Table 1. Patient demographics and disease status at baseline (FAS population).

Characteristic	Placebo ($n = 114$)	CZP 200 mg Q2W ($n = 116$)
Patient demographics and characteristics		
Mean age (SD), years	55.4 (9.8)	56.0 (10.2)
Female, n (%)	88 (77.2)	83 (71.6)
Mean body weight (SD), kg	57.3 (10.0)	57.5 (11.7)
Mean BMI (SD), kg/m^2	23.4 (3.5)	22.8 (3.9)
Mean disease duration (SD), years	5.8 (4.3)	5.4 (4.0)
Mean no. of prior DMARDs (SD), including MTX	1.8 (0.9)	1.9 (1.0)
DMARDs at baseline, n (%)	65 (57.0)	62 (53.4)
Actarit	0 (0.0)	1 (0.9)
Mizoribine	4 (3.5)	4 (3.4)
Tacrolimus hydrate	14 (12.3)	20 (17.2)
Auranofin	1 (0.9)	0 (0.0)
Bucillamine	19 (16.7)	18 (15.5)
Sodium aurothiomalate	4 (3.5)	3 (2.6)
Salazosulfapyridine	37 (32.5)	28 (24.1)
Baseline corticosteroid use, n (%)	81 (71.1)	77 (66.4)
Prior anti-TNF use, n (%)	16 (14.0)	8 (6.9)
RF-positive ($\geq$ 14 IU/mL), n (%)	102 (89.5)	99 (85.3)
Median; mean RF level at baseline (SD), IU/mL	102.0; 274.9 (402.2)	80.5; 297.2 (564.0)
Disease activity status		
Mean DAS28(ESR) (SD)	6.3 (1.0)	6.1 (0.9)
Mean (SD) no. of tender joints (0–68)	17.6 (10.3)	16.2 (9.6)
Mean (SD) no. of swollen joints (0–66)	15.5 (8.6)	13.8 (7.5)
Patient's assessment of pain (100 mm VAS), mean (SD)	57.1 (21.1)	56.6 (21.2)
Patient's assessment of global disease activity (100 mm VAS), mean (SD)	55.6 (21.5)	54.1 (20.7)
Physician's assessment of global disease activity (100 mm VAS), mean (SD)	63.0 (16.9)	58.8 (17.5)
Mean HAQ-DI (SD)	1.21 (0.67)	1.05 (0.68)
mTSS		
Median (Q1, Q3)	23.75 (7.50, 62.00)	15.75 (2.00, 54.50)
Mean (SD)	46.13 (54.43)	36.48 (51.33)
Mean duration of morning stiffness (SD), h	3.81 (6.86)	4.66 (7.29)
SF-36 component scores		
Mean SF-36 PCS (SD)	25.21 ± 11.09	27.73 ± 10.76
Mean SF-36 MCS (SD)	43.58 ± 12.21	46.08 ± 13.66
CRP (mg/dL), geometric mean (CV)	1.6 (146.9)	1.7 (139.8)
ESR (mm/h), geometric mean (CV)	51.0 (56.5)	49.0 (50.3)

BMI, body mass index; CRP, C-reactive protein; CZP, certolizumab pegol; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; MCS, mental component summary; mTSS, modified Total Sharp Score; PCS, physical component summary; RF, rheumatoid factor; SD, standard deviation; VAS, visual analog scale.

maintained to Week 24 (CZP: −0.48, placebo: 0.12; $p < 0.0001$) (Figure 2d, Table 2). Pain (VAS) was also significantly improved from Week 1 (CFB at Week 1; CZP: −18.9, placebo: 2.2; Table 2). Statistically significant improvements at Weeks 12 and 24 were observed in total SF-36 physical and mental components scores (Table 2) and all subscale scores (physical functioning, role-physical, role-emotional, bodily pain, general health, vitality, social functioning and mental health) ($p < 0.0001$ at both time points).

Inhibition of structural damage

Treatment with CZP significantly inhibited the progression of structural damage compared to placebo at Week 24; the mean change in mTSS was 0.48 with CZP, compared to 2.45 with placebo ($p < 0.0001$). Significant differences were also reported in erosion and JSN scores at Week 24 (Figure 3a). The cumulative probability of CFB in mTSS clearly demonstrated the superior structural protection of CZP over placebo (Figure 3b). Significantly more patients who received CZP achieved mTSS non-progression compared to placebo (76.3% vs. 45.6%; $p < 0.0001$).

Treatment efficacy of CZP monotherapy and CZP with non-MTX DMARDs (post-hoc analyses)

At Week 12, ACR20 responses were higher in patients treated with CZP monotherapy (i.e. without concomitant DMARDs) or CZP in combination with non-MTX DMARDs compared to the respective placebo groups (CZP vs. placebo: monotherapy, 59.3% vs. 8.2%, OR [95% CI] 16.4 [5.1, 52.1]; concomitant DMARDs: 74.2% vs. 20.0%, OR [95% CI] 11.5 [5.0, 26.4]).

CZP monotherapy led to significant inhibition of radiographic progression at Week 24 (mean CFB in mTSS 0.68, SD 2.13) compared with placebo (mean 3.65, SD 7.31) (Figure 3a). For patients on CZP in combination with ≥ 1 DMARD, disease progression was similarly inhibited compared to placebo with DMARDs (mean CFB in mTSS: CZP with DMARDs, mean 0.24, SD 1.52; placebo with DMARDs, mean 1.61, SD 3.44).

CZP pharmacokinetics and antibodies to CZP

Geometric mean plasma CZP concentration at 1 week after the first induction dose of 400 mg was 41.2 μg/mL. Mean trough

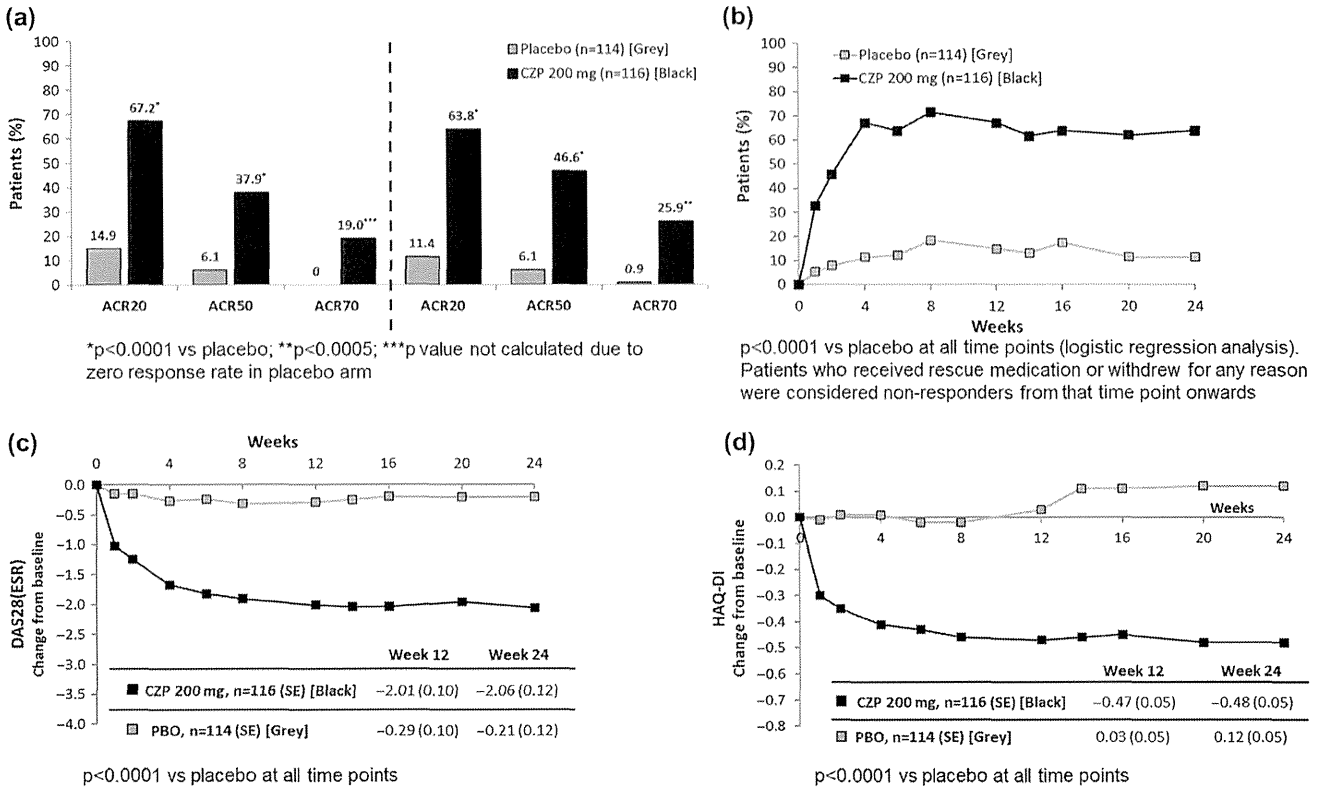


Figure 2. ACR response rates, improvements in DAS28(ESR) and HAQ-DI scores up to Week 24: a) ACR20, ACR50 and ACR70 response rates at Weeks 12 and 24 (FAS population; NRI), b) ACR20 response rate by time (FAS population; NRI), c) Improvements in DAS28(ESR) up to Week 24 (FAS population; LOCF), d) Improvements in HAQ-DI up to Week 24 (FAS population; LOCF).

levels at Weeks 2, 4 and 6 were 33.0 μg/mL, 47.3 μg/mL and 52.7 μg/mL, respectively. During maintenance dosing (200 mg Q2W), mean trough CZP levels reduced to 25.4 μg/mL at Week 12 and to 21.7 μg/mL at Week 24.

Anti-CZP antibodies were found in 18 patients (15.5%) at least once during the study; of these, 6 patients became negative and 12 patients (10.5%) remained positive at Week 24 or at discontinuation. Although the presence of these antibodies was associated

Table 2. Least squares (LS) mean change from baseline or ratio of geometric mean to baseline at Weeks 12 and 24 in ACR core components and other endpoints (FAS population with LOCF).

	Placebo ($n = 114$)		CZP 200 mg Q2W ($n = 116$)	
Characteristic	*Week 12*	*Week 24*	*Week 12**	*Week 24**
LS mean change from baseline (SE)				
Tender joint count	−1.20 (0.74)	−0.63 (0.84)	−9.82 (0.73)	−10.19 (0.84)
Swollen joint count	−0.92 (0.60)	−0.95 (0.63)	−7.97 (0.60)	−8.61 (0.63)
Patient's assessment of pain, 100 mm VAS	−1.9 (2.0)	−1.2 (2.1)	−26.4 (1.9)	−27.5 (2.1)
Patient's assessment of global disease activity, 100 mm VAS	0.5 (1.9)	1.9 (2.1)	−24.5 (1.9)	−23.8 (2.1)
Physician's assessment of global disease activity, 100 mm VAS	−7.8 (1.9)	−6.5 (2.0)	−32.0 (1.9)	−32.3 (2.0)
DAS28(ESR)	−0.29 (0.10)	−0.21 (0.12)	−2.01 (0.10)	−2.06 (0.12)
Duration of morning stiffness, h**	−0.33 (0.43)	0.54 (0.52)	−2.36 (0.43)	−2.40 (0.51)
HAQ-DI	0.03 (0.05)	0.12 (0.05)	−0.47 (0.05)	−0.48 (0.05)
SF-36 component score***				
SF-36 PCS	−0.19 (0.84)	−1.46 (0.90)	8.84 (0.82)	9.27 (0.89)
SF-36 MCS	−1.17 (0.93)	−0.94 (1.00)	5.93 (0.91)	5.24 (0.98)
Geometric mean, ratio to baseline (CV)				
CRP	0.95 (84.32)	1.04 (114.97)	0.31 (148.75)	0.39 (279.74)
ESR	1.0 (38.4)	1.0 (46.1)	0.5 (71.4)	0.6 (78.6)

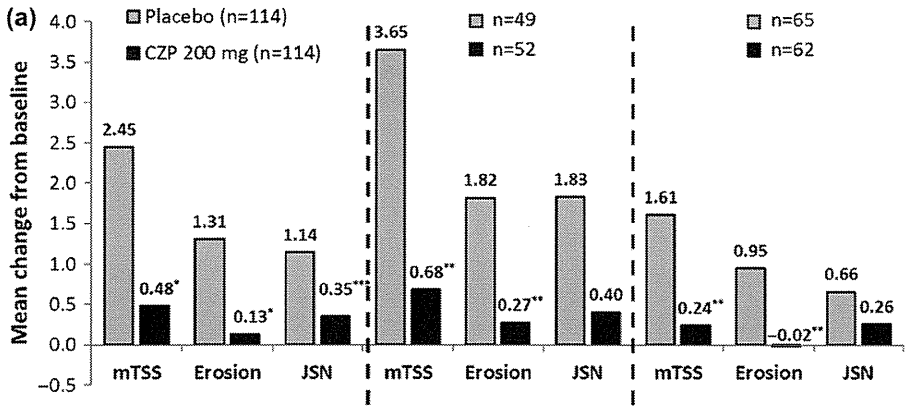
Errors for LS mean values were estimated using standard error (SE), errors for geometric mean values were estimated using CV (coefficient of variation).

ACR, American College of Rheumatology; CRP, C-reactive protein; CV, coefficient of variation; CZP, certolizumab pegol; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; LOCF, last observation carried forward; LS, least squares; MCS, mental component score; PCS, physical component score; SE, standard error; VAS, visual analog scale.

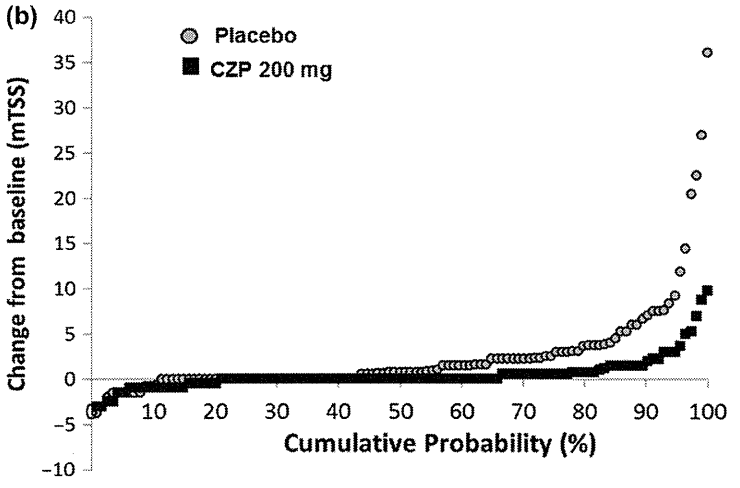
*$p < 0.0001$ for all comparisons of CZP 200 mg versus placebo unless stated otherwise.

**$p = 0.001$ at Week 12.

***$n = 112$ (CZP), $n = 108$ (placebo) at Weeks 12 and 24.



*p<0.0001 vs placebo; **p<0.01; ***p<0.05. ANCOVA with treatment as a factor and rank baseline as a covariate; mTSS, modified total Sharp score; JSN, joint space narrowing; FAS, full analysis set. Linear extrapolation was used to impute missing radiographic data in 96/114 placebo patients (including those who withdrew at Week 16) and 32/114 CZP patients.



mTSS≤0.5 at Week 24, 76.3% vs 45.6%; p<0.0001 (logistic regression)

Figure 3. Radiographic outcomes: a) Inhibition of progression of structural damage: change from baseline at Week 24 (FAS-linear extrapolation), b) Cumulative probability plot of the change from BL in mTSS at Week 24 (FAS-linear extrapolation).

with lower plasma CZP concentrations (mean 4.5 μg/mL vs. 27.8 μg/mL at Week 24 in antibody-positive and antibody-negative patients, respectively), detectable plasma concentrations of CZP were observed at Week 24 in all of the 18 anti-CZP antibody-positive patients (data not shown), with ACR20 response rates maintained in these patients to Week 24 (50.0%).

Safety

TEAEs were reported in 71.6% (83/116) of CZP patients and 58.8% (67/114) of placebo patients, the majority being of mild to moderate intensity (Table 3). Events leading to withdrawal were more frequent in the CZP group. The most frequently reported AE in both groups was nasopharyngitis. Skin rash was more frequent with CZP than placebo. Injection site erythema (three patients, 2.6%), injection site reaction (three patients, 2.6%), administration site reaction (two patients, 1.7%), and injection site hematoma (one patient, 0.9%) were reported in patients treated with CZP. All of these reactions were mild. No administration site reactions were observed in the placebo group.

SAEs were observed in 13 patients (14 events) in the CZP group and in three patients (5 events) in the placebo group (Table 3). The most common SAE in both groups was infections (CZP 3.4% vs. placebo 0.9%). In the CZP group there were four events of serious infection including one event each of *Pneumocystis jiroveci* pneumonia (PCP), pneumococcal pneumonia, herpes zoster and bacterial arthritis. In the placebo group there were two events of serious infection (one event each of cellulitis and influenza), both occurring in the same patient. In the CZP group, one patient died of a rupture of a dissecting aortic aneurysm in the thoracic region, but this was considered unlikely to have been related to study medication. There were no cases of tuberculosis, but there was one report of malignant disease in the placebo group.

Discussion

The efficacy of CZP in combination with MTX [5,6] and of CZP monotherapy [10] in a non-Japanese population has previously been reported. In the J-RAPID study, the effects of CZP plus MTX in a Japanese population of RA patients have been demonstrated [J-RAPID trial, Yamamoto et al. 2013]. Here, we report the effects of CZP 200 mg Q2W without concomitant MTX on signs and symptoms of RA, radiographic progression, physical functioning, and HRQoL in Japanese patients with active RA in whom MTX could not be administered.

While MTX is sometimes referred to as the gold standard in RA treatment, it may be contraindicated in specific patient populations or clinical circumstances, as stated in its package insert [17,18]. It is also important to note that Japanese regulatory approval of MTX was obtained in 1999, approximately 10 years later than the USA, with national health care coverage limited to doses lower than 8 mg/week. Even though MTX doses up to 16 mg/wk were

Table 3. Treatment-emergent AEs (safety population).

AEs	Number of patients (%) Placebo[a] ($n = 114$)	CZP 200 mg Q2W[b] ($n = 116$)
Any AE	67 (58.8)	83 (71.6)
Intensity		
Mild	29 (25.4)	33 (28.4)
Moderate	36 (31.6)	44 (37.9)
Severe[c]	2 (1.8)	6 (5.2)
Treatment-related	24 (21.1)	44 (37.9)
SAE[d] (total)	3 (2.6)[e]	13 (11.2)[f]
Deaths	0	1 (0.9)
AEs leading to withdrawal	3 (2.6)	9 (7.8)
Most common AEs[g] (≥3% in any group)		
Nasopharyngitis	16 (14.0)	20 (17.2)
Rash	0	10 (8.6)
Pharyngitis	5 (4.4)	6 (5.2)
Eczema	3 (2.6)	6 (5.2)
Rheumatoid arthritis	14 (12.3)	5 (4.3)
Abnormal hepatic function	4 (3.5)	4 (3.4)
Hypertension	1 (0.9)	4 (3.4)
Constipation	0	4 (3.4)
Upper respiratory tract infection	4 (3.5)	3 (2.6)
Serious infections and infestations	1 (0.9)[h]	4 (3.4)

[a]Total exposure duration: 34.08 patient-years.
[b]Total exposure duration: 49.43 patient-years.
[c]Severe AE defined as an event that prevents work or daily activities.
[d]SAE, serious adverse event.
[e]Five events in three patients.
[f]14 events in 13 patients.
[g]Preferred terms according to MedDRA terminology.
[h]Two events in the same patient.

approved in 2011, treating RA with high MTX doses is still not standard practice, which often results in the decision to avoid MTX. Therefore, in Japan, it is essential to identify effective treatment options for RA patients without MTX use.

In the HIKARI study, where patients did not receive concomitant MTX and were treated with CZP monotherapy or CZP with non-MTX DMARDs, the response to CZP was statistically significant from as early as Week 1 compared with placebo. ACR20 response rates were substantially improved by Week 4, and were sustained throughout the study. A total of 67% of CZP patients (59% of monotherapy patients and 74% of those using concomitant DMARDs) achieved the ACR20 response at Week 12; this efficacy was maintained to Week 24 (64%). Similar benefits (rapid response at Week 1, maximal efficacy at 4–12 weeks and maintenance to Week 24) were demonstrated for DAS28(ESR) and HAQ-DI. CZP in the absence of concomitant MTX was also associated with improved patient-reported outcomes such as HRQoL and pain (as shown by SF-36 and VAS scores).

All TNF inhibitors have demonstrated inhibition of joint damage progression when combined with MTX. Frequently, however, this beneficial effect is not conserved when TNF inhibitors are administered without MTX [19–21]. The effect of CZP without MTX on progression of bone destruction has not been investigated previously. The present study demonstrates for the first time that CZP without concomitant MTX significantly reduces joint damage progression, with 76.3% of the active treatment group versus 45.6% in the placebo group showing mTSS ≤ 0.5 at Week 24, despite high baseline disease activity. In the overall group there were significant differences in the progression of structural damage between CZP and placebo patients. Furthermore, the inhibitory effect of CZP monotherapy on joint damage progression was significant compared with the respective placebo group, with mean change in mTSS of 0.68 (CZP) compared with 3.65 (placebo) at Week 24. However, when subgroup analysis based on the presence or absence of concomitant DMARDS was performed, the difference only in JSN between CZP and placebo groups did not reach significance, possibly due to the decreased sample size resulting in reduced statistical detectability. These results support the selection of CZP for the reduction of joint damage progression in Japanese patients without MTX. However, in patients receiving oral corticosteroids ($n = 158$, 68.7% at baseline), the possibility of a synergistic effect with CZP on structural damage cannot be excluded.

The formation of anti-drug antibody has been a topic of some debate, as quick clearance of the drug from the system has been associated with a decrease in response to the drug in patients with anti-drug antibody [22]. In this study, anti-CZP antibody formation was observed in 15.5% of patients. However, the plasma CZP concentrations were above the detection limit at Week 24 in all patients, including those with detectable anti-CZP antibody. The rate of anti-CZP antibody formation in this cohort is slightly higher than that observed in clinical trials of TNF inhibitors including CZP as monotherapy conducted in Western countries [23,24], but lower than that observed in a clinical trial conducted in Japan [22]. In the present study, 50.0% of anti-CZP antibody-positive patients achieved ACR20 at Week 24. A recent study of golimumab monotherapy in a Japanese patient population showed that a quarter of patients with low serum golimumab concentrations had low ACR20 response rate relative to the rest of the patients [25]. These studies suggest that clinical response is influenced by drug concentration and can be maintained despite anti-drug antibody formation if the drug level is sufficient.

CZP was generally well tolerated in the present study, with the rate of discontinuation due to AEs being 7.8%. The most common adverse reaction was nasopharyngitis. Consistent with the J-RAPID and FAST4WARD studies, the incidence of administration site reactions observed in this study was low [10].

Treatment guidelines for biologics use in RA described a potential increased risk of infections due to pneumonia, tuberculosis and PCP, and stressed early diagnosis and treatment [26]. In this study, four cases of serious infection with one serious case of PCP were reported in the CZP group compared with two cases in a single patient with placebo, and there were no reports of tuberculosis in either group. Overall, these results concur with postmarketing surveillance on other TNF inhibitors in this population, such as infliximab [27] and etanercept [28].

Limitations of this study include its relatively short duration of 24 weeks, although the safety profile of CZP will be further characterized in the OLE. Patients treated with a previous biologic DMARD must have undergone a 6-month washout period and patients who had received ≥ 2 TNF inhibitors were excluded; therefore these results are not relevant to patients who have received multiple previous TNF inhibitors.

Overall, the HIKARI study demonstrated significant clinical efficacy, structural protection and functional improvement in Japanese patients who did not receive concomitant MTX, albeit over only 24 weeks. This study is the first to confirm that CZP without concomitant MTX (both as monotherapy and in combination with non-MTX DMARDs) is effective in controlling clinical signs and symptoms, including inhibition of radiographic progression, in a Japanese population, and confirms the safety of CZP in this population.

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Conflicts of interest

The competing interests of all authors are provided below.

- KY has served as a consultant for UCB Pharma, Pfizer, Abbott, BMS, Roche, Chugai, Mitsubishi-Tanabe and Eisai and has received research funding from UCB Pharma, Pfizer, Abbott, Santen, Mitsubishi-Tanabe and Eisai.
- TT has served as a consultant for AstraZeneca, Eli Lilly, Novartis, Mitsubishi-Tanabe and Asahi Kasei, has received research support from Abott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Otsuka, Pfizer, Sanofi-Aventis, Santen, Takeda and Teijin, and has served on speaker bureaus for Abbott, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda.
- HY has served as a consultant for, and received research funding from, UCB Pharma, Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda.
- NI has received research funding from Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken and Pfizer and has served on speaker bureaus for Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama and Otsuka.
- YT has received research funding from BMS, MSD, Chugai, Mitsubishi-Tanabe, Astellas, Abbott, Eisai and Janssen and has served on speaker bureaus for UCB Pharma, Mitsubishi-Tanabe, Abbott, Eisai, Chugai, Janssen, Santen, Pfizer, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Otsuka, Actelion, Eli Lilly, Nippon Kayaku, Quintiles Transnational and Ono.
- KE has served as a consultant for UCB Pharma.
- AW has received research support from Astellas, Daiichi-Sankyo, Kyorin, Shionogi, Taisho, Dainippon-Sumitomo, Taiho, Toyama Chemical and Meiji Seika and has served on speaker bureaus for Abott, MSD, Otsuka, GSK, Shionogi, Daiichi-Sankyo, Taisho-Toyama, Dainippon-Sumitomo, Mitsubishi-Tanabe, Toyama Chemical, Bayer and Pfizer.
- HO has served as a consultant for UCB Pharma and Astellas.
- KI is an employe of Otsuka.
- YS is an employee of UCB Pharma.
- DvH has served as a consultant for, and received research support from, AbbVie, Amgen, AstraZeneca, BMS, Centocor, Chugai, Daiichi, Eli Lilly, GSK, Janssen, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB Pharma and Vertex. DvH is also director of Imaging Rheumatology bv.
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Notice of correction

The original version of this article published on 11 November contained an error in the caption of Figure 3. "Cumulative probability plot of the change from BL in mTSS at Week 24 (FAS-linear population)" should have read "Cumulative probability plot of the change from BL in mTSS at Week 24 (FAS-linear extrapolation). This error has been corrected in this version.

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ORIGINAL ARTICLE

Long-term efficacy and safety of certolizumab pegol in Japanese rheumatoid arthritis patients who could not receive methotrexate: 52-week results from an open-label extension of the HIKARI study

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Abstract

Objectives. To evaluate the long-term efficacy and safety of certolizumab pegol (CZP) treatment and to assess the efficacy of two CZP maintenance dosing schedules in Japanese rheumatoid arthritis (RA) patients who could not receive methotrexate (MTX).

Methods. HIKARI double-blind (DB) patients were entered into an open-label extension (OLE) study. Patients withdrawn at 16 weeks due to lack of efficacy and DB completers without a 24-week American College of Rheumatology (ACR)20 response received CZP 200 mg every 2 weeks (Q2W). DB completers with 24-week ACR20 responses were randomized to CZP 200 mg Q2W or CZP 400 mg every 4 weeks.

Results. The ACR20/ACR50/ACR70 response rates of DB completers ($n = 98$) were 82.7%/56.1%/34.7% at OLE entry, and 83.7%/65.3%/48.0% at 52 weeks, respectively. Other clinical, functional, and radiographic outcomes were sustained during long-term administration of CZP, even without MTX. No new unexpected adverse events were observed during long-term CZP treatment. The efficacy and safety of CZP treatment were similar between the two dosing schedules.

Conclusions. Long-term CZP administration is efficacious and safe for RA patients. No obvious differences in clinical efficacy and safety were observed between the two dosing schedules. The choice between two maintenace regimens adds flexibility in administration schedules for RA patients and physicians.

Keywords

Certolizumab pegol, Monotherapy, Rheumatoid arthritis, TNFα, TNF inhibitor

History

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Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease characterized by persistent and chronic joint inflammation [1]. A critical factor in this inflammatory process is the production of TNFα, which causes immune cell activation and chronic inflammation [2]. Introduction of TNF inhibitors in clinical practice has brought significant changes to the treatment of RA. These agents lead to improved signs and symptoms of RA and inhibit further structural joint damage, which restore the physical function and the quality of life in RA patients [3–7].

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Certolizumab pegol (CZP) is a polyethylene glycol (PEG)ylated Fc-free anti-TNFα agent [8,9]. The efficacy of CZP with concomitant methotrexate (MTX) treatment has previously been demonstrated in patients with active RA, who did not respond adequately to MTX alone. These studies include the RAPID1 and RAPID2 studies conducted internationally [10,11] and the J-RAPID study conducted in Japan [12]. However, as MTX is not tolerated by all patients due to side effects related to its anti-metabolite activity [13,14], additional studies were performed to test the ability of CZP to improve disease in RA patients without concomitant MTX treatment. In a 24-week multicenter, double-blind (DB), placebo-controlled study (FAST4WARD), administration of CZP 400 mg every 4 weeks (Q4W) given as monotherapy significantly reduced the signs and symptoms of active RA in patients who had failed at least one prior disease-modifying antirheumatic drug (DMARD) [15]. Moreover, a similar 24-week DB, placebo-controlled HIKARI study, which targeted Japanese RA patients in whom MTX could

not be administered, demonstrated the efficacy and safety of CZP 200 mg administered every 2 weeks (Q2W) without MTX [16]. Additionally, the HIKARI study demonstrated that administration of CZP results in rapid, sustained reductions in signs and symptoms of RA, both as monotherapy and with non-MTX DMARDs. Notably, CZP monotherapy showed significant inhibition of radiographic progression [16].

CZP has been shown to be safe and efficacious in short-term treatment studies [10–12,16]; however, whether the beneficial effects of CZP are maintained during long-term treatment is unclear in Japanese RA patients, especially in the absence of co-treatment with MTX. To this end, we conducted an open-label extension (OLE) study of the HIKARI trial to evaluate the long-term efficacy and safety of CZP treatment in Japanese RA patients who could not be treated with MTX. In this OLE study, we also aimed to compare the efficacy of two maintenance regimens, CZP 200 mg Q2W and CZP 400 mg Q4W. We hereby report the 52-week interim results and post-hoc analysis from the ongoing HIKARI-OLE study.

Material and methods

HIKARI and HIKARI-OLE study design

The HIKARI-OLE study (NCT00850343) is an OLE study of the HIKARI study (NCT00791921). In brief, the HIKARI study (hereinafter referred to as the "DB phase") was a 24-week, phase III, DB study conducted in 65 centers across Japan in patients with active RA, who could not receive MTX due to insufficient efficacy, safety concerns, or previous discontinuation for safety reasons [16]. Eligible patients were aged 20–74 years and had a diagnosis of adult-onset RA as defined by American College of Rheumatology (ACR) criteria [17] of 0.5–15 years' disease duration. The subjects were randomized 1:1 to a CZP or placebo group. In the CZP group, 400 mg of CZP was subcutaneously administered at Weeks 0, 2, and 4. Subsequently, CZP was subcutaneously administered at a maintenance dose of 200 mg Q2W. The primary endpoint of this study was an ACR20 response at week 12 [16]. In this study, the concomitant use of DMARDs other than MTX and leflunomide (hereinafter referred to as non-MTX DMARDs) was permitted if the drug combination and dosage were maintained. The non-MTX DMARDs used included Salazosulfapyridine ($n = 58$), Tacrolimus Hydrate ($n = 34$), Bucillamine ($n = 32$), Mizoribine ($n = 8$), Sodium Aurothiomalate ($n = 4$), Actarit ($n = 1$), and Auranofin ($n = 1$).

The HIKARI-OLE study was conducted between March 25, 2009 and August 12, 2011. In the OLE phase, we divided HIKARI study patients into four groups based on the clinical responses during the DB phase. Patients who did not achieve an ACR20 response both at Weeks 12 and 14 were withdrawn from the DB phase at Week 16, assigned to Group I ($n = 110$), and treated with CZP 200 mg Q2W thereafter. Patients who exhibited an ACR20 response at Week 12 or 14 but failed to achieve an ACR20 response at Week 24 were assigned to Group II ($n = 12$) and also received CZP 200 mg Q2W. Patients who achieved an ACR20 response at Week 12 or 14 as well as at Week 24 were randomized 1:1 to either CZP 200 mg Q2W (Group III, $n = 43$) or CZP 400 mg Q4W (Group IV, $n = 43$) (Figure 1). Of importance, we established this dosing schedule so that the total dose received by patients in Groups III and IV over a 1-month period was the same.

Week 0 of the OLE phase of Groups II, III, and IV (HIKARI DB phase completers: hereinafter referred to as DB completers) corresponds to Week 28 of the DB phase, and Week 0 of the OLE phase of Group I (early escape) corresponds to Week 16 of the DB phase. Patients assigned to the placebo group during the DB phase were also included in this OLE study. A change in dosage or the discontinuation of concomitant DMARDs was permitted after Week 24 of the OLE phase. However, any new addition of concomitant DMARDs or readministration of previously discontinued drugs was not permitted.

The outcome of the study was measurement of continuous efficacy and safety monitoring during the long-term treatment with CZP without MTX. Efficacy outcomes included ACR20 response rates, and changes in Health Assessment Questionnaire Disability Index (HAQ-DI), Disease Activity Score in 28 Joints-Erythrocyte Sedimentation Rate (DAS28-ESR), Short Form-36 Health Survey (SF-36), and Pain Visual Analog Scale (VAS) from HIKARI pre-study baseline. In addition, to measure radiographic disease progression, changes in modified Total Sharp Score (mTSS) from OLE study entry was assessed by linear extrapolation. Comprehensive disease control (CDC) was defined by simultaneous triple criteria: that is, low disease activity (LDA) (DAS28-ESR: ≤ 3.2), functional remission (HAQ-DI: ≤ 0.5), and radiographic nonprogression (yearly ΔmTSS: ≤ 0.5). Comprehensive disease remission (CDR) was also defined by simultaneous triple remission criteria: clinical remission (DAS28-ESR: < 2.6), functional remission (HAQ-DI: ≤ 0.5), and radiographic nonprogression (yearly ΔmTSS: ≤ 0.5). To calculate CDC and CDR for overall DB completers ($n = 98$), yearly ΔmTSS from HIKARI pre-study baseline (linear extrapolation, with nonresponder imputation for patients with no data) was used. Safety outcomes were reported for all patients who received at least one dose of CZP in the OLE study ($n = 208$).

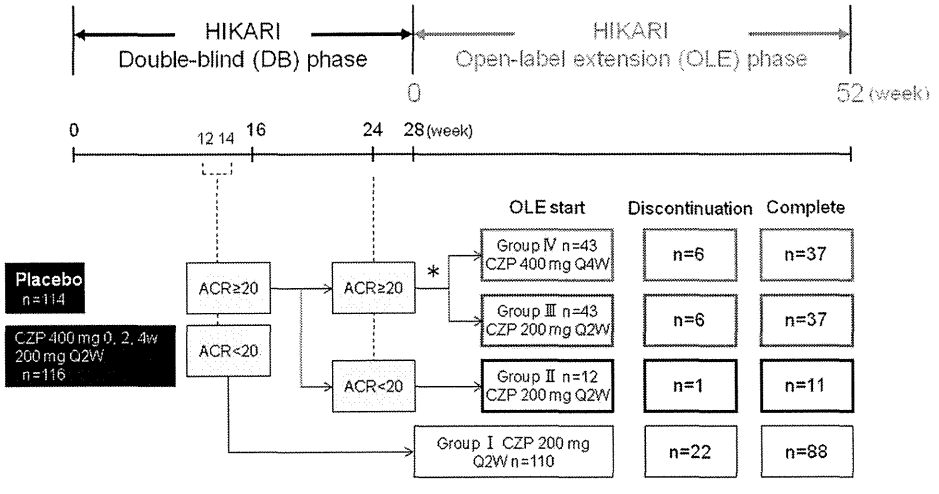

Figure 1. HIKARI-OLE study design. The diagram depicts the breakdown of HIKARI DB study patients into four groups for the OLE phase of the study. *Regardless of their initial DB phase group assignment, patients who achieved an ACR20 response at Week 12 or 14 as well as at Week 24 were randomized (1:1) to either CZP 200 mg Q2W (Group III, $n = 43$) or CZP 400 mg Q4W (Group IV, $n = 43$).

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with the Pharmaceutical Affairs Law Standards for the Conduct of Clinical Trials on Drugs (Ministry of Health, Labour and Welfare Ordinance no. 28, 27 March 1997) and related notifications. Institutional review board approval was obtained at all centers and all patients provided written informed consent.

Post-hoc analyses

Since the OLE study included patients who received placebo during the DB phase, an additional post-hoc analysis of efficacy was performed on patients who received CZP in the DB phase, to observe the effects of continuous CZP treatment during the combined DB and OLE phases of the study. This data set includes patients who were originally assigned to CZP 200 mg treatment groups in the DB phase and completed the DB phase with an ACR20 response at Week 12 or 14 (CZP-DB completers; $n = 81$). Of note, this data set excluded all patients who previously received placebo in the DB phase, even if they completed the phase. We focused on ACR20/ACR50/ACR70 response rates, DAS28-ESR scores, HAQ-DI scores, and disease activity state (high: DAS28-ESR: >5.1, moderate: >3.2 and ≤ 5.1, LDA: ≤ 3.2, and remission: <2.6) in this post-hoc analysis.

Statistical analyses

The efficacy analysis was performed on the full-analysis set (FAS) using the last observation carried forward (LOCF) to impute missing data. We used HIKARI pre-study baseline as baseline values. Safety analyses were performed on all subjects who received at least one dose of CZP during the OLE study. Because the objective of the study was to evaluate the long-term efficacy and safety of CZP treatment, inferential analyses were not performed.

Results

Patient characteristics and disposition of the HIKARI-OLE study

HIKARI DB phase patients were consented to enter the OLE study ($n = 210$). Two hundred and eight patients were included in the efficacy and safety analyses, because two patients withdrew from the OLE study before receiving CZP treatment. During the 52-week treatment, an additional 35 patients withdrew from the study. A few patients withdrew from the study due to an inadequate response (5.8% in total, Table 1). Other reasons for withdrawal are shown in Table 1. A total of 173 patients (83%) completed the 52-week interim period of the OLE phase of the study.

Based on their response during the DB phase, patients were separated into four groups in the OLE phase. Patients with an ACR20 response at Week 24 of the DB phase (DB responders: Groups III and IV) and DB non-responders (Groups I and II) were distinguished in order to evaluate the sustained efficacy of continued long-term CZP treatment. As shown in Table 2, all of these groups included patients who were on placebo during the DB phase. The fraction of patients that received placebo during the DB phase were 78.2% (86 patients), 41.7% (5 patients), 18.6% (8 patients), and 9.3% (4 patients) in Groups I, II, III, and IV, respectively. DB responders were further randomized into two groups to evaluate the efficacy of two different dosing schedules. DB responder patients ($n = 86$) were randomized to either a CZP 200 mg Q2W (Group III, $n = 43$: 35 patients from the CZP group and 8 patients from the placebo group) or a CZP 400 mg Q4W (Group IV, $n = 43$: 39 patients from the CZP group and 4 patients from the placebo group) treatment group as shown in Table 2. At OLE study entry (OLE Week 0), the mean DAS28-ESR scores of Groups I, II, III, and IV were 6.16, 5.26, 3.33, and 3.58, respectively.

Patient demographics and HIKARI pre-study baseline characteristics are summarized in Table 2. Patients who withdrew from the DB phase at Week 16 (Group I) and overall DB completers (Groups II + III + IV) had mean DAS28-ESR scores of 6.27 and 6.11, respectively, at HIKARI pre-study baseline. 44.7% of patients did not receive any DMARDs at the initiation of the DB phase, and remained untreated with DMARDs during the OLE phase of up to 52 weeks.

Long-term CZP treatment sustains the clinical efficacy of CZP

We conducted the HIKARI-OLE study to assess the clinical response obtained after prolonged treatment with CZP without MTX. In Groups I, II, III, IV, and overall DB completers (Groups II + III + IV), the ACR20/ACR50/ACR70 response rates, as calculated from HIKARI pre-study baseline, were increased or sustained for up to 52 weeks of CZP treatment in the OLE phase.

At OLE study entry and at 52 weeks of the OLE phase, the ACR20 response rates were 4.5% and 70.0% for Group I, 8.3% and 83.3% for Group II, 90.7% and 76.7% for Group III, and 95.3% and 90.7% for Group IV, respectively (Figure 2a). The ACR50 response rates were 0.9% and 40.9% for Group I, 0.0% and 58.3% for Group II, 65.1% and 62.8% for Group III, and 62.8% and 69.8% for Group IV, respectively (Figure 2b). The ACR70 response rates were 0.9% and 22.7% for Group I, 0.0% and 16.7% for Group II, 39.5% and 58.1% for Group III, and 39.5% and 46.5% for Group IV, respectively (Figure 2c).

Table 1. Reasons for discontinuation of therapy.

Subject disposition	Group I CZP 200 mg Q2W	Group II CZP 200 mg Q2W	Group III CZP 200 mg Q2W	Group IV CZP 400 mg Q4W	Total (Groups I + II+ III + IV)
Number of subjects, *n* (%)*	110 (100.0)	12 (100.0)	43 (100.0)	43 (100.0)	208 (100.0)
Subjects withdrawn before Week 52, *n* (%)*	22 (20.0)	1 (8.3)	6 (14.0)	6 (14.0)	35 (16.8)
Reason for withdrawal					
Subject's request	7 (6.4)	0 (0.0)	2 (4.7)	0 (0.0)	9 (4.3)
Violation of inclusion/ exclusion criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	5 (4.5)	1 (8.3)	2 (4.7)	4 (9.3)	12 (5.8)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Inadequate response	9 (8.2)	0 (0.0)	2 (4.7)	1 (2.3)	12 (5.8)
Compliance with protocol not possible, for reason other than those above	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.5)
Investigator's judgement	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

*Number of patients (%).

Table 2. Patient demographics and disease status at the HIKARI pre-study baseline (FAS population).

	Group I CZP 200 mg Q2W ($n = 110$)	Group II CZP 200 mg Q2W ($n = 12$)	Group III CZP 200 mg Q2W ($n = 43$)	Group IV CZP 400 mg Q4W ($n = 43$)	Total (Groups I + II+ III + IV) ($n = 208$)
Prior treatment in the double-blind phase, *n* (%)*					
Placebo	86 (78.2)	5 (41.7)	8 (18.6)	4 (9.3)	103 (49.5)
CZP 200 mg	24 (21.8)	7 (58.3)	35 (81.4)	39 (90.7)	105 (50.5)
Mean age (SD), years	55.4 (10.2)	59.3 (6.5)	54.6 (9.7)	55.9 (10.7)	55.5 (10.0)
Female, *n* (%)*	91 (82.7)	7 (58.3)	28 (65.1)	28 (65.1)	154 (74.0)
Mean body weight (SD), kg	56.12 (10.84)	55.92 (9.55)	59.36 (11.11)	58.65 (11.83)	57.30 (11.06)
BMI (SD), kg/m^3	22.95 (3.69)	22.04 (3.20)	23.10 (3.29)	23.06 (4.27)	22.95 (3.70)
Mean disease duration (SD), years	5.78 (4.34)	5.80 (4.02)	5.71 (3.89)	4.74 (3.89)	5.55 (4.13)
Mean no. of prior DMARDs (SD)	1.8 (1.0)	2.1 (1.1)	1.8 (1.0)	2.0 (1.0)	1.8 (1.0)
Prior TNF inhibitor use, *n* (%)*	12 (10.9)	1 (8.3)	6 (14.0)	2 (4.7)	21 (10.1)
Mean no. of DMARDs at baseline (SD)					
0	54 (49.1)	6 (50.0)	15 (34.9)	18 (41.9)	93 (44.7)
>0	56 (50.9)	6 (50.0)	28 (65.1)	25 (58.1)	115 (55.3)
RF-positive (≥ 14 IU/mL), *n* (%)*	98 (89.1)	10 (83.3)	38 (88.4)	34 (79.1)	180 (86.5)
Mean no. (SD) of tender joints (0–68)	17.1 (10.0)	19.4 (11.5)	15.0 (8.9)	18.1 (10.1)	17.0 (9.9)
Mean no. (SD) of swollen joints (0–66)	14.9 (8.1)	16.3 (9.3)	13.6 (6.9)	15.3 (8.8)	14.8 (8.0)
Mean CRP (SD), mg/dL	2.56 (2.13)	1.53 (1.49)	2.84 (1.85)	2.35 (1.90)	2.52 (2.00)
Mean ESR (SD), mm/h	58.3 (26.1)	51.7 (27.8)	51.8 (24.2)	53.2 (24.4)	55.5 (25.5)
DAS28 (ESR)					
Mean (SD)	6.27 (0.96)	6.16 (1.02)	6.03 (0.88)	6.17 (0.90)	6.20 (0.93)
<3.2, *n* (%)*	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.5)
3.2–5.1, *n* (%)*	8 (7.3)	2 (16.7)	3 (7.0)	1 (2.3)	14 (6.7)
>5.1, *n* (%)*	102 (92.7)	10 (83.3)	40 (93.0)	41 (95.3)	193 (92.8)
HAQ-DI (SD)	1.16 (0.67)	1.04 (0.77)	1.15 (0.72)	1.07 (0.69)	1.13 (0.69)
Mean total mTSS (SD)	48.20 (56.01)	44.29 (52.00)	33.66 (47.61)	30.57 (51.62)	41.33 (53.46)

BMI, body mass index; CRP, C-reactive protein; CZP, certolizumab pegol; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; FAS, full-analysis set; HAQ-DI, Health Assessment Questionnaire – Disability Index; mTSS, modified Total Sharp Score; MTX, MTX; RF, rheumatoid factor; SD, standard deviation.
*Number of patients (%).

For overall DB completers (Groups II + III + IV), at OLE study entry and at 52 weeks of the OLE phase, the ACR20 response rates were 82.7% and 83.7%, the ACR50 response rates were 56.1% and 65.3%, and the ACR70 response rates were 34.7% and 48.0%, respectively (Figure 2). A marked improvement in DAS28-ESR was also sustained for up to 52 weeks of the OLE phase (Figure 3a). The DAS28-ESR remission rates (defined as DAS28-ESR <2.6) for overall DB completers were 23.5% and 35.7% at OLE entry and at 52 weeks of the OLE phase, respectively. Improvements in HAQ-DI (Figure 3b), pain VAS, and SF-36 scores were also sustained. The HAQ-DI remission rates (defined as HAQ-DI ≤0.5) for overall DB completers were 58.2% and 68.4% at OLE entry and at 52 weeks of the OLE phase, respectively, indicating that most of patients achieved functional remission. The mean ± SD in 100 mm pain VAS improvement from the HIKARI pre-study baseline was −32.0 ± 23.1 at OLE study entry and maintained at −35.4 ± 27.0 at 52 weeks of the OLE phase. Moreover, the mean ± SD changes of SF-36 scores from HIKARI pre-study baseline at OLE study entry and at Week 52 were 10.3 ± 8.7 and 12.6 ± 12.2 in physical component summary scores and 7.2 ± 11.7 and 5.6 ± 13.4 in mental component summary scores, respectively. Similar to the summary scores, the change in each of the individual eight domains of the SF-36 score was all maintained, indicating sustained improvement in the quality of life of RA patients (data not shown).

In addition to signs and symptoms, and patient-reported outcome indicators, changes in mTSS (ΔmTSS) at Week 52 from OLE study entry were assessed. The mean ± SD and median ΔmTSS were 0.96 ± 4.15 and 0.00 in DB completers, respectively (Figure 4). 69.8% of overall DB completers had a ΔmTSS ≤0.5 at Week 52, suggesting that continued CZP treatment was beneficial in attenuating further joint destruction.

The proportion of DB completers achieving CDC (i.e., DAS28-ESR ≤3.2, HAQ-DI ≤0.5, and ΔmTSS ≤0.5) at OLE study entry and at 52 weeks were 19.4% and 30.6%, respectively. The proportion of DB completers achieving CDR (i.e., DAS28-ESR <2.6, HAQ-DI ≤0.5, and ΔmTSS ≤0.5) at OLE study entry and at 52 weeks were 15.3% and 23.5%, respectively. Together, these data suggest that the clinical, functional, and radiographic benefits obtained after short-term CZP treatment is sustained by long-term treatment with CZP.

Comparable clinical benefit is achieved by the two different maintenance regimens (CZP at 200 mg Q2W vs. 400 mg Q4W)

As a subsidiary objective, we evaluated the clinical efficacy of two different maintenance dosing schedules by randomly assigning patients who achieved an ACR20 response in HIKARI study DB phase into either CZP 200 mg Q2W (Group III) or CZP 400 mg Q4W (Group IV). The ACR20/ACR50/ACR70 rates and changes in DAS28-ESR scores and HAQ-DI scores from HIKARI pre-study baseline were sustained similarly well in both Groups III and IV through 52 weeks of the OLE study phase (Figures 2 and 3). For example, the ACR20 response rates were 90.7% and 76.7% for Group III and 95.3% and 90.7% for Group IV at OLE study entry and at 52 weeks of the OLE phase, respectively (Figure 2a). In addition to clinical parameters, the mean ± SD of ΔmTSS from OLE study entry between Groups III and IV were similar at 0.05 ± 1.97 with a median of 0.00 compared to 0.64 ± 2.05 with a median of 0.00 at Week 52, respectively (Figure 4). At Week 52, 78.9% and 67.6% of patients had a ΔmTSS ≤0.5 in Groups III and IV, respectively. These data suggest that both regimens are similarly effective at inhibiting radiographic progression. Thus, both CZP maintenance regimens can be used to sustain the clinical efficacy of CZP for long-term treatment.

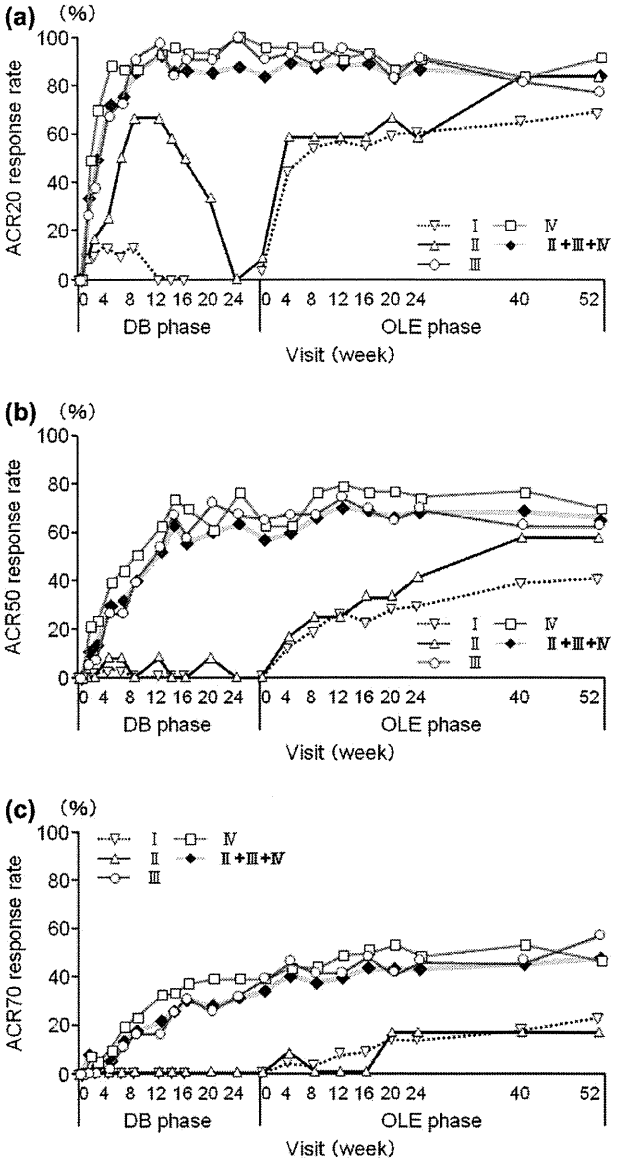

Figure 2. The ACR20/ACR50/ACR70 rates in patients from each treatment group. The percentages of patients in Groups I ($n = 110$), II ($n = 12$), III ($n = 43$), IV ($n = 43$), and patients in Groups II + III + IV combined (DB completers, $n = 98$) who achieved an (a) ACR20, (b) ACR50, or (c) ACR70 response were plotted over time for the DB and the OLE phase of the study (FAS population and LOCF imputation). Of note, Week 0 of the OLE phase of Group I (early escape) corresponds to Week 16 of the DB phase. There are no points in the missing section of the graph for Group I.

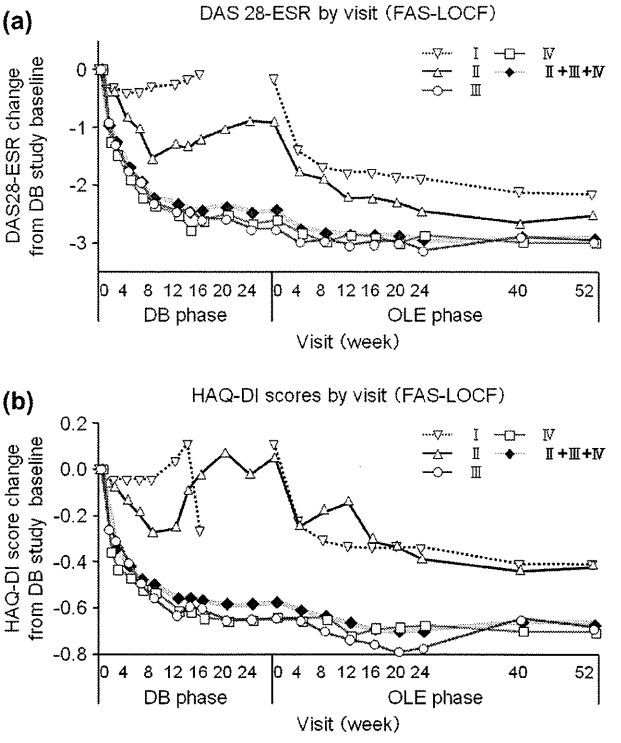

Figure 3. The change of DAS28-ESR and HAQ-DI over HIKARI pre-study baseline in patients from each treatment group. Changes in (a) DAS28-ESR and (b) HAQ-DI from HIKARI pre-study baseline of Groups I ($n = 110$), II ($n = 12$), III ($n = 43$), IV ($n = 43$), and patients in Groups II + III + IV combined (DB completers, $n = 98$) were plotted against time for the DB and the OLE phase of the study (FAS population and LOCF imputation). Of note, Week 0 of the OLE phase of Group I (early escape) corresponds to Week 16 of the DB phase. There are no points in the missing section of the graph for Group I.

Assessment of sustained clinical efficacy of long-term CZP treatment by a post-hoc analysis through the DB and OLE phase

All groups (I–IV) of the OLE study protocol included patients who were originally randomized to the placebo group during the 24-week DB phase of HIKARI study (Table 2). In order to observe the effects of continuous CZP treatment during the combined DB and OLE phases of the study, conducting analyses in the original groups that include placebo-treated patients during the DB phase, was thought to be inadequate. Thus, we performed a post-hoc analysis that only includes patients who were originally assigned to the CZP treatment group in the DB phase and completed the DB phase with an ACR20 response at Week 12 or 14 (CZP-DB completers; $n = 81$). In further analyses, CZP-DB completers included in this post-hoc analysis described above were divided into two subgroups: Patients who were on CZP monotherapy ($n = 34$) and those who were treated with CZP plus non-MTX DMARDs ($n = 47$).

Compared to OLE study entry, the ACR20, ACR50, and ACR70 response rates in CZP-DB completers were all maintained up to Week 52 of the OLE phase of HIKARI study (Figure 5). 86.4% (70/81) of CZP-DB completers receiving 200 mg CZP during the DB phase continued treatment with CZP to 52 weeks of the OLE phase, with the ACR20/ACR50/ACR70 responses rates of 81.5%/63.0%/48.1% at Week 52, respectively (Figure 5). Moreover, compared to OLE study entry, the mean changes in DAS28-ESR scores and HAQ-DI scores from HIKARI pre-study baseline in CZP-DB completers were also sustained up to 52 weeks of the OLE phase (Figure 6). Furthermore, achievement of LDA and remission rates (defined as DAS28-ESR ≤ 3.2 and < 2.6, respectively) in CZP-DB completers was sustained during the 52-week period of the OLE phase. In CZP-DB completers receiving CZP with or without non-MTX DMARDs, the combined rates of LDA and remission (DAS28-ESR ≤ 3.2) were 46.8% and 35.3%, respectively, at OLE entry, and 53.2% and 47.1%, respectively, at Week 52 (Figure 7). The remission rates (DAS28-ESR < 2.6) were 29.8% and 23.5%, respectively, at OLE entry, and 40.4% and 32.4%, respectively, at Week 52 (Figure 7). Therefore, this post-hoc analysis demonstrates that long-term CZP treatment, regardless of the concomitant use of non-MTX DMARDs, sustains clinical efficacy, even when the analysis set is restricted to patients who have achieved an ACR20 clinical response after 12–14 weeks of CZP treatment.

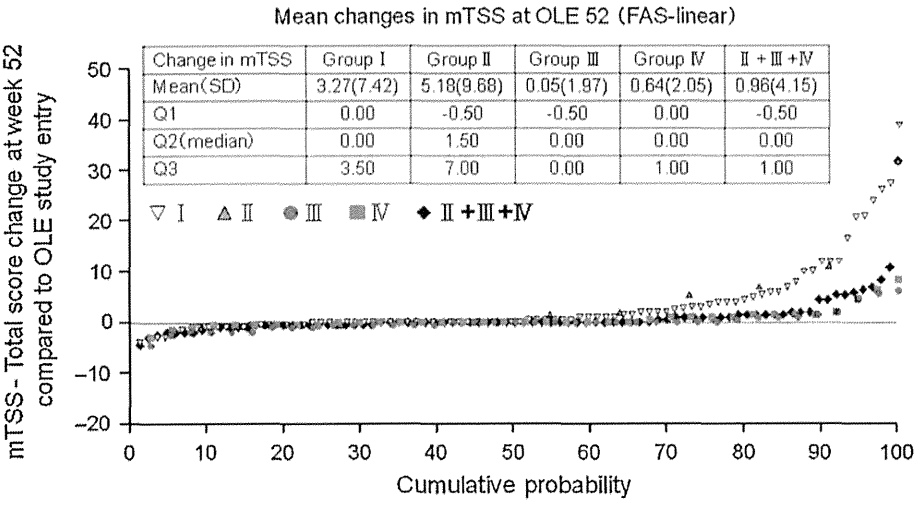

Figure 4. Inhibition of progression of structural damage: cumulative probability plot representing the change from OLE study entry in mTSS at Week 52 (FAS population and linear extrapolation). The graph depicts the cumulative probability of patients displaying a particular change in mTSS from OLE study entry in Groups I ($n = 89$), II ($n = 11$), III ($n = 38$), IV ($n = 37$), and patients in Groups II + III + IV combined (DB completers, $n = 86$).

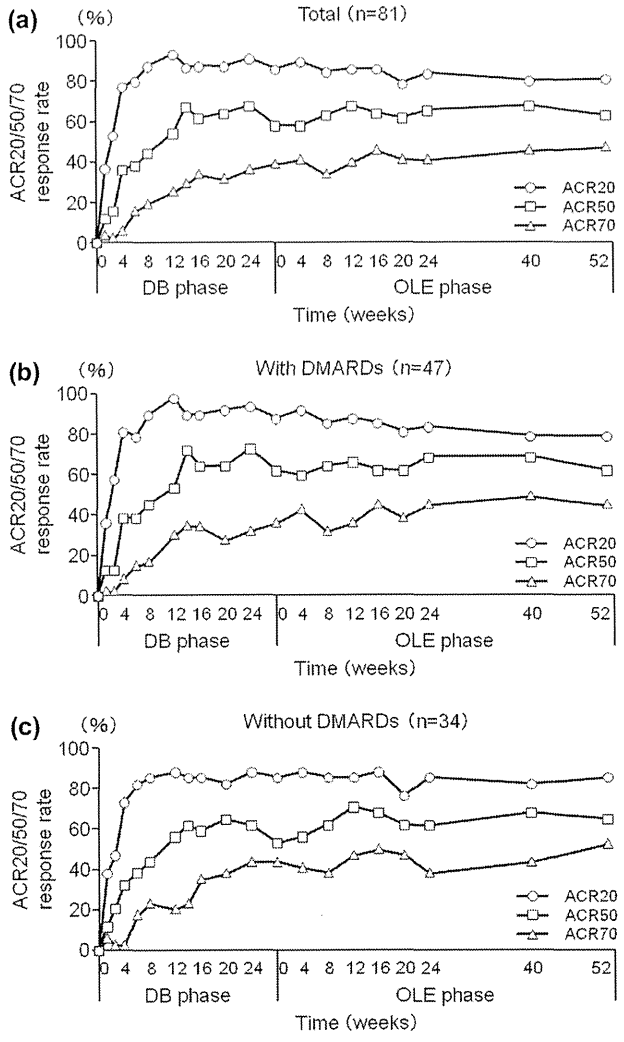

Figure 5. Post-hoc analysis of ACR20/50/80 response rates in patients from Groups II, III, and IV excluding those who were in the placebo group during the DB phase (CZP-DB completers). The percentages of patients who achieved an ACR20, ACR50, and ACR70 response of (a) all CZP-DB completers ($n = 81$), (b) CZP-DB completers treated with additional non-MTX DMARDs ($n = 47$), and (c) CZP-DB completers treated without additional non-MTX DMARDs ($n = 34$) were plotted against time for the DB and the OLE phase of the study (LOCF imputation).

Adverse events reported in patients with long-term CZP treatment

During the 52-week OLE phase, 179 patients (86.1%) experienced adverse events (AEs) and 29 patients (13.9%) experienced serious AEs (SAEs) (Table 3). Among SAEs, five patients (2.4%) reported joint-related events, two patients (1.0%) reported infections, and two patients (1.0%) developed colonic polyps. Two patients (1.0%) developed a malignancy (gastric cancer and non-Hodgkin's lymphoma). Nasopharyngitis, eczema, and upper respiratory tract infection represented the most common AEs, which were mostly mild to moderate (76.9%). No tuberculosis infections or deaths were reported. The overall AE rate was similar among all groups (Groups I–IV). None of these AEs were unanticipated. Together, these data suggest that long-term CZP treatment for 52 weeks of the OLE phase was well-tolerated by patients (Table 3).

Discussion

Previous clinical studies have demonstrated the benefits of CZP in improving RA disease parameters after short-term treatment of 24 weeks duration [10–12,15]. Similar data were obtained in the DB placebo-controlled HIKARI study, which was designed to investigate the short-term efficacy of CZP in patients who could not receive MTX [16]. Since the clinical efficacy and safety of long-term CZP treatment without MTX is unknown in Japanese RA patients, we conducted an OLE study of the HIKARI study. This OLE study was designed to evaluate the safety of long-term CZP treatment and to assess whether the clinical benefit obtained from the 24-week treatment period in the HIKARI study could be sustained by extending the treatment for another 52 weeks. As a subsidiary objective, we utilized the OLE study to evaluate the standard dosing schedule (CZP 200 mg Q2W) compared to another optional dosing schedule (CZP 400 mg Q4W).

Relating to the primary objective of our study, our data demonstrate that long-term CZP treatment continues to maintain the clinical benefit of CZP obtained after 24 weeks of treatment. All outcome parameters including high ACR response rates, and changes in DAS28-ESR scores, SF-36 scores, and pain VAS were sustained by long-term CZP treatment in DB completers. In addition, clinical remission was observed in 35.7% of patients with long-term treatment at 52 weeks of the OLE study. Functional remission was also observed in 68.4% at 52 weeks of the OLE phase, indicating that most of patients achieved functional remission. Furthermore, patients treated with long-term CZP did not

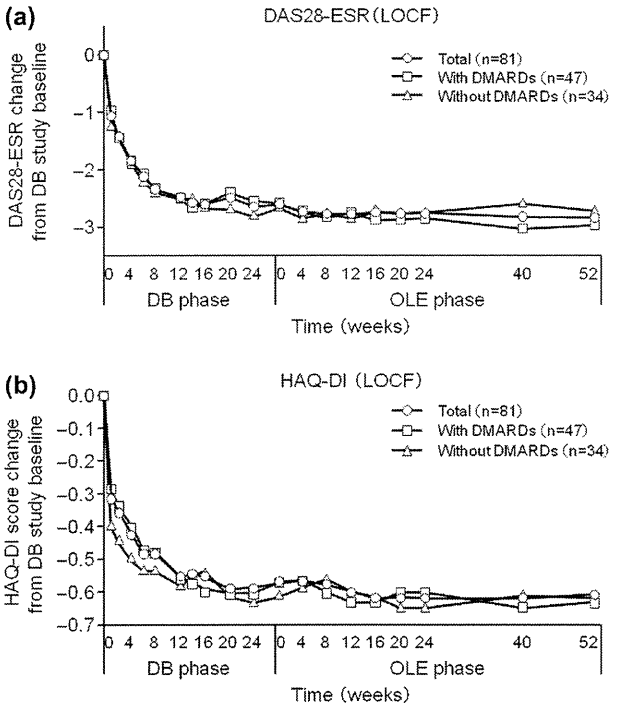

Figure 6. Post-hoc analysis of changes in (a) DAS28-ESR and (b) HAQ-DI scores from HIKARI pre-study baseline in patients from Groups II, III, and IV excluding those who were in the placebo group during the DB phase (CZP-DB completers). The DAS28-ESR and HAQ-DI scores of all CZP-DB completers ($n = 81$), CZP-DB completers treated with additional non-MTX DMARDs ($n = 47$), and CZP-DB completers treated without additional non-MTX DMARDs ($n = 34$) were plotted against time for the DB and the OLE phase of the study (LOCF imputation).

incur further joint destruction, since 69.8% of the patients had a ΔmTSS ≤ 0.5. Therefore, long-term CZP treatment appears to be effective at controlling RA disease progression. The low withdrawal rate (5.8%) of patients from the OLE study due to insufficient response further supports this notion. Importantly, long-term CZP treatment was well-tolerated by patients. No unexpected new AEs were detected in patients treated with long-term CZP compared to those observed in previous clinical studies involving short-term CZP treatment.

Anti-TNFα antibodies other than CZP that are currently in clinical use are full antibodies consisting of an Fc region and an antigen-binding Fab region [18]. In contrast, CZP is a humanized Fab' fragment fused to a 40-kD PEG moiety without an Fc region. One disadvantage of Fab' fragments relates to their shorter *in vivo* half-life due to the hastened clearance of Fab' fragments in the absence of an Fc region. However, the attachment of a PEG moiety to the Fab' fragment has overcome this instability of Fab' fragments and has extended the plasma half-life of CZP to about 2 weeks. Due to the extended half-life, a CZP maintenance dosing schedule with a longer interval is possible. Our data demonstrate that patients treated at Q2W (CZP 200 mg) or Q4W (CZP 400 mg) intervals (Group III vs. Group IV) exhibited similar clinical responsiveness and safety to long-term CZP treatment. This is important as patients and physicians gain the flexibility of choosing between the two different dosing schedules based on their needs. In some patients, a Q4W schedule might decrease the number of doctor visits. In others, a Q2W schedule might be favorable to allow closer monitoring of disease symptoms.

The design of HIKARI-OLE study included patients who were previously on placebo during the DB phase of HIKARI study. To observe the effects of continuous CZP treatment throughout the combined DB and OLE phases of the study (80 weeks), an additional post-hoc analysis was performed on CZP-DB completers who received CZP during the DB phase. Restricting our data analysis to this population clearly showed that long-term CZP treatment sustained the clinical, functional, and radiographic efficacy of CZP against disease, even in the absence of non-MTX DMARDs (CZP monotherapy). Thus, we conclude that long-term treatment for up to 80 weeks is beneficial for a sustained positive response to CZP even when used as monotherapy.

MTX is a critical therapeutic component in the treatment of RA [14,19]. MTX co-treatment is recommended in patients who receive CZP therapy because the development of anti-CZP antibodies is lower in patients that are treated with CZP plus MTX compared to those treated with CZP as monotherapy (data not shown). However, it is not uncommon for patients to be intolerant to MTX therapy. In fact, it is said that ~30% of patients receive biologics as monotherapy in the United States [20,21] and in European countries such as the UK [22]. A recently reported meta-analysis demonstrated that a number of biologics including etanercept, adalimumab, and tocilizumab were effective as monotherapy in improving ACR20/ACR50/ACR70 response rates [23]. With regards to CZP, data from the FAST4WARD study conducted in Europe and the United States showed that CZP monotherapy for 24 weeks effectively reduced the signs and symptoms of active RA in patients [15]. Similarly, the HIKARI DB study conducted on Japanese patients showed that CZP administration without

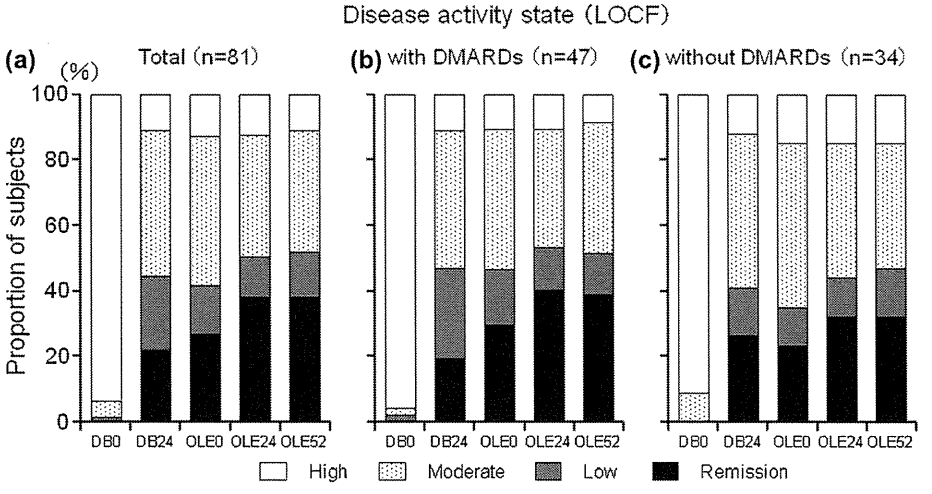

Figure 7. Post-hoc analysis of disease activity states in patients from Groups II, III, and IV excluding those who were in the placebo group during the DB phase (CZP-DB completers). The proportions of patients with high (defined as DAS28-ESR > 5.1), moderate (> 3.2 and ≤ 5.1), low (≤ 3.2), or remission (< 2.6) disease activity states among (a) all CZP-DB completers ($n = 81$), (b) CZP-DB completers treated with additional non-MTX DMARDs ($n = 47$), and (c) CZP-DB completers treated without additional non-MTX DMARDs ($n = 34$) at DB Week 0 (DB0), DB Week 24 (DB24), OLE Week 0 (OLE0), OLE Week 24 (OLE24), and OLE Week 52 (OLE52) are shown (LOCF imputation).

Table 3. Treatment-emergent adverse events.

	Group I CZP 200 mg Q2W ($n = 110$)	Group II CZP 200 mg Q2W ($n = 12$)	Group III CZP 200 mg Q2W ($n = 43$)	Group IV CZP 400 mg Q4W ($n = 43$)	Total (Groups I + II+ III + IV) ($n = 208$)
Any adverse event, *n* (%)*	94 (85.5)	11 (91.7)	36 (83.7)	38 (88.4)	179 (86.1)
Intensity, *n* (%)*					
Mild	37 (33.6)	4 (33.3)	9 (20.9)	21 (48.8)	71 (34.1)
Moderate	49 (44.5)	6 (50.0)	21 (48.8)	13 (30.2)	89 (42.8)
Severe	8 (7.3)	1 (8.3)	6 (14.0)	4 (9.3)	19 (9.1)
Treatment-related[a], *n* (%)*	52 (47.3)	5 (41.7)	21 (48.8)	21 (48.8)	99 (47.6)
Death, *n* (%)*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most common adverse events (≥ 5% in any group), *n* (%)					
Constipation	8 (7.3)	1 (8.3)	2 (4.7)	1 (2.3)	12 (5.8)
Bronchitis	7 (6.4)	0 (0.0)	3 (7.0)	2 (4.7)	12 (5.8)
Herpes zoster	7 (6.4)	0 (0.0)	2 (4.7)	2 (4.7)	11 (5.3)
Nasopharyngitis	21 (19.1)	2 (16.7)	11 (25.6)	13 (30.2)	47 (22.6)
Pharyngitis	8 (7.3)	0 (0.0)	3 (7.0)	3 (7.0)	14 (6.7)
Upper respiratory tract infection	7 (6.4)	0 (0.0)	5 (11.6)	4 (9.3)	16 (7.7)
Rheumatoid arthritis	8 (7.3)	2 (16.7)	4 (9.3)	6 (14.0)	20 (9.6)
Eczema	10 (9.1)	2 (16.7)	5 (11.6)	2 (4.7)	19 (9.1)
Serious adverse events, *n* (%)*	15 (13.6)	2 (16.7)	7 (16.3)	5 (11.6)	29 (13.9)
Serious adverse events (≥ 0.5% in any group), *n* (%)					
Colonic polyp	0 (0.0)	1 (8.3)	1 (2.3)	0 (0.0)	2 (1.0)
Pneumonia	0 (0.0)	1 (8.3)	1 (2.3)	0 (0.0)	2 (1.0)
Arthropathy	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.3)	2 (1.0)
Rheumatoid arthritis	1 (0.9)	0 (0.0)	0 (0.0)	2 (4.7)	3 (1.4)

*Number of patients (%).
[a]Treatment-emergent adverse events for which the relationship to the study drug cannot be ruled out.

MTX (both as monotherapy and in combination with non-MTX DMARDs) significantly relieved RA symptoms and radiographic progression of disease [16]. Our current post-hoc analysis investigated the clinical efficacy of CZP without MTX treatment over a ~80-week period (28 weeks during the DB phase + > 52 weeks during the OLE phase) in CZP-DB completers. Our data support the long-term use of CZP for treatment of RA for sustaining clinical efficacy either as monotherapy or in combination with non-MTX DMARDs.

In summary, our data suggest that continuous CZP treatment provides long-term clinical, functional, and radiographic benefits either as monotherapy or in conjunction with non-MTX DMARDs in Japanese RA patients, who could not receive MTX. Remarkably, the efficacy of CZP is maintained as monotherapy until 80 weeks. Long-term treatment was well-tolerated with no new unexpected AEs observed. Both the Q2W and Q4W dosing schedules of CZP were similarly effective at sustaining the clinical response to CZP. One limitation of our study was that this was an OLE study and therefore was not blinded. However, we still believe that our data still suggest that long-term CZP treatment is beneficial for continued suppression of RA. Thus, we propose that patients who could not receive MTX should undergo continuous long-term treatment of CZP at either a Q2W or Q4W schedule to obtain long-lasting relief from RA symptoms.

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(K. Nagasawa), Oribe Clinic of Rheumatism and Medicine (M. Oribe), Otsuka Clinic of Medicine and Rheumatism (E. Otsuka), Kumamoto Saishunso National Hospital (S. Mori), Kumamoto Orthopaedic Hospital (M. Sakaguchi), Center for Arthritis and Clinical Rheumatology Matsubara Clinic (S. Matsubara), Shimin-No-Mori Hospital (T. Hidaka), and Kagoshima Red Cross Hospital (T. Matsuda).

Conflict of interest

The competing interests of all authors are provided below.

- Y. Tanaka has received research funding from BMS, MSD, Chugai, Mitsubishi-Tanabe, Astellas, Abbvie and Daiichi-Sankyo and has served on speaker bureaus for UCB, Mitsubishi-Tanabe, Abbott, Abbvie, Eisai, Chugai, Janssen, Pfizer, Takeda, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Eli Lilly, Quintiles, MSD and Asahi Kasei.
- K. Yamamoto has served as a consultant for UCB, Pfizer, Abbott, BMS, Roche, Chugai, Mitsubishi-Tanabe and Eisai and has received research funding from UCB, Pfizer, Abbott, Santen, Mitsubishi-Tanabe and Eisai.
- T. Takeuchi has served as a consultant for AstraZeneca, Eli Lilly, Novartis, Mitsubishi-Tanabe and Asahi Kasei, has received research support from Abott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Otsuka, Pfizer, Sanofi-Aventis, Santen, Takeda and Teijin, and has served on speaker bureaus for Abbott, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda.
- H. Yamanaka has served as a consultant for, and received research funding from, UCB, Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda.
- N. Ishiguro has received research funding from Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken and Pfizer and has served on speaker bureaus for Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama and Otsuka.
- K. Eguchi has served as a consultant for UCB.
- A. Watanabe has received research support from Daiichi-Sankyo, Kyorin, Shionogi, Taisho, Dainippon-Sumitomo, Taiho, Toyama Chemical and Meiji Seika and has served on speaker bureaus for MSD, GSK, Shionogi, Daiichi-Sankyo, Taisho-Toyama, Dainippon-Sumitomo, Mitsubishi-Tanabe and Pfizer.
- H. Origasa has served as a consultant for UCB and Astellas.
- T. Shoji is an employee of UCB.
- N. Miyasaka has received research support from Pfizer, Takeda, Mitsubishi-Tanabe, Chugai, Abbott, Eisai and Astellas.
- T. Koike has served on speaker bureaus for UCB, Pfizer, Chugai, Abbott, Mitsubishi-Tanabe, Takeda, Eisai, Santen, Astellas, Taisho-Toyama, BMS, Teijin and Daiichi-Sankyo.

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ORIGINAL ARTICLE

Long-term efficacy and safety of certolizumab pegol in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: 52-week results from an open-label extension of the J-RAPID study

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Abstract

Objectives. To evaluate the long-term efficacy and safety of certolizumab pegol (CZP) plus methotrexate treatment and to assess the efficacy of two CZP maintenance dosing schedules in Japanese rheumatoid arthritis (RA) patients with an inadequate response to methotrexate.

Methods. J-RAPID double-blind patients were entered into an open-label extension (OLE) study. Patients withdrawn due to lack of efficacy at 16 weeks and double-blind completers without a week-24 American College of Rheumatology (ACR) 20 response received CZP 200 mg every other week (Q2W) plus methotrexate. Double-blind completers with week-24 ACR20 responses were randomized to CZP 200 mg Q2W plus methotrexate or CZP 400 mg every 4 weeks plus methotrexate.

Results. The ACR20/ACR50/ACR70 response rates of double-blind completers ($n = 204$) were 89.7%/67.2%/36.3% at OLE entry and 95.6%/84.8%/58.3% at 52 weeks, respectively. Other clinical, functional and radiographic outcomes were sustained with long-term CZP plus methotrexate. Long-term treatment with CZP was well-tolerated with no new unexpected adverse events observed. The efficacy and safety of CZP treatment were similar between the two dosing schedules.

Conclusions. Continued CZP administration with methotrexate maintained efficacy over 52 weeks and was well-tolerated for Japanese RA patients. No obvious differences in clinical efficacy and safety were observed between the two dosing schedules, giving flexibility in maintenance administration schedules.

Keywords

Certolizumab pegol, Clinical study, Rheumatoid arthritis, TNFα, TNF inhibitor

History

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Introduction

TNFα plays a central role in the pathogenesis of rheumatoid arthritis (RA). After the introduction of TNF inhibitors in clinical practice, the management of RA has dramatically changed [1,2]. Early initiation of TNF inhibitors is beneficial not only because they improve the signs and symptoms of RA, but also because they improve physical function and inhibit structural damage, particularly when used in combination with methotrexate (MTX) [3–5]. TNF inhibitors control RA symptoms and suppress functional and structural damages in the long-term, resulting in improved overall outcomes for RA patients [6,7].

In Japan, four TNF inhibitors (infliximab, adalimumab, etanercept and golimumab) have been introduced in clinical practice over the last 10 years [8]. As a relatively new member of the TNFα inhibitor family, certolizumab pegol (CZP) was developed as a novel polyethylene glycolylated (PEG) Fc-free anti-TNFα agent [9,10] and is approved for the treatment of adults suffering from RA not responding to conventional therapy. The efficacy and safety of CZP has been demonstrated in patients with active RA in pivotal international clinical studies [11,12]. In addition, CZP has been shown to improve the signs and symptoms of RA, and decrease disease activity in J-RAPID (concomitant use with MTX) [13] and HIKARI (without MTX) studies performed in Japan [14].

Long-term administration of CZP plus MTX has been previously reported [15], where sustained improvement in RA

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clinical signs and symptoms including radiographic progression and safety was shown. The aim of the current study was to determine whether the beneficial effects of CZP are sustained during long-term treatment in Japanese RA patients who showed an inadequate response to MTX treatment. To evaluate the long-term efficacy and safety of CZP treatment, we conducted an open-label extension (OLE) study of the J-RAPID study. As a subsidiary objective, we also compared the efficacy of two separate maintenance dosing schedules, CZP 200 mg given every 2 weeks (Q2W) and CZP 400 mg given every 4 weeks (Q4W). We hereby report the 52-week interim results and post-hoc analysis from the ongoing J-RAPID OLE study.

Materials and methods

J-RAPID and J-RAPID OLE study design

The J-RAPID OLE study (NCT00851318) is an OLE study of the J-RAPID study (NCT00791999) [13]. In brief, the J-RAPID study [hereinafter referred to as "double-blind (DB) phase"] was a 24-week, Phase II/III, DB study conducted in 66 centers across Japan. Eligible patients were aged from 20 to 74 years and had a diagnosis of RA by the ACR (1987) criteria [16] with at least nine tender and nine swollen joints at screening and baseline. Moreover, the patients must have met at least one of the following criteria at screening: erythrocyte sedimentation rate (ESR) of ≥ 30 mm/hour or C-reactive protein (CRP) of ≥ 1.5 mg/dL. Patients must have received treatment with MTX (with or without folic acid) for ≥ 6 months before study drug administration, with the MTX dose fixed for ≥ 2 months beforehand and within the range of 6–8 mg/week. Patients with extensive comorbidities were excluded from the study. Refer to [13] for detailed inclusion and exclusion criteria of the J-RAPID study. Japanese patients with active RA and an inadequate response to MTX received either CZP or placebo while continuing to receive stable doses of MTX. In the DB phase, the subjects were randomly assigned 1:1:1:1 into four groups: subcutaneous CZP 100, 200 or 400 mg plus MTX, or placebo (saline) plus MTX, every 2 weeks. Patients randomized to CZP plus MTX received induction doses of 200 mg (100 mg group) or 400 mg (200 and 400 mg groups) at weeks 0, 2 and 4. All patients continued to receive MTX at the same dosage taken at DB phase entry (6–8 mg/week). The primary endpoint of this study was an ACR20 response at week 12.

The J-RAPID OLE study was conducted between April 1, 2009 and August 22, 2011. In the OLE phase, we divided J-RAPID DB phase patients into four groups based on responses to treatment during the DB phase. Patients who did not achieve an ACR20 response at both weeks 12 and 14 were withdrawn from the DB phase at week 16, assigned to Group I ($n = 81$) and treated with CZP 200 mg Q2W plus MTX thereafter. Patients who exhibited an ACR20 response at weeks 12 or 14 but failed to achieve an ACR20 response at week 24 were assigned to Group II ($n = 19$) and also received CZP 200 mg Q2W plus MTX. Patients who achieved an ACR20 response at week 12 or 14 as well as at week 24 were randomized 1:1 to either CZP 200 mg Q2W plus MTX (Group III, $n = 93$) or CZP 400 mg Q4W plus MTX (Group IV, $n = 92$) (Figure 1). Of importance, we established this dosing schedule so that the total dose received by patients in Groups III and IV over a 1-month period was the same.

Week 0 of the OLE phase of Groups II, III and IV (J-RAPID DB phase completers: hereinafter referred to as DB completers) corresponds to week 28 of the DB phase and week 0 of the OLE phase of Group I (early escape) corresponds to week 16 of the DB phase. Patients assigned to the placebo group during the DB phase were also included in this OLE study. Discontinuation of concomitant MTX was not permitted during the OLE phase up to week 52. A change in MTX dosage was permitted after week 24 of the OLE phase, if it was not greater than the original dose (6–8 mg/week).

The outcome of the study was the measurement of continuous efficacy and safety monitoring during long-term treatment with CZP plus MTX. Efficacy outcomes included ACR20 response rates, and changes in Health Assessment Questionnaire Disability Index (HAQ-DI), Disease Activity Score in 28 Joints-Erythrocyte Sedimentation Rate (DAS28-ESR), the Short Form-36 Health Survey (SF-36) and Pain Visual Analog Scale (VAS) from J-RAPID pre-study baseline. In addition, to measure radiographic disease progression, changes in the modified Total Sharp Score (mTSS) from OLE study entry was assessed by linear extrapolation. Comprehensive disease control (CDC) was defined by the simultaneous achievement of the following three criteria: low disease activity

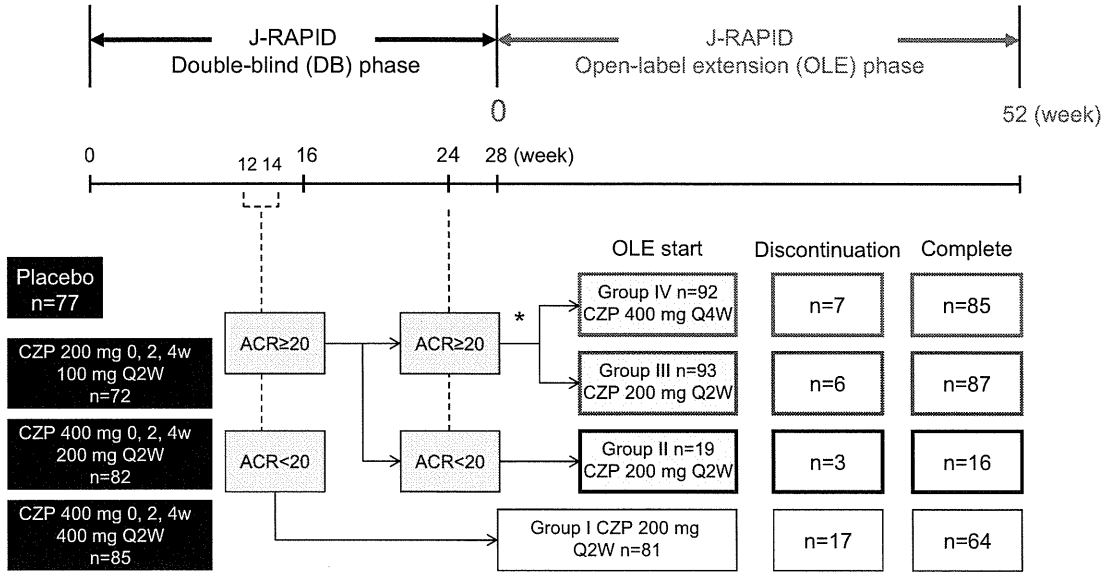


Figure 1. J-RAPID OLE study design. The diagram depicts the breakdown of J-RAPID DB study patients into four groups for the OLE phase of the study. *Regardless of their initial DB phase group assignment, patients who achieved an ACR20 response at weeks 12 or 14 as well as at week 24 were randomized (1:1) to either CZP 200 mg Q2W (Group III, $n = 93$) or CZP 400 mg Q4W (Group IV, $n = 92$).

(DAS28-ESR ≤ 3.2), functional remission (HAQ-DI ≤ 0.5) and radiographic non-progression (yearly ΔmTSS ≤ 0.5). Similarly, comprehensive disease remission (CDR) was defined by simultaneously achieving the following: clinical remission (DAS28-ESR < 2.6), functional remission (HAQ-DI ≤ 0.5) and radiographic non-progression (yearly ΔmTSS ≤ 0.5). To calculate CDC and CDR for overall DB completers ($n = 204$), yearly ΔmTSS from J-RAPID pre-study baseline (linear extrapolation, with non-responder imputation for patients with no data) was used. Safety outcomes were reported for all patients who received at least one dose of CZP in the OLE study ($n = 285$).

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with the Pharmaceutical Affairs Law Standards for the Conduct of Clinical Trials on Drugs (Ministry of Health, Labour and Welfare Ordinance no. 28, 27 March 1997) and related notifications. Institutional review board approval was obtained at all centers and all patients provided written informed consent.

Post-hoc analyses

Since the OLE study included patients who received placebo during the J-RAPID DB phase, an additional post-hoc analysis of clinical efficacy was performed on patients who received CZP in the DB phase, to observe the effects of continuous CZP treatment during the combined DB and OLE phases of the study. This data set includes patients who were originally assigned to CZP 100, 200 and 400 mg treatment groups in the DB phase and completed the DB phase (CZP-DB completers). We focused on ACR20/ACR50/ACR70 response rates, DAS28-ESR scores, HAQ-DI scores and the disease activity state (high: DAS28-ESR > 5.1, moderate: > 3.2 and ≤ 5.1, low disease activity (LDA): ≤ 3.2 and remission: < 2.6) in this post-hoc analysis.

Statistical analyses

The efficacy analysis was performed on the full-analysis set (FAS) using the last observation carried forward (LOCF) to impute missing data. We used J-RAPID pre-study parameters as baseline values. Safety analyses were performed on all subjects who received at least one dose of CZP during the OLE study. Because the objective of the study was to evaluate the long-term efficacy and safety of CZP treatment, inferential analyses were not performed.

Results

Patient characteristics and disposition of the J-RAPID OLE study

We obtained informed consent from 286 J-RAPID DB phase patients to enter the OLE study. Because one patient withdrew from the OLE study before receiving CZP treatment, a total of 285 patients were included in the efficacy and safety analyses. During the 52-week treatment, an additional 33 patients withdrew from the study resulting in a total of 252 patients (88.4%) completing the 52-week interim period of the OLE study. A few patients (2.5%) withdrew from the study due to an inadequate response (Table 1). All reasons for study withdrawal are listed in Table 1.

A summary of patient demographics and J-RAPID pre-study baseline characteristics is shown in Table 2. Patients were divided into four groups in the OLE phase based on their response during the DB phase. It was important to distinguish patients with an ACR20 response at week 24 of the DB phase (DB responders: Groups III and IV) and DB non-responders (Groups I and II) to evaluate the sustained efficacy of continued long-term CZP treatment. As shown in Table 2, all of these groups included patients who were on placebo during the DB phase. The fraction of patients that received placebo during the DB phase was 55.6% (45 patients), 31.6% (6 patients), 10.8% (10 patients) and 9.8% (9 patients) in Groups I, II, III and IV, respectively. DB responders were further divided into two groups to evaluate the efficacy of two different dosing regimens. DB responder patients ($n = 185$) were randomized to either CZP 200 mg Q2W (Group III, $n = 93$: 83 CZP patients, 10 placebo patients) or CZP 400 mg Q4W (Group IV, $n = 92$: 83 CZP patients, 9 placebo patients) as shown in Table 2. At OLE study entry (OLE week-0), the mean DAS28-ESR scores of Groups I, II, III and IV were 6.08, 5.12, 3.22 and 3.20, respectively.

Clinical efficacy is sustained by long-term CZP plus MTX treatment

The J-RAPID OLE study was designed to evaluate whether the benefits obtained after short-term CZP plus MTX treatment could be sustained by prolonged treatment. To this end, we analyzed the outcomes of Groups I, II, III, IV and overall DB completers (Groups II + III + IV) after up to 52 weeks of long-term CZP treatment in the OLE phase. ACR20/ACR50/ACR70 response rates, calculated from the J-RAPID pre-study baseline, were increased or sustained for up to 52 weeks in the OLE phase. At OLE study entry and at 52 weeks of the OLE phase, the ACR20 response rates were 7.5% and 76.5% for Group I, 36.8% and 84.2% for Group II, 95.7% and 98.9% for Group III, and 94.6% and 94.6% for Group IV, respectively (Figure 2a). The ACR50 response rates were 0% and 48.1% for Group I, 0% and 57.9% for Group II, 77.4% and 87.1% for Group III, and 70.7% and 88% for Group IV, respectively (Figure 2b). The ACR70 response rates were 0% and 30.9% for Group I, 0% and 31.6% for Group II, 39.8% and 64.5% for Group III, and 40.2% and 57.6% for Group IV, respectively (Figure 2c). For overall DB completers

Table 1. Reasons for discontinuation of therapy.

Subject disposition	Group I CZP 200 mg Q2W	Group II CZP 200 mg Q2W	Group III CZP 200 mg Q2W	Group IV CZP 400 mg Q4W	Total (Groups I + II + III + IV)
Number of subjects, n (%)*	81 (100.0)	19 (100.0)	93 (100.0)	92 (100.0)	285 (100.0)
Subjects withdrawn before week 52, n (%)*	17 (21.0)	3 (15.8)	6 (6.5)	7 (7.6)	33 (11.6)
Reason for withdrawal					
Subject's request	3 (3.7)	1 (5.3)	1 (1.1)	1 (1.1)	6 (2.1)
Violation of inclusion/exclusion criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	7 (8.6)	1 (5.3)	2 (2.2)	5 (5.4)	15 (5.3)
Pregnancy	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	2 (0.7)
Inadequate response	5 (6.2)	1 (5.3)	1 (1.1)	0 (0.0)	7 (2.5)
Compliance with protocol not possible, for reason other than those above	2 (2.5)	0 (0.0)	1 (1.1)	0 (0.0)	3 (1.1)
Investigator's judgment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Number of patients (%).

Table 2. Patient demographics and disease status at J-RAPID pre-study baseline (FAS population).

	Group I CZP 200 mg Q2W ($n = 81$)	Group II CZP 200 mg Q2W ($n = 19$)	Group III CZP 200 mg Q2W ($n = 93$)	Group IV CZP 400 mg Q4W ($n = 92$)	Total (Groups I + II+ III + IV) ($n = 285$)
Prior treatment in the double-blind phase, n (%)*					
Placebo	45 (55.6)	6 (31.6)	10 (10.8)	9 (9.8)	70 (24.6)
CZP 100 mg	14 (17.3)	5 (26.3)	22 (23.7)	24 (26.1)	65 (22.8)
CZP 200 mg	11 (13.6)	5 (26.3)	29 (31.2)	29 (31.5)	74 (26.0)
CZP 400 mg	11 (13.6)	3 (15.8)	32 (34.4)	30 (32.6)	76 (26.7)
Mean age (SD), years	51.8 (10.7)	51.3 (13.7)	52.9 (11.0)	54.1 (11.0)	52.8 (11.1)
Female, n (%)*	67 (82.7)	16 (84.2)	76 (81.7)	77 (83.7)	236 (82.8)
Mean body weight (SD), kg	56.30 (12.00)	54.27 (9.57)	55.81 (11.34)	54.92 (9.47)	55.56 (10.83)
Mean disease duration (SD), years	5.74 (3.94)	5.44 (3.78)	5.94 (4.18)	6.00 (4.16)	5.87 (4.06)
Mean no. of prior DMARDs (SD), excluding MTX	0.8 (0.9)	0.9 (1.0)	0.6 (0.7)	0.5 (0.7)	0.6 (0.8)
Prior TNF inhibitor use, n (%)*	21 (25.9)	4 (21.1)	10 (10.8)	7 (7.6)	42 (14.7)
Mean MTX dose (SD), mg/week	7.5 (0.9)	7.9 (0.5)	7.5 (0.8)	7.5 (0.9)	7.5 (0.8)
RF-positive (≥ 14 IU/mL), n (%)*	73 (90.1)	16 (84.2)	79 (84.9)	83 (90.2)	251 (88.1)
Mean no. (SD) of tender joints (0–68)	21.1 (10.1)	18.4 (11.6)	20.2 (11.7)	18.6 (8.8)	19.8 (10.4)
Mean no. (SD) of swollen joints (0–66)	18.2 (9.2)	17.2 (10.9)	16.3 (8.0)	16.8 (7.9)	17.1 (8.5)
Mean CRP (SD), mg/dL	2.68 (2.40)	2.40 (2.16)	2.03 (1.87)	2.17 (2.13)	2.28 (2.14)
Mean ESR (SD), mm/h	53.6 (24.1)	58.0 (21.3)	49.8 (23.2)	51.5 (21.8)	52.0 (22.9)
DAS28 (ESR)					
Mean (SD)	6.52 (0.77)	6.37 (0.73)	6.22 (0.81)	6.21 (0.83)	
< 3.2, n (%)*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3.2–5.1, n (%)*	0 (0.0)	1 (5.3)	4 (4.3)	10 (10.9)	15 (5.3)
> 5.1, n (%)*	81 (100.0)	18 (94.7)	89 (95.7)	82 (89.1)	270 (94.7)
HAQ-DI (SD)	1.23 (0.66)	1.03 (0.63)	1.08 (0.63)	1.04 (0.60)	1.11 (0.63)
Mean total mTSS (SD)	46.73 (52.61)	60.41 (46.53)	56.79 (62.23)	53.52 (52.20)	53.10 (55.35)

CRP, C-reactive protein; CZP, certolizumab pegol; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire – Disability Index; mTSS, modified Total Sharp Score; MTX, methotrexate; RF, rheumatoid factor; SD, standard deviation.
*Number of patients (%).

(Groups II + III + IV), at OLE study entry and at 52 weeks of the OLE phase, the ACR20 response rates were 89.7% and 95.6%, the ACR50 response rates were 67.2% and 84.8%, and the ACR70 response rates were 36.3% and 58.3%, respectively (Figure 2). A marked improvement in DAS28-ESR was also sustained for up to 52 weeks of the OLE phase for overall DB completers (Figure 3a). DAS28-ESR remission rates (defined as DAS28-ESR < 2.6) for overall DB completers were 28.4% and 42.6% at OLE study entry and 52 weeks of the OLE phase, respectively.

Improvements in quality of life indicators including HAQ-DI (Figure 3b) and SF-36 were maintained by long-term CZP treatment. The HAQ-DI remission rates (defined as HAQ-DI ≤ 0.5) for overall DB completers were 66.7% and 77.5% at OLE entry and at 52 weeks of the OLE phase, respectively, indicating that most patients achieved functional remission. The mean ± SD changes of SF-36 scores from J-RAPID pre-study baseline at OLE study entry and at week 52 were 11.93 ± 10.03 and 13.60 ± 10.54 in physical component summary scores and 5.56 ± 11.07 and 5.21 ± 11.17 in mental component summary scores, respectively. In fact, an individual assessment of all eight domains of the SF-36 revealed sustained improvement in each component of the SF-36 score (data not shown). Moreover, the 100 mm pain VAS improvement was maintained, with a mean ± SD change from J-RAPID pre-study baseline of − 33.8 ± 22.1 at OLE study entry and − 39.2 ± 23.2 at 52 weeks of the OLE phase.

In addition to signs and symptoms, and patient-reported outcomes, changes from OLE study entry in mTSS (ΔmTSS) were assessed. The mean ± SD and median ΔmTSS at week 52 were 1.15 ± 4.80 and 0.00 in DB completers, respectively (Figure 4). At week 52, 68.3% of DB completers displayed radiographic non-progression, that is a ΔmTSS ≤ 0.5.

The proportion of DB completers achieving comprehensive disease control (CDC: i.e. DAS28-ESR ≤ 3.2, HAQ-DI ≤ 0.5, and ΔmTSS ≤ 0.5) at OLE study entry and at 52 weeks was 25.5% and 35.8%, respectively. The proportion of DB completers achieving comprehensive disease remission (CDR: i.e. DAS28-ESR < 2.6, HAQ-DI ≤ 0.5, and ΔmTSS ≤ 0.5) at OLE study entry and at 52 weeks was 17.2% and 26.0%, respectively. Together, these data suggest that the clinical, functional and radiographic benefits obtained after short-term CZP treatment are sustained by long-term treatment with CZP.

The two dosing schedules (CZP at 200 mg Q2W vs. 400 mg Q4W) combined with MTX similarly sustain the clinical efficacy of CZP

In both randomized arms (Groups III and IV), the high ACR20/ACR50/ACR70 rates and the high changes from J-RAPID pre-study baseline in DAS28-ESR and HAQ-DI scores were sustained through 52 weeks of the OLE phase (Figures 2 and 3). For example, the ACR20 response rates at OLE study entry and at 52 weeks of the OLE phase were 95.7% and 98.9% for Group III and 94.6% and 94.6% for Group IV, respectively (Figure 2a). In addition to clinical parameters, the ΔmTSS from OLE study entry between the two dosing regimens were similar throughout the OLE study (Figure 4). At week 52, 69.0% and 67.5% of patients had a ΔmTSS ≤ 0.5 in Groups III and IV, respectively, suggesting that both regimens were similarly effective at inhibiting radiographic progression. Thus, both CZP maintenance regimens similarly sustained clinical efficacy of CZP during the OLE study phase.

Assessment of sustained clinical efficacy of combined long-term CZP plus MTX treatment by a post-hoc analysis through the DB and OLE phase

Since all arms of the OLE protocol (Groups I, II, II and IV) included patients who were originally randomized to the placebo group during the DB phase (Table 2), a post-hoc analysis was performed only on data from patients who were originally assigned to one of the CZP treatment groups in the DB phase and completed the DB phase with an ACR20 response at week 12 or 14 (CZP-DB completers). This was an important analysis to observe the effects

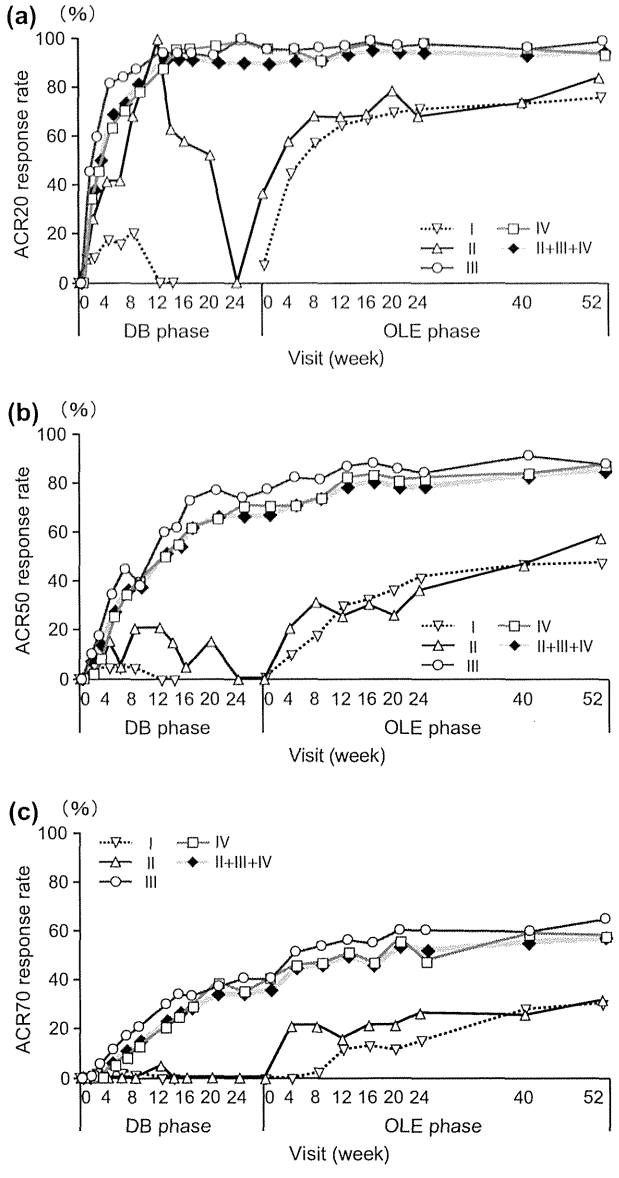


Figure 2. The ACR20/ACR50/ACR70 response rates in patients from each treatment group. The percentages of patients in Groups I ($n = 81$), II ($n = 19$), III ($n = 93$), IV ($n = 92$) and patients in Groups II + III+IV combined (DB completers, $n = 204$) who achieved an (a) ACR20, (b) ACR50, or (c) ACR70 response were plotted over time for the DB and the OLE phase of the study (FAS population, LOCF imputation). Of note, week 0 of the OLE phase of Group I (early escape) corresponds to week 16 of the DB phase. There are no points in the missing section of the graph for Group I.

of continuous CZP treatment during the DB and OLE phases of the study. In this post-hoc analysis, we focused on ACR20/ACR50/ACR70 response rates, DAS28-ESR scores, HAQ-DI scores and the disease activity state (LDA and remission). The efficacy results are summarized in Figures 5–7 for the patients who were originally randomized to either CZP 100, 200 or 400 mg in the DB phase and received either CZP 200 mg Q2W + MTX (Groups II and III) or CZP 400 mg Q4W + MTX (Group IV) in the OLE phase.

The ACR20/ACR50/ACR70 response rates in CZP-DB completers were sustained with long-term CZP treatment up to week 52 compared with OLE study entry (Figure 5). For example, 87.3% (55/63) of CZP-DB completers receiving 200 mg CZP during the DB phase continued treatment with CZP to 52 weeks of the OLE phase, with the ACR20/ACR50/ACR70 response rates of 96.8%/88.9%/49.2% at week 52, respectively (Figure 5).

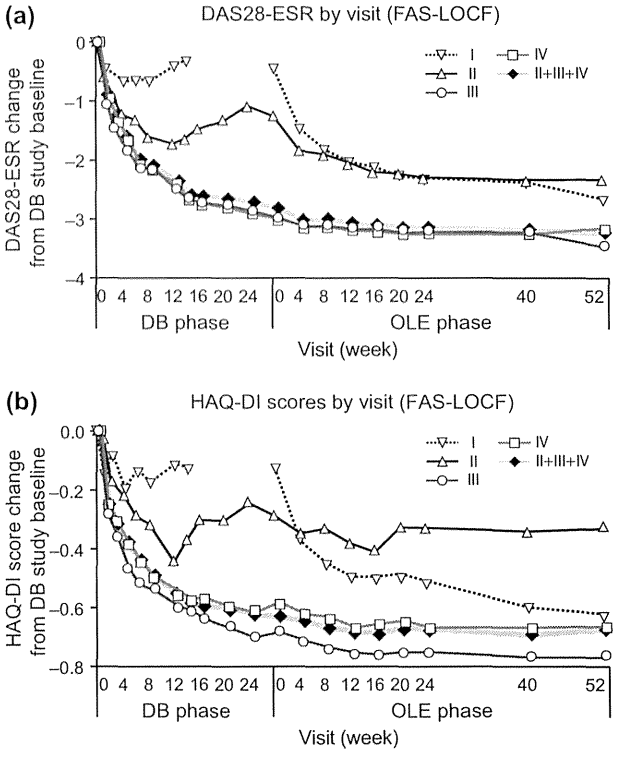
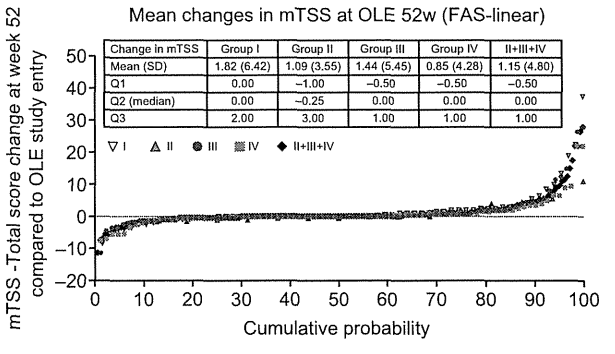


Figure 3. The changes of DAS28-ESR and HAQ-DI over J-RAPID pre-study baseline in patients from each treatment group. Changes in (a) DAS28-ESR and (b) HAQ-DI from J-RAPID pre-study baseline of Groups I ($n = 81$), II ($n = 19$), III ($n = 93$), IV ($n = 92$) and patients in Groups II + III+IV combined (DB completers, $n = 204$) were plotted against time for the DB and the OLE phase of the study (FAS population, LOCF imputation). Of note, week 0 of the OLE phase of Group I (early escape) corresponds to week 16 of the DB phase. There are no points in the missing section of the graph for Group I.

Moreover, the mean changes in DAS28-ESR scores and HAQ-DI scores, from J-RAPID pre-study baseline, were also sustained up to 52 weeks of the OLE phase (Figure 6a, b). Furthermore, the analysis of disease activity states demonstrated that both LDA and remission rates (defined as DAS28-ESR ≤ 3.2 and < 2.6, respectively) were sustained during the 52-week period of the OLE phase. The proportion of patients who were in LDA and remission (DAS28-ESR ≤ 3.2) was 47.1%, 52.4% and 57.0% at OLE entry, and 54.9%, 61.9% and 61.5% at week 52, in CZP-DB completers receiving 100, 200 and 400 mg CZP during the



Change in mTSS	Group I	Group II	Group III	Group IV	II+III+IV
Mean (SD)	1.82 (6.42)	1.09 (3.55)	1.44 (5.45)	0.85 (4.28)	1.15 (4.80)
Q1	0.00	−1.00	−0.50	−0.50	−0.50
Q2 (median)	0.00	−0.25	0.00	0.00	0.00
Q3	2.00	3.00	1.00	1.00	1.00

Figure 4. Inhibition of progression of structural damage: cumulative probability plot representing the change from OLE study entry in mTSS at week 52 (FAS population, linear extrapolation). The graph depicts the cumulative probability of patients displaying a particular change in mTSS from OLE study entry in Groups I ($n = 67$), II ($n = 16$), III ($n = 87$), IV ($n = 83$) and patients in Groups II + III+IV combined (DB completers, $n = 186$).