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ORIGINAL ARTICLE

Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: The HIKARI randomized, placebo-controlled trial

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Abstract

Objective. This 24-week, placebo-controlled, double-blind, randomized study (NCT00791921) investigated efficacy and safety of certolizumab pegol (CZP) in Japanese rheumatoid arthritis (RA) patients in whom methotrexate (MTX) cannot be administered.

Methods. A total of 230 patients were randomized to subcutaneous CZP 200 mg (induction dosing: 400 mg at Weeks 0, 2 and 4) or placebo every 2 weeks.

Results. ACR20 responses with CZP were rapid and significant versus placebo at Week 1, sustained to Week 12 (67.2% vs. 14.9%) and Week 24 (63.8% vs. 11.4%). Week 24-modified Total Sharp Score (mTSS) change from baseline (CFB) was 0.48 (CZP) versus 2.45 (placebo). CZP treatment was associated with higher Week 12 ACR20 responses versus placebo (with non-MTX disease modifying antirheumatic drugs [DMARDs], 74.2% vs. 20.0%; without [monotherapy], 59.3% vs. 8.2%) and inhibition of radiographic progression at Week 24 (mTSS CFB; with non-MTX DMARDs, 0.24 vs. 1.61; monotherapy, 0.68 vs. 3.65). Incidences of serious adverse events were 11.2% (CZP) and 2.6% (placebo); one CZP patient died of dissecting aortic aneurysm.

Conclusion. CZP treatment with and without non-MTX DMARDs in Japanese patients in whom MTX cannot be administered resulted in rapid, sustained reductions in RA signs and symptoms. Notably, CZP monotherapy showed significant inhibition of radiographic progression.

Keywords

Certolizumab pegol, Monotherapy, Randomized controlled trial, Rheumatoid arthritis, Tumor necrosis factor-alpha inhibitor

History

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Introduction

The efficacy of inhibiting tumor necrosis factor alpha (TNF- α) in the management of rheumatoid arthritis (RA) has been demonstrated in both Japanese and non-Japanese patients [1–8].

Certolizumab pegol (CZP) is a PEGylated Fc-free anti-TNF- α agent. The efficacy of CZP plus methotrexate (MTX) has previously been demonstrated in patients with active RA who did not respond adequately to disease-modifying antirheumatic drugs (DMARDs) including MTX in the RAPID 1 and RAPID 2 studies [5,6]. Treatment with CZP plus MTX has also shown a rapid

reduction of RA signs and symptoms and inhibition of structural joint damage in Japanese patients with active RA who had an inadequate response to MTX [Yamamoto et al. 2013].

However, MTX cannot be administered in all patients due to lack of efficacy, tolerability concerns or contraindications related to its antimetabolite action [9]. The efficacy of CZP treatment without concomitant DMARDs (i.e. monotherapy) for non-Japanese patients with active RA who had failed to respond to DMARDs has been demonstrated in the FAST4WARD trial [10].

The objective of the HIKARI study was to investigate the efficacy and safety of CZP 200 mg every 2 weeks (Q2W) in Japanese patients with active RA in whom MTX cannot be administered.

Materials and methods

Study overview

HIKARI was a 24-week, phase 3, multicenter, double-blind, randomized placebo-controlled study (NCT00791921) conducted

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between 19 November 2008 and 16 September 2010 in 66 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.

Patients were randomized 1:1 to subcutaneous CZP 200 mg or saline placebo Q2W after a 1–4 week screening period. Block randomization was used to allocate participants to treatment arms. The random allocation sequence was generated using uniform random numbers from SAS® RANUNI function. The study drug allocation center was responsible for preparation and storage of the randomization table, study drug allocation and confirmation of indistinguishability of study drugs, while the registration center was responsible for assignment of study drug numbers to patients. Patients randomized to CZP received 400 mg induction doses at Weeks 0, 2 and 4. Patients randomized to placebo received an equivalent injection regimen. Study drug administration was performed by non-blinded personnel who were not allowed to engage in other study activities.

Patients who did not achieve an ACR20 response (i.e. $\geq 20\%$ improvement according to American College of Rheumatology [ACR] criteria [11]) at Weeks 12 and 14 (ACR20 non-responders) were withdrawn at Week 16 and were eligible to enter an open-label extension (OLE) study thereafter.

The study was carried out in accordance with the Declaration of Helsinki and 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 written informed consent provided by all patients.

Patients

Eligible patients were aged 20–74 years and had a diagnosis of adult-onset RA as defined by ACR criteria of 0.5–15 years' disease duration [12]. Patients unable to receive MTX therapy due to prior insufficient efficacy or safety concerns were eligible to enter this study; MTX treatment must have been terminated ≥ 28 days prior to study entry. Patients must have failed treatment with, or been resistant to, ≥ 1 prior DMARDs (including MTX). Active disease was defined as ≥ 6 tender joints (68 joints evaluated) and ≥ 6 swollen joints (66 joints evaluated) at screening and baseline, and at least one of either erythrocyte sedimentation rate (ESR) ≥ 28 mm/h or C-reactive protein (CRP) ≥ 2.0 mg/dL.

Non-MTX DMARDs were permitted provided that doses were fixed from ≥ 28 days before study drug administration to the end of the trial. Other permitted drugs were: non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors at doses that were stable for ≥ 14 days before study entry; sedatives; influenza and pneumococcus vaccines (all other live or attenuated vaccines were prohibited); one dose of intramuscular or intra-articular corticosteroid up to 8 weeks after study commencement; and oral corticosteroids (up to 10 mg/day prednisone equivalent).

Patients with inflammatory arthritis other than RA were excluded. Other exclusion criteria included previous treatment with biologic DMARDs in the 6 months preceding the study (3 months for etanercept); any investigational drug in the preceding 3 months; ≥ 2 TNF inhibitors; and failure to respond to previous TNF inhibitor therapy in the initial phase. Those patients who had displayed severe hypersensitivity or anaphylactic reaction to previous biologic DMARDs were excluded. Azathioprine and cyclosporine were not permitted in the 28 days prior to the start of trial drug administration and they, along with intravenous corticosteroids and intra-articular hyaluronic acid, were prohibited throughout the study.

Patients with any indication of current or past tuberculosis (by clinical history, chest X-ray and/or positive tuberculin reaction test) were excluded unless preventive therapy by isoniazid was taken.

Study assessments

Efficacy assessments were carried out over the 24-week treatment period as follows: at baseline, Weeks 1, 2, 4, 6, 8, 12, 14, 16, 20 and 24 or time of discontinuation. Safety was assessed at every visit and at 12-week follow-up. Patients not proceeding to the OLE underwent a further follow-up examination 12 weeks after final dose.

The primary efficacy endpoint was ACR20 response rate at Week 12. The secondary efficacy endpoint was ACR20 response rate at Week 24.

Additional endpoints included: ACR20 response at other time points; ACR50 and ACR70 response rates; ACR core component scores: number of tender and swollen joints, assessment of physical function by the Health Assessment Questionnaire Disability Index (HAQ-DI), patient's and physician's global assessment of disease activity (100 mm visual analog scale [VAS]), patient assessment of arthritic pain (VAS), CRP and ESR; prevention of progression of joint destruction (change in modified Total Sharp Score [mTSS]) at Week 24; duration of morning stiffness; Disease Activity Score 28-joint assessment with ESR (DAS28[ESR]) and European League Against Rheumatism (EULAR) response [13].

The structural integrity of the joints was assessed using the van der mTSS [14,15]. Radiographs of hands and feet at baseline and Week 24 or discontinuation were independently and blindly assessed by two experienced readers. Joint erosion was assessed in 44 joints and joint space narrowing (JSN) in 42 joints, and mean scores across readers were used for analysis. Erosions and JSN were summed to obtain mTSS, and mTSS non-progression was defined as change from baseline (CFB) in mTSS ≤ 0.5 units.

Health-related quality-of-life (HRQoL) was assessed at baseline, Weeks 12 and 24 using the Short Form-36 Health Survey (SF-36) [16].

Post-hoc analyses on patients receiving either CZP monotherapy or CZP with concomitant non-MTX DMARDs were performed to examine the effect on ACR20 response rates at Week 12 and on radiographic progression at Week 24.

Plasma samples were analyzed for determination of CZP concentration, and anti-CZP antibodies were also measured at every visit to Week 8, then at Weeks 12 and 24 or at the time of discontinuation. Safety assessments included adverse events (AEs), laboratory findings, body weight and vital signs. Serious AEs (SAEs) were those that resulted in death, were life-threatening, required or prolonged hospitalization, or resulted in significant disability, incapacity or congenital anomalies/birth defects.

Statistical analysis

Sample size was based on previous clinical experience in monotherapy trials with an expected 20% ACR20 response in the placebo group and $\geq 42\%$ in the CZP group. A projected 91 patients were needed in each group to detect superiority of CZP 200 mg over placebo with 90% power at a two-sided significance level of 0.05. The target number of patients was 200 (full analysis set [FAS]), 100 patients per group, to allow for dropouts.

The primary population for efficacy analysis was the FAS of patients who received ≥ 1 study drug dose and provided ≥ 1 efficacy data thereafter. The safety population contained all patients who received ≥ 1 study drug dose.

ACR responses were determined using non-responder imputation (NRI). Patients who violated study protocol, received rescue medication or withdrew for any reason were considered non-responders from that time point.

ACR intergroup comparisons between CZP and placebo groups were carried out using logistic regression analysis, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Changes in ACR core components and in total tender and swollen joint counts between baseline and Week 24 were examined using analysis of covariance (ANCOVA) with baseline value as covariate and last observation carried forward (LOCF) imputation for missing data. Changes from baseline to the assessment time point for DAS28(ESR), SF-36 and duration of morning stiffness were analyzed using ANCOVA (LOCF) with treatment group as a factor and baseline value as covariate. For EULAR response (good, moderate or no response), intergroup comparisons using logistic regression at each time point were conducted using LOCF imputation.

For radiographic outcomes, in patients in whom administration was discontinued before Week 24, Week 24 values were estimated employing linear extrapolation using values obtained at the discontinuation visit. To examine change in rank from baseline, ANCOVA was performed using rank of baseline mTSS as covariate and treatment as a factor.

Treatment-emergent AEs (TEAEs) included all events from after administration of study drug until the last evaluation visit (not including the safety follow-up visit). TEAEs were coded by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) terminology (v11.1).

Results

Patient characteristics and disposition

A total of 230 patients (FAS) with active RA, 63.5% of which experienced safety problems or had safety concerns with MTX use, entered this study and were randomized to CZP 200 mg ($n = 116$) or placebo ($n = 114$). Fewer patients treated with CZP ($n = 24$) than placebo ($n = 88$) withdrew because of insufficient efficacy at Week 16, with 82 (70.7%) and 18 (15.8%) patients, respectively, completing 24 weeks of the double-blind study (Figure 1). The remaining 10 patients in the CZP group withdrew due to withdrawal of consent ($n = 1$), AEs ($n = 8$) and failed drug administration more than twice ($n = 1$) (Figure 1). In the placebo group, eight patients withdrew due to withdrawal of consent ($n = 2$), AEs ($n = 2$), lack of efficacy at times other than Week 12 or Week 14

($n = 2$), protocol non-compliance ($n = 1$) or failed drug administration more than twice ($n = 1$) (Figure 1). Demographics and baseline characteristics were similar between CZP and placebo groups with mean DAS28(ESR) > 6 at baseline (Table 1).

Just over half of all patients were receiving non-MTX DMARDs at baseline; in the active group, 53.4% of patients were treated with CZP plus concomitant DMARDs compared with 46.6% treated with CZP monotherapy (i.e. no additional DMARDs).

Clinical efficacy

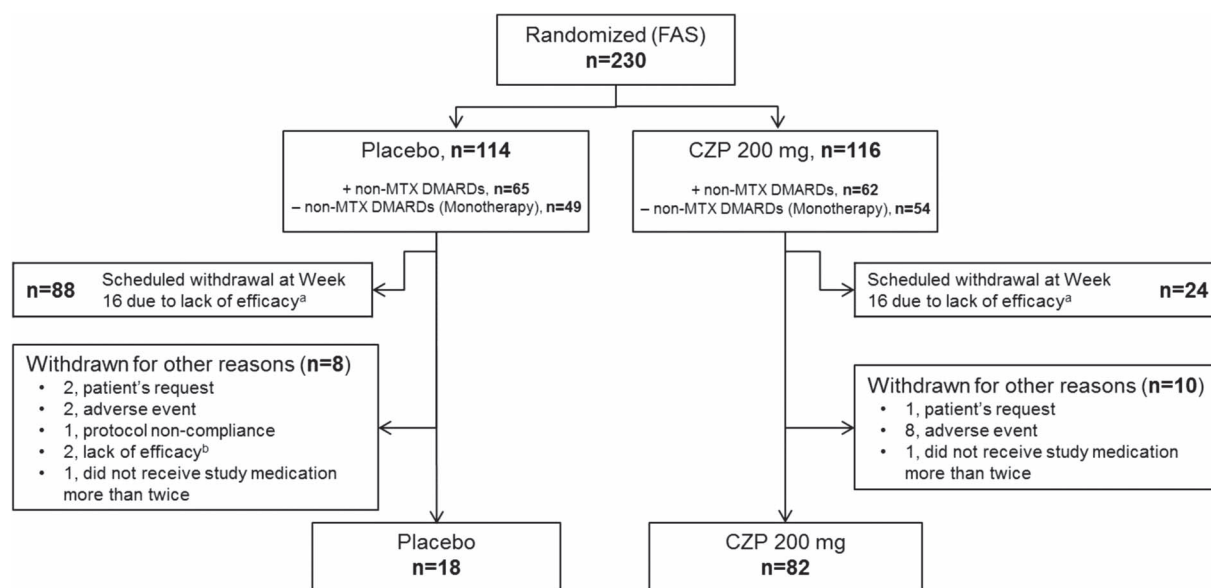
ACR20 responses were statistically significantly higher in the CZP group ($n = 116$) than in the placebo group ($n = 114$), at Weeks 12 and 24 (Figure 2a). Statistical significance was also reported for ACR50 responses at Weeks 12 and 24 and for ACR70 responses at Week 24. For ACR70 at Week 12, statistical analysis could not be performed due to zero response rate in the placebo group (Figure 2a).

The onset of response with CZP was rapid, with significantly greater ACR20 rates compared to placebo reported from Week 1 (32.8% vs. 5.3%; $p < 0.0001$). The ACR20 response peaked at Week 4 and was sustained to Week 24 (Figure 2b). ACR50 response was also rapid, with significant improvements compared to placebo reported from Week 1 ($p < 0.05$) (data not shown). CZP treatment was associated with significant improvement in all ACR core components (Table 2).

Mean DAS28(ESR) scores were significantly improved with CZP from Week 1 (Figure 2c). Significantly higher remission rates (DAS28[ESR] < 2.6) at Week 24 were achieved with CZP (16.4%) than with placebo (0.9%; $p < 0.005$). Moderate or good EULAR responses were more frequent among patients receiving CZP at Weeks 12 and 24 (82.8 and 77.6%, respectively) than placebo (28.1% and 21.9%, respectively; statistical analysis not undertaken).

HRQoL

Improvements in HAQ-DI with CZP over placebo were significant at Week 1 (CZP: -0.30 , placebo: -0.01 ; $p < 0.0001$) and



^aACR20 response was not achieved at Week 12 and Week 14. ^bEfficacy of study drug was insufficient at times other than at Week 12 and Week 14. Patients not showing an ACR20 response at Week 12 and Week 14 were withdrawn from the study at Week 16 and were eligible to enter an open-label extension, as were patients completing the study.

Figure 1. Patient disposition.

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

Characteristic	Placebo (n = 114)	CZP 200 mg Q2W (n = 116)
<i>Patient demographics and characteristics</i>		
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 (≥ 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)
<i>Disease activity status</i>		
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 $\pm$ 11.09	27.73 $\pm$ 10.76
Mean SF-36 MCS (SD)	43.58 $\pm$ 12.21	46.08 $\pm$ 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 $\mu\text{g/mL}$. Mean trough

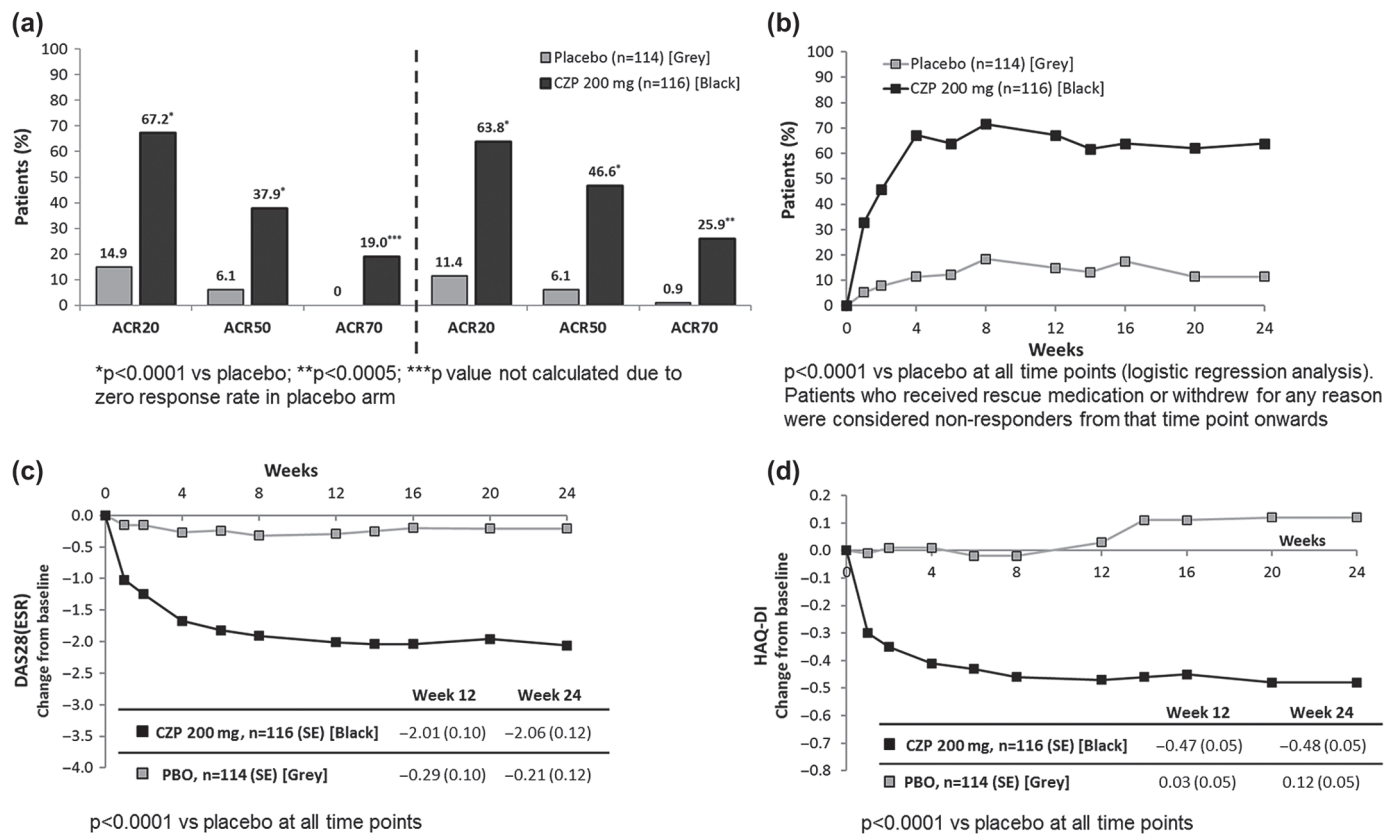


Figure 2. ACR response rates, improvements in DAS28(ESR) and HAQ-DI scores up to Week 24: a) ACR20, ACR50 and ACR70 response rates at Weeks 12 and 24 (FAS population; NRI), b) ACR20 response rate by time (FAS population; NRI), c) Improvements in DAS28(ESR) up to Week 24 (FAS population; LOCF), d) Improvements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

Characteristic	Placebo (n = 114)		CZP 200 mg Q2W (n = 116)	
	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.

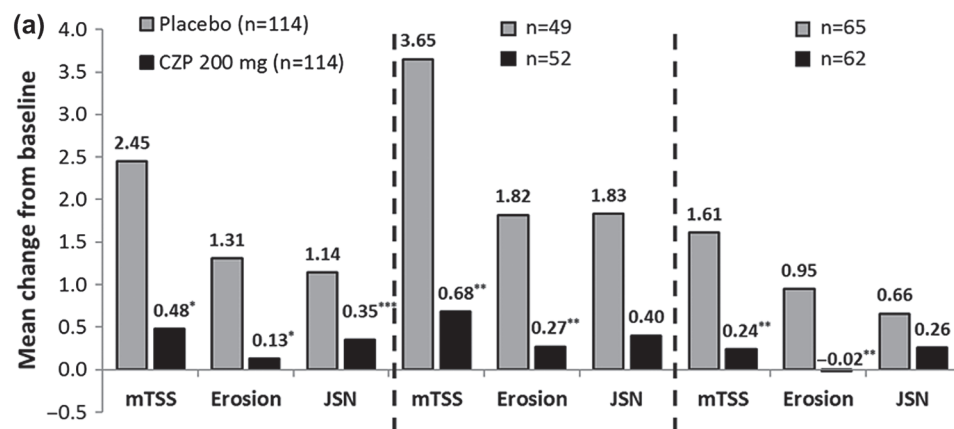
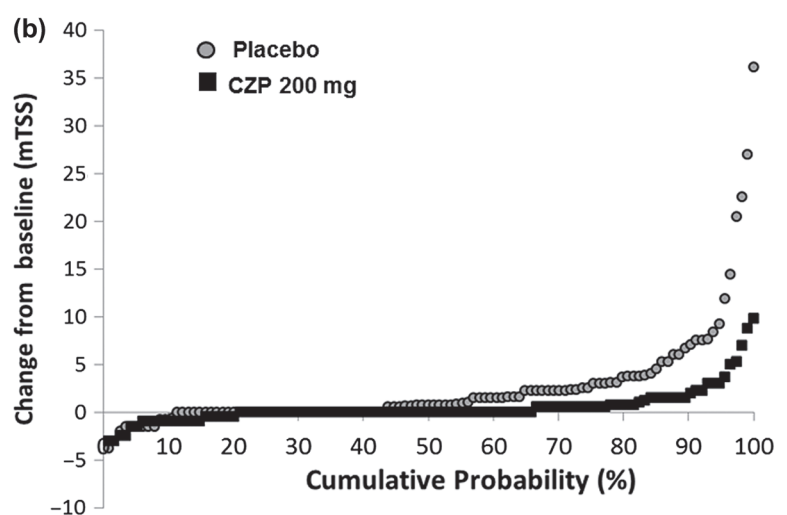


Figure 3. Radiographic outcomes: a) Inhibition of progression of structural damage: change from baseline at Week 24 (FAS-linear extrapolation), b) Cumulative probability plot of the change from BL in mTSS at Week 24 (FAS-linear extrapolation).

* $p < 0.0001$ 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)

with lower plasma CZP concentrations (mean 4.5 $\mu\text{g/mL}$ vs. 27.8 $\mu\text{g/mL}$ 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 (<i>n</i> = 114)	CZP 200 mg Q2W ^b (<i>n</i> = 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 ($\geq 3\%$ 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)

^aTotal exposure duration: 34.08 patient-years.^bTotal exposure duration: 49.43 patient-years.^cSevere AE defined as an event that prevents work or daily activities.^dSAE, serious adverse event.^eFive events in three patients.^f14 events in 13 patients.^gPreferred terms according to MedDRA terminology.^hTwo 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 Abbott, 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 Abbott, 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 employee 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.