdraw therapy in early RA MTX-naive patients (37), but this strategy has been shown to be less successful in patients who have failed to respond to DMARDs with longer disease duration (35,38).

The AE profile of CZP in this study, including the open-label extension, was consistent with previously reported studies (7,9,11,21) and also in line with other anti-TNF therapies; no new safety signals for CZP were identified (37,39).

A limitation of this study is that it was not designed to test the equivalence or inferiority of the 2 CZP maintenance doses. However, by directly comparing the data, for most efficacy parameters maintenance of response is similar regardless of dosing schedule. Further research is required to confirm that there is a similar radiographic response between the 2 maintenance doses. Additional limitations of this study are that analyses of stratification by prior anti-TNF exposure at baseline were post hoc and therefore no statistical tests could be conducted, particularly in view of the small sample size and the limited duration of followup. Further, patients with prior anti-TNF therapy at baseline had stopped their treatment due to a variety of reasons; nevertheless, primary anti-TNF treatment failure patients who did not respond to anti-TNF therapy were excluded, so this small subset could not be examined. Although efficacy data were not analyzed by the reason for therapy discontinuation, data from the REALISTIC study have shown that response rates were similar among CZP patients irrespective of whether they discontinued anti-TNF therapy due to reasons of safety or efficacy (21).

In conclusion, in RA patients on background MTX therapy who achieved an initial clinical response to 16 weeks of CZP treatment, the less frequent dosing regimen of CZP 400 mg every 4 weeks was comparable to the CZP 200 mg every 2 weeks maintenance dose, independent of prior anti-TNF use. This may allow patients to have flexibility in dosing between the 2 schedules, providing more convenient, less frequent dosing for some patients without impacting the clinical efficacy or safety of treatment.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Furst had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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