

Efficacy and safety of certolizumab pegol in combination with methotrexate in methotrexate-inadequate responder Chinese patients with active rheumatoid arthritis: 24-week results from a randomised, double-blind, placebo-controlled phase 3 study

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Abstract Objective

To evaluate the efficacy and safety of certolizumab pegol (CZP) in combination with methotrexate (MTX) in Chinese patients with active rheumatoid arthritis (RA) and an inadequate response to MTX.

Methods

This 24-week, phase 3, double-blind, placebo-controlled study was conducted in 30 centres across China. A total of 430 patients were randomised 3:1 to receive CZP 200 mg every 2 weeks (loading dose: 400 mg CZP at Weeks 0, 2 and 4) plus MTX or placebo (PBO) plus MTX. The primary endpoint was ACR20 response at Week 24, for which the superiority of CZP+MTX over PBO+MTX was evaluated. Additional parameters for clinical efficacy, health outcomes, immunogenicity and safety were assessed.

Results

At Week 24, 54.8% of CZP+MTX patients and 23.9% of PBO+MTX patients achieved ACR20 (odds ratio: 3.9, $p < 0.001$). CZP+MTX patients also achieved greater improvements in HAQ-DI, higher ACR50/70 responses and higher DAS28(ESR) remission rate at Week 24. Rapid onset of response to CZP+MTX was observed as early as Week 1 for most of the clinical, functional and patient-reported outcomes. Incidences of treatment-emergent adverse events (TEAEs) were similar between treatment arms. Serious TEAEs were reported by 6.3% of CZP+MTX patients and 2.7% of PBO+MTX patients. No new safety signals were observed.

Conclusion

CZP in combination with MTX showed an acceptable safety profile, a rapid onset of response and sustained effects in reducing the signs and symptoms of RA and improving physical function in Chinese patients with RA and an inadequate response to MTX.

Key words

tumour necrosis factor-alpha, DMARD, certolizumab pegol, rheumatoid arthritis, Chinese

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease. Tumour necrosis factor (TNF) is a key mediator of the inflammation and joint damage characteristic of RA (1-4). Anti-TNF therapy effectively reduces the signs and symptoms of RA, improves physical function and decreases the progression of structural damage (5-13). Anti-TNF drugs are recommended in combination with methotrexate (MTX) in patients who do not show an adequate response to conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) including MTX (14, 15). In 2012, the prevalence of RA in China was estimated at 0.28% (16), representing a significant economic and societal burden (17, 18). Anti-TNFs currently approved in China include infliximab (IFX), adalimumab (ADA), etanercept (ETN) (original and local products, and golimumab (GOL)). The majority of Chinese patients with RA receiving anti-TNFs are on combination therapy (89.5%), with MTX being the most commonly used concomitant conventional synthetic DMARD (19). Despite the use of anti-TNFs and conventional synthetic DMARDs, unmet needs remain in the treatment of Chinese patients with RA, as evident from the low remission rates reported in recent cross-sectional studies (19-22).

Although anti-TNFs show comparable overall results in clinical trials, they have different molecular structures and pharmacokinetics, and exhibit distinctive safety and efficacy profiles at the patient level (23, 24). For example, a recent study comparing certolizumab pegol (CZP) and ADA showed that more than half of the patients who experienced primary failure to one anti-TNF responded following switch to the other anti-TNF (25). Among the five existing anti-TNFs, CZP is the only PEGylated Fc-free anti-TNF (26). The removal of the IgG Fc region inhibits CZP from interacting with Fc receptors, including the neonatal Fc receptor (27-29). A recent pharmacokinetic study in pregnant women indicated no to minimal placental transfer of CZP, suggesting a lack of foetal exposure during the third trimester of pregnancy, sup-

porting continuation of CZP treatment throughout pregnancy when it is necessary to control disease activity related to chronic inflammatory disease (28). A second study also demonstrated minimal transfer of CZP into the breast milk of CZP-treated mothers affected by chronic inflammatory diseases, indicating that continuation of CZP treatment is compatible with breast-feeding (30). The efficacy of CZP used in combination with MTX in patients with RA who do not respond adequately to MTX monotherapy was previously demonstrated in the international Rheumatoid Arthritis Prevention of Structural Damage (RAPID) 1 and 2 studies (7, 10). The objective of the RAPID-China (RAPID-C) study, reported here, was to investigate the efficacy and safety of CZP *versus* placebo (PBO) in combination with MTX in Chinese patients with active RA and an inadequate response to MTX.

Materials and methods

Study overview

RAPID-C was a 24-week, phase 3, multicentre, double-blind, randomised, PBO-controlled study (NCT02151851) conducted in 30 centres across China between 23 July 2014 and 17 June 2016. Patients with active RA and an inadequate response to MTX were randomised 3:1 at baseline (Week 0) to treatment with CZP plus MTX or with PBO plus MTX, using an interactive response technology (IRT) system based on a predetermined randomisation schedule from a third-party provider who was otherwise not involved in this study.

Patients randomised to CZP treatment received loading doses of CZP 400 mg (2 subcutaneous injections of 200 mg each) at Weeks 0, 2 and 4, followed by CZP 200 mg every 2 weeks thereafter (Q2W). Patients randomised to PBO treatment received 2 subcutaneous injections of PBO at Weeks 0, 2 and 4 to maintain blinding, followed by PBO injection Q2W. All patients were to continue their MTX treatment, with or without folic acid, at the same dose and route of administration as at entry into the study. Patients who did not achieve an ACR20 response ($\geq 20\%$ improvement according to the criteria of the American

College of Rheumatology [ACR]) (31) at Weeks 12 and 14 were withdrawn from the study at Week 16.

Both patients and investigators were blinded to the study medication patients received. All study medication was provided in prefilled syringes of identical appearance and appropriately labelled to maintain blinding. CZP and PBO differ in viscosity and colour; designated, unblinded personnel administered the study medication in such a manner to ensure that investigators and patients remained blinded (*e.g.* by eye coverings for patients at the time of injection). Other unblinded staff included: some pharmacovigilance staff from the sponsor reporting serious adverse events (SAEs) to regulatory authorities, staff responsible for study medication-related documentation, staff analysing C-reactive protein (CRP), anti-CZP antibody and CZP plasma concentration, and staff involved in documenting erythrocyte sedimentation rate (ESR) values. All other staff were blinded throughout the study, and were not involved in any activities pertaining to the receipt, handling, or administration of study medication.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Institutional review board approval was obtained at all centers. Written informed consent was provided by all patients.

Patients

Eligible patients were ≥ 18 years of age with a diagnosis of RA for at least 6 months according to the 1987 ACR classification criteria (32). At screening and baseline, eligible patients must have had at least 6 tender joints and at least 6 swollen joints, and met at least one of the following two criteria: ESR ≥ 30 mm/hour, CRP > 15 mg/L.

Patients must have received MTX for at least 3 months prior to the baseline visit, with a stable route of administration and dosing regimen of ≥ 10 mg/wk for at least 2 months prior to the baseline visit. Patients who failed to respond to previous treatment with an anti-TNF were excluded. Concomitant stable doses of NSAIDs/COX-2 inhibitors and oral corticosteroids (≤ 10 mg prednisone equivalent daily) were permitted.

Patients were excluded if they had a diagnosis of any other inflammatory or non-inflammatory arthritis. Also excluded were patients with known tuberculosis (TB) infection, patients at high risk of acquiring TB or patients with latent TB infection (unless receiving appropriate prophylaxis). Patients were defined as having latent TB if they had a positive Interferon Gamma Release Assay (IGRA) result, but without symptoms of TB. During the study, patients who developed signs or symptoms of active TB or evidence of latent TB were assessed by a TB specialist and were discontinued from the study if the diagnosis was confirmed. Patients with an active or a history of malignancy were excluded, except for cervical or basal cell carcinoma successfully treated ≥ 5 years before screening. Patients with a history of chronic infection, a history or signs and symptoms suggesting of a lymphoproliferative disorder, or a history of blood dyscrasias were also excluded.

Study assessments

The primary efficacy endpoint was the ACR20 response at Week 24. Secondary efficacy endpoints were ACR50, ACR70 and change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24.

Other efficacy endpoints included: ACR20, ACR50 and ACR70 response at Weeks 1, 2, 4, 6, 8, 12, 14, 16 and 20; change from baseline in individual ACR core component scores at all time-points collected which included: tender joint count (TJC; 68 joints), swollen joint count (SJC; 66 joints), patient's assessment of arthritis pain (PtAAP) using visual analogue scale (VAS), patient's global assessment of disease activity (PtGADA)-VAS, physician's global assessment of disease activity (PhGADA)-VAS and HAQ-DI; ratio to baseline in CRP level at all time-points collected; change from baseline in Disease Activity Score 28-joint assessment with ESR (DAS28[ESR]) at all time-points collected, and the rate of DAS28(ESR) remission (defined as DAS28[ESR] < 2.6) at Week 24.

Health outcome variables included change from baseline in Bristol Rheumatoid Arthritis Fatigue-Multidimen-

sional Questionnaire (BRAF-MDQ) total score at Weeks 1, 4, 8 and 12.

Immunogenicity was assessed by enzyme-linked immunosorbent assay (ELISA) for anti-CZP antibodies at baseline and at Weeks 1, 2, 4, 6, 8, 12 and 24.

Safety assessment included the incidence of treatment-emergent adverse events (TEAEs) and SAEs over the treatment period. All adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1. SAEs were defined as those that resulted in initial inpatient hospitalisation or prolongation of hospitalisation, were life-threatening, resulted in death, significant or persistent disability or incapacity, or congenital anomaly or birth defect, or important medical events that may have jeopardised the patient and may have required medical or surgical intervention to prevent one of the other abovementioned outcomes.

Statistical analysis

Based on an expected ACR20 response rate of 30% for PBO+MTX and $\geq 50\%$ for CZP+MTX, the detection of the clinically relevant difference of 20% at a 2-sided significance level of 5% for a 3:1 (CZP:PBO) ratio with 90% power required 360 patients to be randomised (33). To meet the regulatory requirement of having at least 300 patients on active treatment, 400 patients were to be randomised, giving approximately 93% statistical power. Since there was only one confirmatory test, adjustment to multiplicity of the type-I error was not necessary.

The primary efficacy analysis was a test of superiority of CZP over PBO for the primary endpoint of ACR20 response at Week 24, using logistic regression with factors for treatment and region. Non-responder imputation (NRI) was used in the assessment of ACR responses, where patients who received rescue medication or withdrew for any reason were considered non-responders from that time point onward. ACR50 and ACR70 at Week 24, and ACR responses at all other time points collected were analysed using the same model as for the primary analysis. Previously it has

been demonstrated that non-response to CZP within 3 months of treatment is predictive of non-response after 12 months of therapy (34), thus the NRI for missing data was deemed a reasonable imputation method.

Change from baseline in HAQ-DI at Week 24 and at all other time points collected, and change from baseline in TJC and SJC were analysed using an analysis of covariance (ANCOVA) model with treatment and region as factors and baseline value as a covariate. Last observation carried forward (LOCF) was the imputation method used for missing data. DAS28(ESR) remission rate at Week 24 was analysed using a logistic regression model with factors for treatment and region and baseline value of DAS28(ESR) as a covariate. Change from baseline in DAS28(ESR) was analysed using an ANCOVA model with treatment and region as factors and baseline value as a covariate. When normality assumptions were not met, Wilcoxon rank sum test was used. Changes from baseline in PhGADA-VAS, PtAAP-VAS, PtGADA-VAS and BRAF-MDQ total score were analysed using an ANCOVA model with treatment as a factor and baseline value as a covariate. Ratio to baseline of CRP was analysed using a log-transformed ANCOVA model with treatment and site as factors and the log-transformed baseline value as a covariate. All *p*-values presented are nominal except for ACR20 at Week 24.

The full analysis set (FAS), consisting of all randomised patients who received at least 1 dose of study medication and provided any efficacy data after the first administration, was used for all efficacy analyses. The safety set (SS), consisting of all patients who received at least 1 dose of study medication, was used for all safety analyses. The percentages of patients reporting each category of AEs were presented. Incidence rates (IRs) were calculated per 100 patient-years (PY), with 95% confidence intervals (CIs) presented.

Results

Patient characteristics and disposition

A total of 430 patients were randomised to CZP+MTX (n=316) or PBO+MTX (n=114), with 186 and 38 patients com-

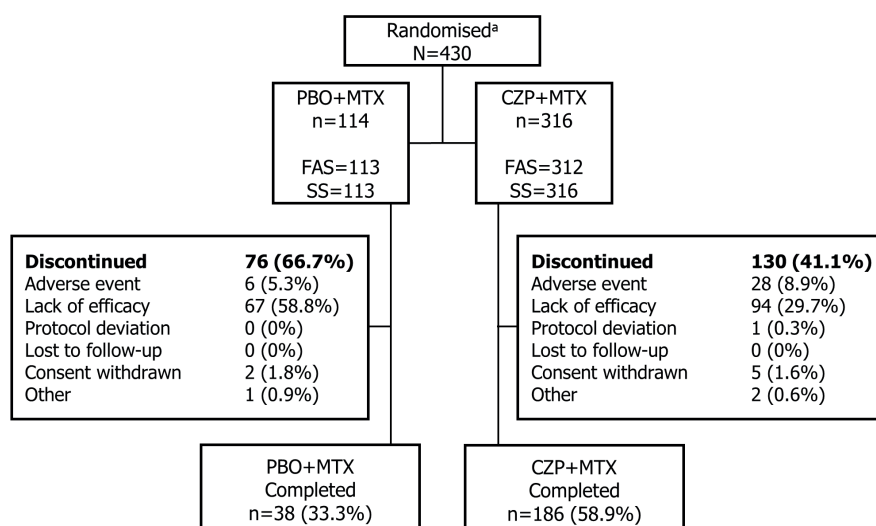


Fig. 1. Patient disposition. ^aOne patient was withdrawn due to taking prohibited medication prior to the administration of any study medication, and was not included in any analysis set.

Table I. Demographic and baseline characteristics.

	PBO+MTX (n=113)	CZP+MTX (n=316)
Age (years), mean (SD)	47.1 (11.1)	48.2 (11.8)
Female, n (%)	95 (84.1)	268 (84.8)
BMI (kg/m ²), mean (SD)	22.3 (3.0)	22.4 (3.7)
Number of previous DMARDs (excl. MTX), mean (SD)	1.2 (1.2)	1.2 (1.1)
Prior LEF use, n (%)	56 (49.6)	176 (55.7)
Baseline MTX dose, mean (SD)	10.8 (1.7)	10.6 (1.6)
Previous corticosteroid use, n (%)		
Yes*	38 (33.6)	104 (33.3)
No*	75 (66.4)	208 (66.7)
Previous anti-TNFs, n (%)		
0	90 (79.6)	250 (79.1)
1	16 (14.2)	49 (15.5)
≥2	7 (6.2)	17 (5.4)
Time since first diagnosis of RA (years), mean (SD)	6.6 (6.9)	7.0 (6.6)
RF ≥14 IU/mL, n (%)	106 (93.8)	291 (92.1)
Anti-CCP ≥7 IU/mL, n (%)	101 (89.4)	279 (88.3)
Tender joint count, mean (SD)	21.7 (12.8)	22.5 (13.2)
Swollen joint count, mean (SD)	14.0 (9.9)	14.1 (9.0)
DAS28(ESR), mean (SD)	6.6 (1.1)	6.7 (1.0)
DAS28(ESR) LDA (<3.2), n (%)*	1 (0.9)	0 (0)
DAS28(ESR) MDA (3.2 to 5.1), n (%)*	6 (5.3)	11 (3.5)
DAS28(ESR) HDA (>5.1), n (%)*	106 (93.8)	301 (96.5)
CRP (mg/L), mean (SD)	28.0 (31.7)	26.2 (29.4)
CRP ≤15 mg/L, n (%)*	54 (47.8)	147 (47.1)
CRP >15 mg/L, n (%)*	59 (52.2)	165 (52.9)
ESR (mm/hour), mean (SD) [range]	62.9 (29.2) [10.0–136.0]	61.8 (29.4) [5.0–150.0]

SS. *Reported for FAS. BMI: body mass index; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; CZP: certolizumab pegol; DAS28: 28-joint Disease Activity Score; DMARD: disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; LEF: leflunomide; MTX: methotrexate; PBO: placebo; RF: rheumatoid factor; SD: standard deviation.

Percentages are calculated based on the number of non-missing observations. Number of missing observations not shown separately.

pleting 24 weeks of the double-blind treatment respectively (Fig. 1). The most common reason for discontinuation was lack of efficacy (94 patients

[29.7%] with CZP+MTX, 67 patients [58.8%] with PBO+MTX). The majority of these cases (93/94 patients in CZP+MTX group, 66/67 patients in

PBO+MTX group) were mandatory withdrawal at Week 16 for patients who did not achieve an ACR20 response at Weeks 12 and 14. The second most common reason for discontinuation was adverse events (7.0%).

The treatment groups were well-balanced with respect to demographic characteristics, RA history and baseline disease activity (Table I). The overall mean time since diagnosis of RA was 6.9 years, with 76.9% of patients entering the study ≥ 2 years since diagnosis. The mean baseline MTX dose was 10.7 mg/week, with 83.9% of patients having a MTX dose of < 12.5 mg/week. The majority of patients (79.3%) had no prior exposure to anti-TNFs. The overall baseline disease characteristics reflected severe active RA and high disease burden; $> 90\%$ of patients had a DAS28(ESR) score of > 5.1 , and mean CRP and ESR values were 26.65 mg/L and 62.11 mm/hour, respectively.

The mean duration of study medication exposure was 142.0 days for the CZP+MTX group and 127.4 days for the PBO+MTX group. The total exposure was 137.9 PY with CZP+MTX and 43.6 PY with PBO+MTX, reflecting the 3:1 randomisation ratio as well as the fact that a higher percentage of PBO+MTX patients discontinued due to lack of efficacy.

Clinical efficacy

The RAPID-C study met its primary endpoint; a significantly greater proportion of patients randomised to CZP+MTX achieved an ACR20 response at Week 24 (54.8%, 171/312 patients, 95% CI [49.3, 60.2]) compared with patients randomised to PBO+MTX (23.9%, 27/113 patients, 95% CI [17.0, 32.5]; odds ratio [OR]: 3.90, 95% CI [2.38, 6.38], $p < 0.001$, Fig. 2A). A comprehensive set of sensitivity analyses was performed, and confirmed the robustness of these results.

Consistent with the primary result, significantly higher ACR50 and ACR70 response rates were reported at Week 24 in patients receiving CZP+MTX compared with those receiving PBO+MTX (ACR50: 36.5%, 114/312 patients, 95% CI [31.4, 42.0] vs. 7.1%, 8/113 patients, 95% CI [3.6, 13.4]; OR: 7.64, 95% CI

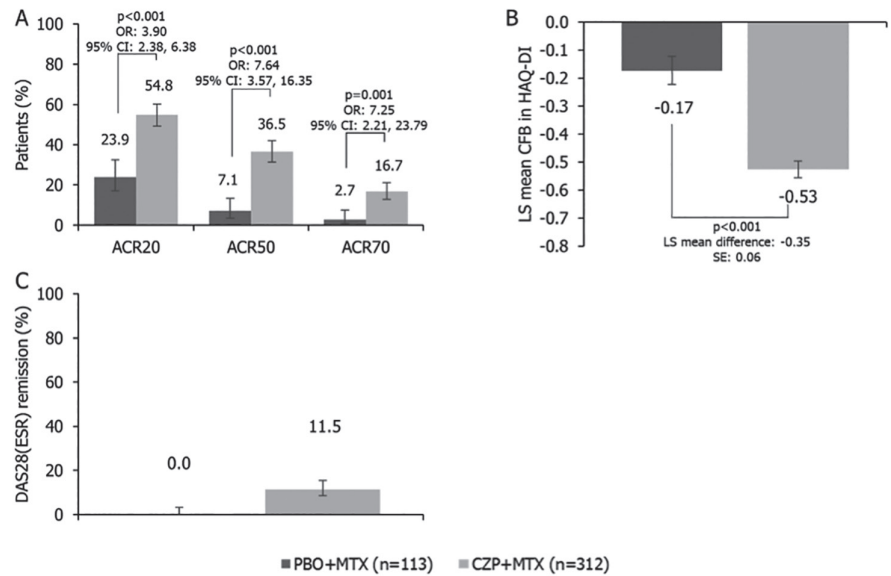


Fig. 2. Major efficacy endpoints. (A) ACR20, ACR50 and ACR70 response rates at Week 24 (FAS, NRI). (B) Improvements in HAQ-DI at Week 24 (FAS, LOCF). (C) DAS28(ESR) remission (defined as DAS28(ESR) < 2.6) at Week 24 (FAS, NRI); OR and p -value were not calculated due to the absence of patients achieving remission in PBO+MTX group. Error bars represent 95% CIs in (A) and (C), and standard error in (B). All p -values are nominal except for ACR20. CFB, change from baseline; LS, least-squares; OR, odds ratio.

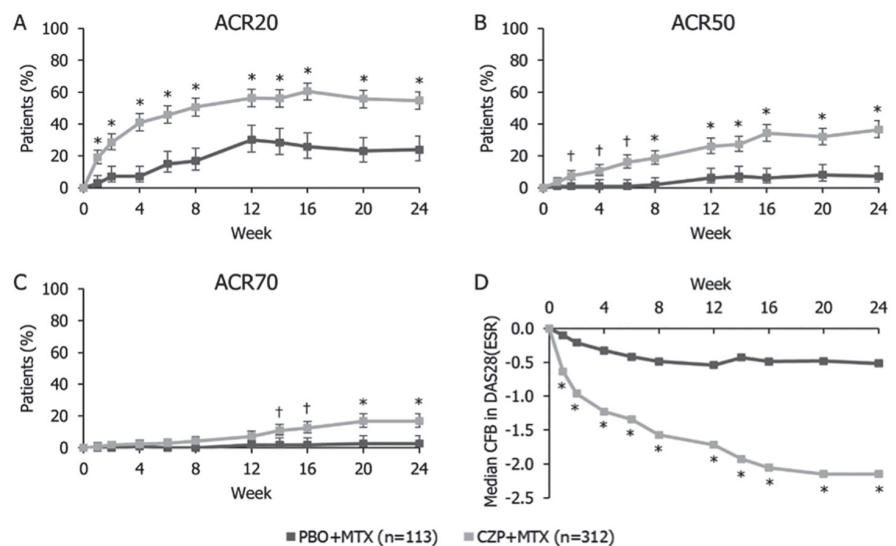


Fig. 3. Improvements in major efficacy outcomes over time. (A-C) ACR response rates by visits (FAS, NRI). (D) Improvements in DAS28(ESR) by visits (FAS, LOCF); median CFB (change from baseline) values analysed by Wilcoxon rank sum test due to absence of normal distribution for all time points except Weeks 16 and 20. $^{\dagger}p \leq 0.05$ vs. PBO+MTX; $*p \leq 0.001$ vs. PBO+MTX. All p -values are nominal except for ACR20 at Week 24. Error bars represent 95% CIs.

[3.57, 16.35], $p < 0.001$; ACR70: 16.7%, 52/312 patients, 95% CI [12.9, 21.2] vs. 2.7%, 3/113 patients, 95% CI [0.9, 7.5]; OR: 7.25, 95% CI [2.21, 23.79], $p = 0.001$; Fig. 2A). By Week 24 significant improvements in HAQ-DI were observed for patients receiving CZP+MTX compared with those receiving PBO+MTX. Least-squares (LS)

mean change from baseline in HAQ-DI was -0.53 for CZP+MTX patients and -0.17 for PBO+MTX patients, with an LS mean difference versus PBO+MTX of -0.35 (95% CI: -0.46, -0.24, $p < 0.001$; Fig. 2B). Similarly, compared with PBO+MTX patients, a greater proportion of CZP+MTX patients achieved DAS28(ESR) remission at Week 24

Table II. Summary of treatment-emergent adverse events (TEAEs).

	PBO+MTX (n=113)		CZP+MTX (n=316)	
	n ^a (%)	IR (95% CI)	n ^a (%)	IR (95% CI)
Total patient-years (PY) at risk		43.6		137.9
Mean duration of exposure (days)		127.4		142.0
Any TEAEs	82 (72.6)	415.1 (330.2, 515.3)	229 (72.5)	372.7 (326.0, 424.2)
Any SAEs	3 (2.7)	6.9 (1.4, 20.3)	20 (6.3)	14.9 (9.12, 23.1)
TEAEs leading to discontinuations	6 (5.3)	14.1 (5.2, 30.7)	28 (8.9)	21.1 (14.0, 30.4)
Drug-related TEAEs	48 (42.5)	–	145 (45.9)	–
Severe TEAEs	2 (1.8)	–	20 (6.3)	–
Deaths	0 (0.0)	–	1 (0.3)	–
AEs of interest and other specific SAEs				
System Organ Class				
Preferred Term				
Serious infections	0 (0.0)	0	6 (1.9)	4.4 (1.6, 9.5)
Pneumonia	0 (0.0)	0	2 (0.6)	1.5 (0.2, 5.3)
Tuberculous infections	0 (0.0)	0	4 (1.3)	2.9 (0.8, 7.5)
Pulmonary TB	0 (0.0)	0	2 (0.6)	1.5 (0.2, 5.3)
Pericarditis TB	0 (0.0)	0	1 (0.3)	0.7 (0.0, 4.0)
TB pleurisy	0 (0.0)	0	1 (0.3)	0.7 (0.0, 4.1)
Serious hepatobiliary disorders ^b	1 (0.9)	2.3 (0.1, 12.8)	2 (0.6)	1.5 (0.2, 5.3)
Liver injury	0 (0.0)	0	2 (0.6)	1.5 (0.2, 5.3)
MACE ^c	1 (0.9)	2.3 (0.1, 12.8)	0	0
Early systemic hypersensitivity reaction (SMQ) ^d	0 (0.0)	0	4 (1.3)	2.9 (0.8, 7.5)
Hepatic disorders (SMQs) ^e	19 (16.8)	49.1 (29.6, 76.7)	61 (19.3)	51.1 (39.1, 65.6)
Malignancies (SMQs) ^f	0 (0.0)	0	1 (0.3)	0.7 (0.0, 4.0)

SS. TEAEs were classified according to MedDRA version 15.1. ^aNumber of patients experiencing at least one event in each category; ^bSponsor defined search criteria; based on medical review of Hepatic Disorders (SMQs); ^cSponsor defined search criteria, included fatal and serious non-fatal myocardial infarctions, cerebrovascular events, and congestive heart failures based on MedDRA terms and medical reviews; ^dSMQ: “anaphylactic reaction” with onset “less than 2 hours”; ^eSMQs: “cholestasis and jaundice of hepatic origin”, “hepatic failure, fibrosis, and cirrhosis and other liver damage related conditions”, “hepatitis, noninfectious”, “liver related investigations, signs and symptoms” and “liver related coagulation and bleeding disturbances”; ^fSMQs: “malignant tumours” or “malignant or unspecified tumours”. IR, incidence rate per 100 patient-years; MACE, major adverse cardiovascular events; SAEs, serious TEAEs; SMQ, Standardized Medical Dictionary for Regulatory Activities Query; TB, tuberculosis/tuberculous.

(11.5%, 36/312 patients, 95% CI [8.5, 15.6], vs. 0%, 0/113 patients, 95% CI [0.0, 3.3], Fig. 2C).

Rapid responses were observed for almost all outcomes in patients receiving CZP+MTX. From Week 1 onward, the proportion of CZP+MTX patients achieving an ACR20 response was consistently higher *versus* PBO+MTX patients at all time-points data were collected (Fig. 3A). Greater proportions of CZP+MTX patients achieved ACR50 and 70 responses compared with PBO+MTX patients ($p \leq 0.05$) from Week 2 and Week 14 onward respectively (Fig. 3B-C). By Week 1, improvements in all ACR core components (Fig. S1A-G) and change from baseline in DAS28(ESR) (Fig. 3D) were greater for CZP+MTX treated patients compared with PBO+MTX treated patients. For most ACR core components, maximal levels of response were achieved by Week 16 and maintained through Week 24. Particularly, the ratios to baseline of CRP (Fig. S1C) and ESR (not shown) levels decreased sharply, reaching max-

imal response levels as early as Week 1 and Week 4, respectively.

Health outcomes and patient-reported outcomes

Compared with PBO+MTX, patients receiving CZP+MTX reported greater reduction from baseline values in PtAAP-VAS, PtGADA-VAS, HAQ-DI and BRAF-MDQ for all time-points collected, with p -values < 0.05 from Week 1. By Week 1, mean changes from baseline exceeded the minimum clinically important difference (MCID) for PtAAP-VAS and PtGADA-VAS (Fig. S1E-F), by Week 2 for HAQ-DI, and by Week 4 for BRAF-MDQ (Fig. S1G-H). For PBO+MTX, mean changes from baseline in these outcomes did not reach the MCID at any point during 24 weeks of treatment.

Safety

The percentages of patients reporting TEAEs and drug-related TEAEs were similar for both treatment arms (Table II). The IRs of the most frequently

reported ($\geq 5\%$ in any group) TEAEs by preferred term (PT) were similar or lower in CZP+MTX group than in PBO+MTX group.

The percentage of patients reporting severe TEAEs was higher in CZP+MTX group than in PBO+MTX group. The IR of TEAEs leading to discontinuation was higher in patients receiving CZP+MTX than PBO+MTX (Table II). SAEs were reported in 20 patients (6.3%) receiving CZP+MTX and 3 patients (2.7%) receiving PBO+MTX; of these, the number of patients experiencing an SAE in the System Organ Class of Infections and Infestations was the highest (6 patients, 1.9%; IR: 4.4/100 PY, 95% CI [1.6, 9.5] in CZP+MTX group, vs. no cases in PBO+MTX group). Four patients in the CZP+MTX group had TEAEs of early systemic hypersensitivity reactions (1 SAE of anaphylactic shock that led to study discontinuation, 1 TEAE of drug hypersensitivity and 2 TEAEs of rash).

During the study, there were 4 cases identified as tuberculosis: 2 pulmonary

TB (both discontinued), 1 pericarditis TB and 1 TB pleurisy (discontinued) with the event onset 99 and 18, 123, and 37 days after the start of CZP, respectively. Only the latter was considered latent TB at screening and the patient received rifampicin as prophylaxis 1 month prior to study drug administration.

One patient from the CZP+MTX group experienced an SAE of lung adenocarcinoma that was considered related to study medication. No cases of malignancy were reported in the PBO+MTX group.

Immunogenicity

A total of 14 (out of 316) CZP+MTX treated patients (4.5%) tested positive for anti-CZP antibodies (>2.4 units/mL) on at least one on-treatment visit assessed. Anti-CZP antibody positivity was not detected at baseline or Weeks 1, 2, 4 and 6, but was observed from Week 8 to Week 24 (data not shown). The proportion of ACR20 responders at Week 24 was lower in anti-CZP antibody-positive patients (21.4%, vs. 56.4% for anti-CZP antibody-negative patients).

Discussion

In this study, treatment with CZP in combination with MTX was shown to significantly reduce the signs and symptoms of RA, and improve physical function in Chinese patients with active RA who inadequately responded to MTX. The primary and secondary efficacy endpoints were met, confirming the superiority of CZP used in combination with MTX over PBO with MTX in this MTX inadequate responder patient population.

Consistent with the results from previous international studies (7, 10, 35), greater percentages of patients treated with CZP+MTX achieved ACR20, ACR50, ACR70 responses and DAS28(ESR) remission at Week 24 compared with patients treated with PBO+MTX. By Week 24 of RAPID-C, the ACR20/50/70 response rates among CZP+MTX patients (54.8%/36.5%/16.7%) were similar to those reported in the RAPID1 (58.8%/37.1%/21.4%) and RAPID2 (57.3%/32.5%/15.9%) studies. At Week 24, although ACR20 response in the PBO+MTX group in RAPID-C was

higher than in RAPID1 and RAPID2, the more stringent ACR50 and ACR70 responses were comparable to those observed in the previous CZP studies. Furthermore, comparative improvements in efficacy observed for patients receiving CZP+MTX vs. PBO+MTX was in line with the ACR20, 50 and 70 results reported in Chinese patients for other anti-TNF clinical studies with similar study designs (36-38).

Results for health outcomes and patient-reported outcomes were consistent with those reported in previous international studies (7, 10). Compared with PBO+MTX, CZP+MTX treated patients reported greater reduction in pain, disease activity and fatigue, and achieved greater improvements in physical function. For the majority of all clinical, functional and patient-reported outcomes in this study, rapid onset of the effect of CZP+MTX was observed. The ACR20 response rate showed marked increase at Week 1, approached maximal response level by Week 12, and was sustained through Week 24. Decrease from baseline in PtAAP-VAS and PtGADA-VAS exceeded MCID by Week 1, BRAF-MDQ total score exceeded MCID by Week 4, and HAQ-DI exceeded MCID by Week 2. Such rapid and sustained beneficial effects of CZP+MTX have been consistently observed in previous international CZP studies (7, 10, 35). A total of 14 (4.5%) CZP+MTX patients tested positive for anti-CZP antibodies at one or more time points during treatment, in line with the results from previous international studies (7, 10).

In this study, the incidence of TEAEs was similar between the PBO+MTX and the CZP+MTX groups and in line with that previously reported for Japanese patients with RA (J-RAPID) (35). The incidence of serious infections was higher with CZP+MTX than with PBO+MTX, consistent with other anti-TNF treatments and earlier studies of CZP (7, 10). There were few serious opportunistic infections, with 4 cases of confirmed TB. Two TEAEs of liver injury were reported in the CZP+MTX group. One case was with elevated ALT and AST, but no increase in bilirubin, and was considered not related to study

medication. The other case was severe liver injury considered mostly likely due to concomitant TB prophylactic medications. Overall, the incidence of any hepatic disorders was similar between the PBO+MTX and the CZP+MTX groups. One SAE of lung adenocarcinoma was reported in a CZP+MTX patient 171 days after the first CZP injection, 15 days after the completion of the study. This case was without metastases and lymph nodes, and was resolved 26 days after onset. The patient had been receiving MTX treatment since 2010; as has been reported, the use of MTX may be associated with elevated risk of malignancy (39). No new safety signals were observed for CZP in this population of Chinese patients.

Limitations of the study exist inherent to the study design. An active comparator was not used in this study, preventing the direct comparison of the efficacy and safety of CZP with other anti-TNFs. In line with other anti-TNF studies in Asian patients, the study duration was only 24 weeks, however, the long-term safety of CZP in this Chinese population was further assessed during the open-label extension of this study. Taken together, the results from the RAPID-C study confirmed that CZP used in combination with MTX has an acceptable safety profile, and exhibited rapid and sustained effects up to 24 weeks in reducing the signs and symptoms of RA and improving the physical function in Chinese patients with RA and an inadequate response to MTX monotherapy.

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