OPEN ACCESS

EXTENDED REPORT

Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial

J S Smolen,[1] P Emery,[2,3] G F Ferraccioli,[4] W Samborski,[5] F Berenbaum,[6] O R Davies,[7] W Koetse,[8] O Purcaru,[7] B Bennett,[9] H Burkhardt[10]

Handling editor Tore K Kvien

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2013-204632).

For numbered affiliations see end of article.

Correspondence to
Professor Josef S Smolen, Department of Medicine 3, Division of Rheumatology, Medical University of Vienna, Waehringer Guertel 18-20, Vienna A-1090, Austria; josef.smolen@wienkav.at, josef.smolen@meduniwien.ac.at

Received 19 September 2013
Revised 9 December 2013
Accepted 14 December 2013
Published Online First 14 January 2014

CrossMark

To cite: Smolen JS, Emery P, Ferraccioli GF, *et al*. *Ann Rheum Dis* 2015;**74**:843–850.

ABSTRACT

Objectives This 52-week, randomised, double-blind phase IIIb study assessed efficacy and safety of certolizumab pegol (CZP) as add-on therapy to non-biologic disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) patients with low to moderate disease activity, and stopping therapy in patients in sustained remission.

Methods Patients were randomised 1:1 to CZP (400 mg at weeks 0, 2 and 4, then 200 mg every 2 weeks) or placebo (every 2 weeks) plus current non-biologic DMARDs. At week 24, patients who achieved the primary endpoint of Clinical Disease Activity Index (CDAI) remission at both weeks 20 and 24 stopped study treatment and continued in the study until week 52.

Results Of 194 patients (CZP=96; placebo=98), >90% had moderate disease activity at baseline. Significantly more CZP patients met the primary endpoint than placebo patients (week 20 and 24 CDAI remission rates: 18.8% vs 6.1%; $p \leq 0.05$). At week 24, 63.0% vs 29.7% of CZP versus placebo patients ($p<0.001$) achieved LDA. Disease activity score (ESR) based on 28-joint count and Simplified Disease Activity Index remission rates were also significantly higher with CZP versus placebo (19.8% vs 3.1%; $p \leq 0.01$ and 14.6% vs 4.1%; $p \leq 0.05$). CZP patients reported improvements in physical function versus placebo (mean Health Assessment Questionnaire-Disability-Index change from baseline: CZP, −0.25 vs placebo, −0.03; $p \leq 0.01$). During the period following withdrawal of CZP or placebo, only 3/17 prior CZP patients and 2/6 prior placebo patients maintained CDAI remission until week 52, but CZP reinstitution allowed renewed improvement. Adverse and serious adverse event rates were comparable between CZP and placebo groups.

Conclusions Addition of CZP to non-biologic DMARDs is an effective treatment in RA patients with predominantly moderate disease activity, allowing low-disease activity or remission to be reached in a majority of the patients. However, the data suggest that CZP cannot be withdrawn in patients achieving remission.

Trial registration number NCT00674362.

INTRODUCTION

Non-biologic disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), are standard therapy for rheumatoid arthritis (RA). While some patients have only a minimal response, continuing to show high-disease activity (HDA), and others attain remission, the majority achieve significant improvement but continue to have low to moderate disease activity (MDA).[1–4] MDA is associated with a significant burden for patients and society regarding quality of life, productivity, comorbidities and costs when compared with remission.[2 5–9] Furthermore, patients with MDA are likely to experience joint damage progression and loss of function with conventional DMARD therapy.[2 3 8] For these reasons, the 'Treat-to-Target' paradigm, together with the European League Against Rheumatism (EULAR) recommendations for RA management, advocates clinical remission as the main target for RA patients.[10 11] Recently, the definition of remission in RA has now been updated by ACR and EULAR, using Boolean- and index-based criteria; the latter employ the remission definitions by the simplified and clinical disease activity indices (Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI)).

Few randomised clinical trials have specifically investigated RA treatments in patients with low disease activity (LDA)/MDA, although data from post-hoc analyses, open-label studies and registries suggest that anti-TNFs are efficacious.[7 12–14] Furthermore, there is little information regarding treatment adjustment once stringent remission is attained. Current EULAR recommendations state that once patients are in sustained remission, biologic therapies can be slowly reduced.[11] Potential benefits of drug withdrawal include reduced healthcare costs, safety and convenience.

Certolizumab pegol (CZP) is a PEGylated Fab' anti-TNF demonstrated to be efficacious and well tolerated in phase III clinical trials in RA patients with MDA/severe disease activity.[15–22] However, in these studies, the vast majority of patients had HDA (mean disease activity score (disease activity score (ESR) based on 28-joint count (DAS28) values 6.4 to 7.0).[15 17 22] Here, we present results from the CERTAIN (CERTolizumab pegol in the treatment of RA: remission INduction and maintenance in patients with LDA) study, NCT00674362, which evaluated efficacy and safety of CZP as add-on therapy to current non-biologic DMARDs in patients with LDA/MDA. We also investigated whether CZP can be withdrawn when patients achieve remission and, if lost, whether remission/LDA could be regained upon CZP reinstitution.

METHODS

Patients

Eligible patients (≥18 years of age) had a diagnosis of RA[23] (6 months–10 years), LDA/MDA at

screening and baseline (defined by CDAI >6 and ≤16, ≥2 tender joints (28-joint count, TJC), ≥2 swollen joints (28-joint count, SJC) and either erythrocyte sedimentation rate (Westergren-ESR) ≥28 mm/h or C-reactive protein (CRP) >10 mg/L). Patients must have received mono or combination DMARD therapy (MTX, leflunomide, sulfasalazine and/or hydroxychloroquine) for ≥6 months (dose stable ≥2 months) prior to baseline, with corticosteroid dose stable >1 month (for exclusion criteria, see online supplementary material).

Study design

CERTAIN was a randomised, double-blind, placebo-controlled 52-week (24-week treatment and 28-week follow-up period) phase IIIb study (figure 1A) conducted between June 2008 and December 2010. All patients, recruited from centres in Austria, France, Germany, Italy and Poland, provided written consent. The study protocol was approved by Ethics Committees at each centre and performed according to Declaration of Helsinki.

Patients were randomised in a 1:1 ratio to CZP or placebo. CZP patients received subcutaneous 400 mg CZP at weeks 0, 2 and 4, followed by 200 mg CZP every 2 weeks (Q2W) thereafter, controls receiving identical injections of 0.9% saline Q2W, administered by unblinded site personnel. Randomisation was performed centrally using an interactive voice-response system. All patients continued their conventional DMARDs throughout. At week 24, patients were divided depending on remission status: non-remitters (patients not achieving CDAI remission (CDAI≤2.8) at both weeks 20 and 24) were discontinued and given the opportunity to receive CZP in an open-label extension study (NCT00843778); remitters (patients in CDAI remission at weeks 20 and 24) stopped randomised treatment (CZP or placebo), stayed in the study until week 52 continuing their concomitant therapies blinded to original treatment. Remitters who flared (CDAI≥11 at 2 visits, 4 weeks apart) between weeks 24 and 50 were retreated with the same dosing regimen of CZP as used originally up to and including week 50, before entering the open-label extension. To maintain blinding of the first study period, prior placebo-treated patients who achieved remission also received CZP if they flared.

Efficacy and safety evaluations

Efficacy evaluations were performed every 4 weeks from weeks 0 to 52 (for exceptions, see online supplementary material). Adverse events (AEs) were assessed Q2W. Primary efficacy endpoint was the proportion of patients in stable CDAI remission (CDAI≤2.8) at both weeks 20 and 24.

Secondary efficacy endpoints included the proportion of patients with DAS28(ESR)<2.6 and ACR-EULAR index-based SDAI remission (SDAI≤3.3)[24] at both weeks 20 and 24, ACR20, ACR50 and ACR70 responders at week 24, and change from baseline in Health Assessment Questionnaire-Disability-Index (HAQ-DI), Patient's Assessment of Arthritis Pain (100 mm visual analogue scale (VAS)), fatigue (11-point scale), Patient's Global Assessment of Disease Activity (PtGA; VAS), SF-36 (Physical Component Summary (PCS), Mental Component Summary (MCS)) and time from stopping treatment to loss of remission (CDAI≥2.8) at 2 consecutive visits. SDAI and DAS28 (ESR) loss of remission (SDAI>3.3 and DAS28(ESR)≥2.6 at two consecutive visits) were similarly assessed. Exploratory objectives included CDAI, SDAI and DAS28(ESR) over the 24-week treatment period. ACR-EULAR Boolean-based remission criteria using four variables (SJC and TJC≤1, CRP≤1 mg/dL and PtGA≤1) and three variables (SJC and TJC≤1 and PtGA≤1) were analysed posthoc.[24] The impact of patients' disease activity on work productivity was an exploratory objective and measured using the Work Productivity and Activity Impairment-RA (WPAI-RA) questionnaire (for details, see online supplementary material).

Safety analysis was performed up to week 52 plus 12-week safety follow-up (for details, see online supplementary material).

Statistical analysis

Sample size was calculated assuming 25% of patients in the placebo-treated group and at least 50% in the CZP-treated group would achieve remission (CDAI≤2.8) at both weeks 20 and 24. Planned sample size was 170 patients (85 for each treatment group) to achieve ≥90% power to show a statistically significant difference in proportions of patients in remission at both weeks 20 and 24. A two-sided Fisher's exact test, significance level of 0.05 (α), was used.

Efficacy analyses were performed on the intent to treat (ITT) population (all randomised patients). The proportion of patients in CDAI/SDAI/DAS28(ESR) remission and ACR responder rates were analysed using logistic regression models with treatment and geographic region as factors, from which ORs were estimated and presented with confidence intervals (CIs) and corresponding p values. Missing data were imputed by non-responder imputation (NRI) for CDAI, DAS28(ESR) and SDAI remission rates, ACR responder rates and ACR-EULAR Boolean remission. Patients who withdrew for any reason or received rescue medication were considered non-responders from that time point onwards. All continuous data were analysed on the ITT population using analysis of covariance (ANCOVA) models with treatment and geographic region as factors and baseline value as covariate using last observation carried forward (LOCF) imputation. Safety analyses included all patients receiving study medication (CZP or placebo).

RESULTS

Patients

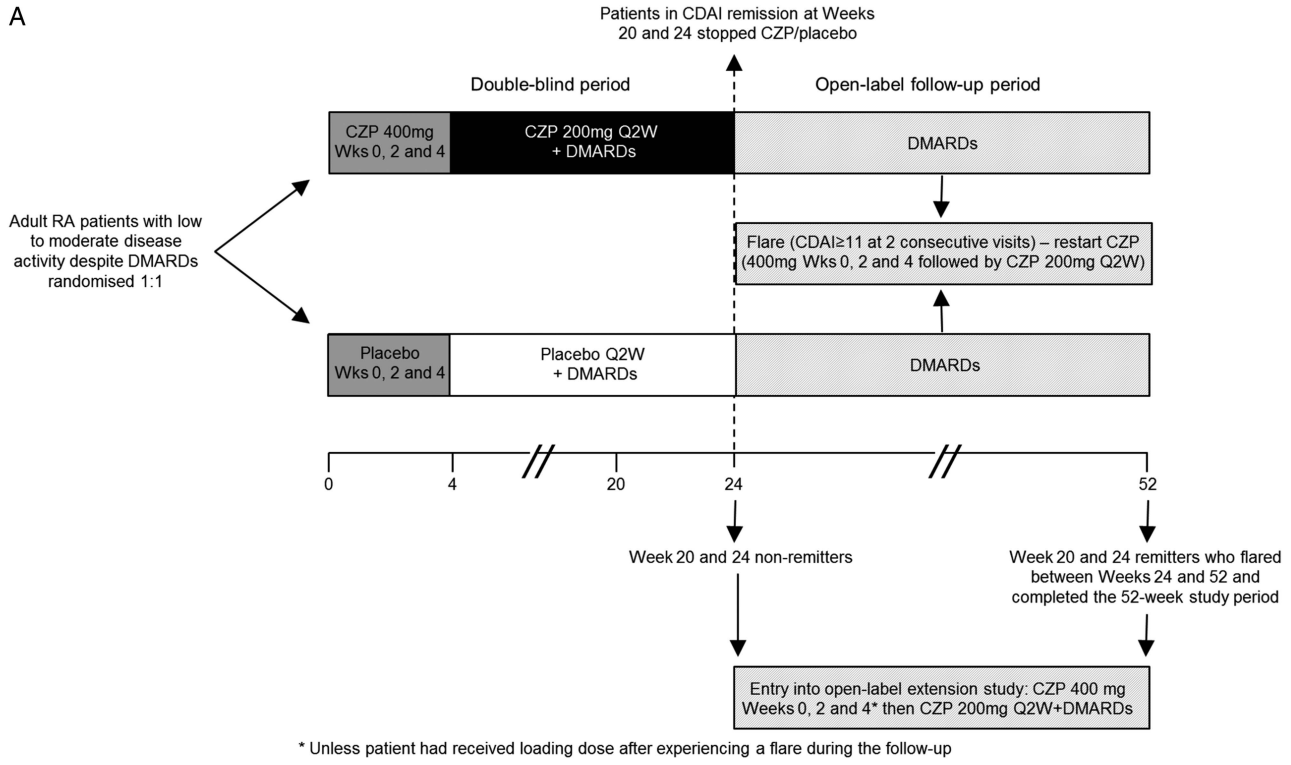
In total, 194 patients were randomised to placebo (n=98) or CZP (n=96); 80 (81.6%) and 84 (87.5%) patients, respectively, completed 24 weeks of treatment (figure 1B). Baseline characteristics were similar between groups (table 1), with>90% in MDA (CDAI>10). Two CZP-randomised patients had HDA (CDAI>22) at baseline, but were nevertheless included in the ITT population. In line with inclusion criteria, patients had low joint counts at baseline (mean TJC: 3.8; mean SJC: 3.3). Despite MDA, functional impairment was high (mean HAQ-DI: 1.1). Impairments in overall work and daily activities and thus economic burden were also substantial (see online supplementary figure S2).

Clinical efficacy

Double-blind period: up to week 24

Significantly more CZP-treated than placebo-treated patients reached the primary endpoint, CDAI remission at both weeks 20 and 24 (18.8% vs 6.1%; p≤0.05) (figure 2A), fewer than expected. Further, significantly more CZP than placebo patients had DAS28(ESR) or SDAI remission at both weeks 20 and 24 (figure 2A).

Mean CDAI and SDAI scores in CZP-treated patients improved from baseline by week 4, while worsening on placebo treatment (figure 2B, see online supplementary figure S1). Mean change from baseline DAS28(ESR) also improved on CZP, remaining stable on placebo (see online supplementary figure S1). Over twice as many CZP-treated versus placebo-treated patients achieved LDA/remission at week 24 (63.0% vs 29.7%, 42.4% vs 16.5%



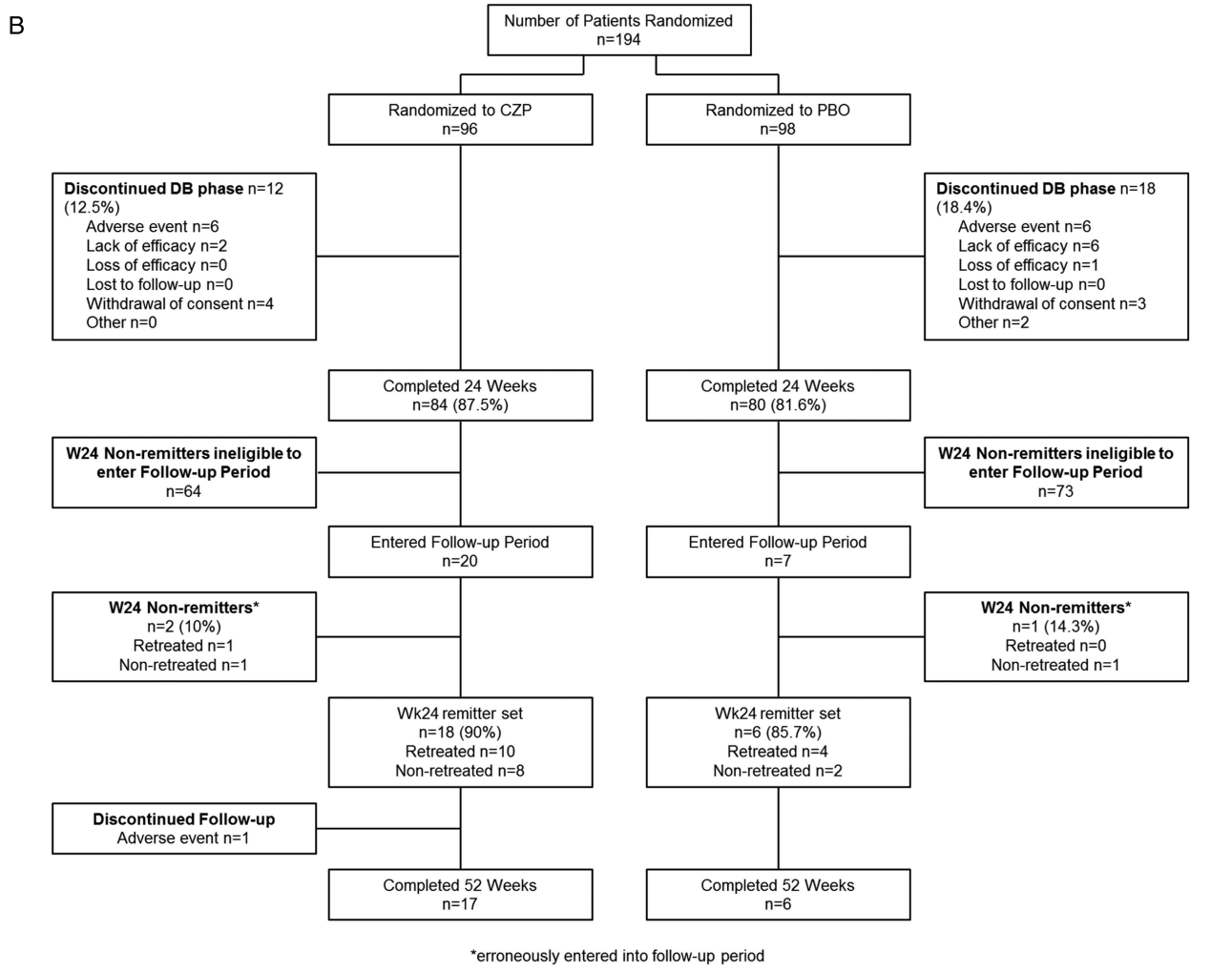


Figure 1 (A) Study design and (B) CONSORT diagram showing patient flow.

Table 1 Patient demographics and baseline characteristics of the ITT population

	All patients		Weeks 20 and 24 remitters*		Weeks 20 and 24 non-remitters†	
	Placebo (n=98)	CZP (n=96)	Prior placebo (n=6)	Prior CZP (n=18)	Prior placebo (n=74)	Prior CZP (n=66)
Age (years), mean (SD), median (min–max)	54.0 (12.4), 56.0 (18–78)	53.6 (11.9), 55.0 (25–76)	65.3 (4.5), 66.5 (58–70)	55.4 (10.7), 55.5 (33–72)	52.6 (11.7), 55.0 (18–74)	51.9 (12.5), 54.0 (25–76)
Female (%)	76.5%	84.4%	66.7%	83.3%	77.0%	86.4%
Body mass index (kg/m^3), mean (SD)	27.3 (5.1)	26.6 (5.6)	28.9 (2.6)	28.0 (6.3)	27.3 (5.3)	26.2 (5.8)
Disease duration (years), mean (SD), median (Q1—Q3)	4.7 (3.3), 4.2 (1.7–7.8)	4.5 (3.5), 3.5 (1.9–7.0)	2.6 (2.4), 2.0 (0.9–3.0)	3.6 (2.9), 2.8 (1.1–6.0)	4.8 (3.1), 4.5 (1.9–8.0)	4.7 (3.3), 4.0 (2.0–7.0)
Previous‡ DMARDs use (%)						
0	35.7%	30.2%	83.3%	61.1%	32.6%§	23.1%§
1	33.7%	41.7%	16.7%	27.8%	34.8%§	44.9%§
2	19.4%	16.7%	0%	11.1%	20.7%§	17.9%§
>2	11.2%	11.5%	0%	0%	12.0%§	14.1%§
Previous non-MTX DMARDs use (%)	44.9%	50.0%	16.7%	33.3%	46.7%	53.8%
Concomitant MTX use (%)	80.6%	84.4%	100%	88.9%	78.4%	81.8%
RF positive (≥14 IU/mL) (%)	67.3%	74.0%	100%	94.4%	72.2%	80.3%
TJC, mean (SD)	3.9 (1.6)	3.7 (1.5)	5.5 (2.3)	3.7 (1.3)	3.8 (1.5)	3.7 (1.5)
SJC, mean (SD)	3.2 (1.3)	3.4 (1.5)	2.7 (0.5)	3.3 (1.0)	3.3 (1.4)	3.4 (1.7)
CDAI, mean (SD)	13.3 (1.9)	13.5 (2.2)	13.3 (2.6)	13.0 (1.8)	13.3 (1.9)	13.6 (2.4)
SDAI, mean (SD)	14.7 (2.6)	14.6 (2.6)	14.2 (2.6)	14.5 (2.4)	14.5 (2.4)	14.7 (2.8)
DAS28(ESR), mean (SD)	4.5 (0.3)	4.5 (0.4)	4.7 (0.4)	4.5 (0.4)	4.4 (0.3)	4.5 (0.5)
HAQ-DI, mean (SD)	1.0 (0.6)	1.1 (0.6)	0.5 (0.3)	0.9 (0.6)	1.1 (0.6)	1.2 (0.6)
CRP (mg/L), median (min–max)	8.0 (2.9–107.0)	6.0 (2.9–70.0)	10.0 (2.9–14.0)	4.5 (2.9–70.0)	7.0 (2.9–107.0)	5.5 (2.9–57.0)
ESR (mm/h), median (min–max)	30.5 (8.0–86.0)	32.0 (6.0–98.0)	37.0 (28.0–43.0)	33.0 (16.0–58.0)	30.0 (8.0–86.0)	32.0 (6.0–98.0)

*Baseline at study start for those patients in sustained remission at weeks 20 and 24 and had at least one visit in the open-label follow-up period.
†Baseline at study start for those patients who did not sustain remission at weeks 20 and 24 but were otherwise eligible to enter the open-label follow-up period.
‡Medications stopped more than 6 months prior to baseline visit.
§Baseline at study start for those patients who did not sustain remission at weeks 20 and 24, n=92 (placebo), n=78 (prior CZP).
CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; CZP, certolizumab pegol; DAS28(ESR), disease activity score (ESR) based on 28-joint count; ESR, erythrocyte sedimentation rate; HAQ-I, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SJC, Swollen joint count; TJC, Tender joint count.

and 65.2% vs 31.9% for CDAI, DAS28 and SDAI, respectively, all p<0.001) (figure 2C, see online supplementary figure S1), which was already observable at week 12. Furthermore, at week 24, more patients on placebo than CZP had HDA (figure 2C).

ACR-EULAR Boolean remission was achieved at week 24 by over twice as many CZP-treated than placebo-treated patients (Boolean 4: CZP=10.4%, placebo=5.1%; Boolean 3: CZP=14.6%, placebo=5.1%). ACR20, ACR50 and ACR70 response rates were higher at week 24 in the CZP group than the placebo group (ACR20, 36.5% vs 15.3%, OR 3.25 (95% CI 1.59 to 6.65); p≤0.001; ACR50, 20.8% vs 7.1%, OR 3.58 (95% CI 1.34 to 9.54); p≤0.05; ACR70, 9.4% vs 3.1%, OR 3.08 (95% CI 0.77 to 12.25); not significant although numerically threefold higher).

CZP-treated patients reported significant improvements in patient-reported outcomes compared with placebo (see online supplementary table S1 and figure 3A). Marked improvements in physical function were observed from week 4 onwards in CZP-treated compared with placebo-treated patients (figure 3A). Improvements were also seen in pain and fatigue assessments (figure 3B and C). Furthermore, patients who received CZP reported significant improvements at week 24 in both SF-36 PCS and MCS compared with those receiving placebo. Mean changes from baseline were PCS 6.0 vs 1.7, p≤0.01; MCS 4.0 vs 0.5, p≤0.05 (observed data, see online supplementary table S1).

At baseline, 32.6% patients were employed overall (35.9% in the CZP group and 29.3% in the placebo group). Over 24 weeks, CZP-treated patients reported on average greater reductions in absenteeism, presenteeism, overall work impairment and daily activity impairment compared with placebo-treated patients (see online supplementary figure S2). The percentage of work time missed due to RA (absenteeism) decreased on average from 11.0% at baseline to 3.3% at week 24 in the CZP group, whereas in the placebo group the impairment increased by week 24 (on average from 1.5% at baseline to 5.6% at week 24). The percentage of impairment while working due to RA (presenteeism) decreased on average from 35.3% at baseline to 23.6% at week 24 in the CZP group but did not change in the placebo group (37.7% at baseline compared with 38.5% at week 24) (see online supplementary figure S2).

Open-label follow-up period: up to week 52

Patients in sustained remission stopped CZP or placebo treatment at week 24, while maintaining their established DMARD regimens, blinded to initial treatment allocation. In total, 6 placebo-treated and 17 CZP-treated patients entered the follow-up period and were eligible for inclusion in the analysis.

Of subjects completing 52 weeks of treatment, CDAI remission was maintained in 3/17 prior CZP-treated and 2/6 placebo-treated patients. At week 52, 7/17 prior CZP and 2/6 prior placebo patients had CDAI LDA/remission.

Ten of seventeen patients in the prior CZP group flared to MDA or HDA, and all achieved remission or LDA when retreated with CZP. Four patients in the prior placebo group flared; CZP treatment resulted in two patients achieving remission, one LDA and one MDA. Median time to loss of CDAI remission (in all patients) was 42.5 days (see online supplementary figure S3).

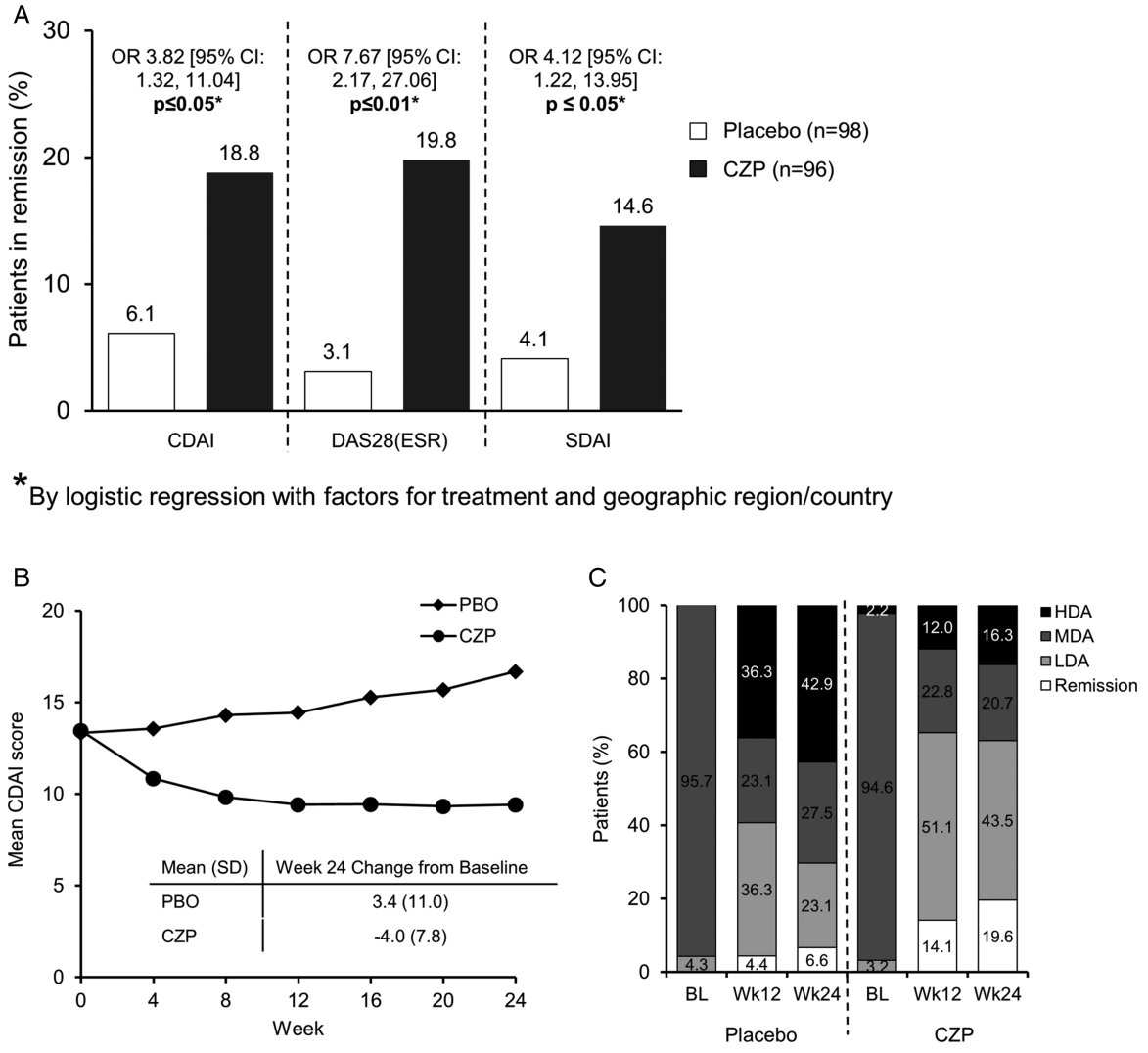
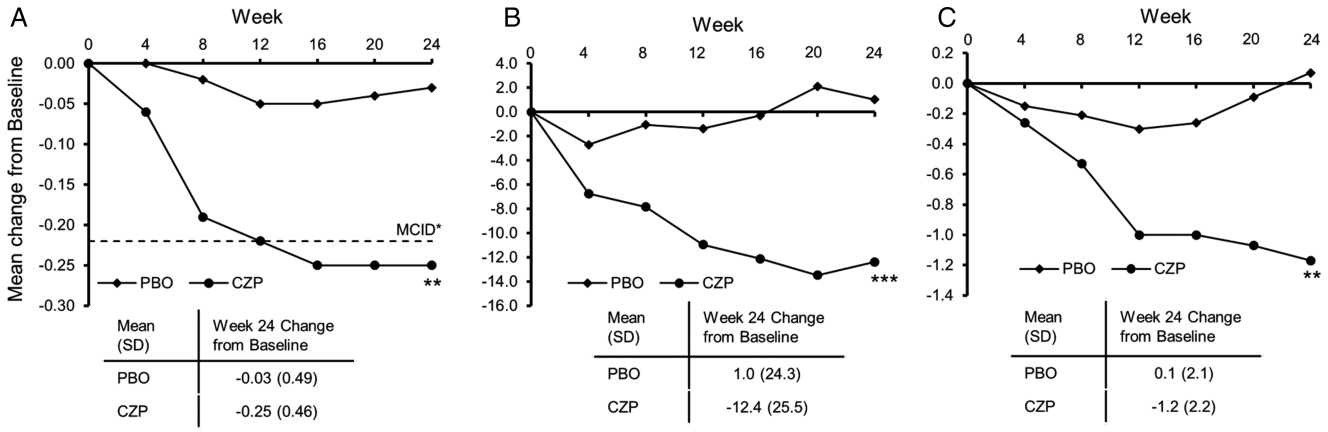


Figure 2 (A) Clinical Disease Activity Index (CDAI), Disease activity score (ESR) based on 28-joint count and Simplified Disease Activity Index remission at both Weeks 20 and 24 (intent to treat (ITT) population, non-responder imputation); (B) mean CDAI scores up to week 24 (ITT population, last observation carried forward); (C) CDAI disease state at baseline, week 12 and week 24 (ITT population, LOCF).



*MCID: Minimal Clinical Important Difference, defined as 0.22 for HAQ-DI; **p≤0.01 (CZP – PBO LS mean difference in change from Baseline); ***p≤0.001(CZP – PBO LS mean difference in change from Baseline).

Figure 3 Improvements in (A) physical function (Health Assessment Questionnaire-Disability-Index), (B) pain (visual analogue scale) and (C) Fatigue Assessment Scale (FAS) over 24 weeks (ITT population, last observation carried forward).

Safety

AEs occurred in 68.8% and 67.3% of patients in the CZP and placebo groups, respectively, during the 24-week double-blind period (table 2; see online supplementary material). The most frequently reported AEs with CZP during the 24-week double-blind period were infections and infestations (36.5%), gastrointestinal disorders (19.8%), and musculoskeletal and connective tissue disorders (15.6%), with rates comparable in placebo-treated patients (37.8%, 13.3% and 19.4%, respectively). Incidence of SAEs was 5.2% for the CZP group (one event each of irritable bowel syndrome, otitis media, haemophilus sepsis, polyarthritis, intervertebral disc protrusion and RA) and 7.1% for the placebo group (one event each of pneumonia, tendon rupture, joint effusion, cerebrovascular accident, granulomatosis with polyangiitis (Wegener's), pleurisy and two malignancies (breast cancer and basal cell carcinoma)).

Table 2 Treatment-emergent adverse events in the safety population during the double-blind period

	Double-blind period	
	Placebo (n=98)	CZP (n=96)
Any AE, n (%)	66 (67.3%)	66 (68.8%)
Drug related, n (%)	26 (26.5%)	29 (30.2%)
Infections and infestations	37 (37.8%)	35 (36.5%)
Serious AEs, n (%)	7 (7.1%)	5 (5.2%)
Serious infections, n (%)	1 (1.0%)	2 (2.1%)
Malignancies	2 (2.0%)	0
AE leading to death, n (%)	0	0
AE leading to withdrawal*	6 (6.1%)	6 (6.3%)
Most common AE†		
System order class		
Preferred term		
Infections and infestations	37 (37.8%)	35 (36.5%)
Bronchitis	5 (5.1%)	3 (3.1%)
Gastroenteritis	3 (3.1%)	1 (1.0%)
Herpes simplex	1 (1.0%)	3 (3.1%)
Influenza	2 (2.0%)	3 (3.1%)
Nasopharyngitis	11 (11.2%)	10 (10.4%)
Rhinitis	2 (2.0%)	3 (3.1%)
Upper respiratory tract infection	4 (4.1%)	6 (6.3%)
Urinary tract infection	5 (5.1%)	6 (6.3%)
Gastrointestinal disorders	13 (13.3%)	19 (19.8%)
Diarrhoea	6 (6.1%)	5 (5.2%)
Abdominal pain	2 (2.0%)	4 (4.2%)
Abdominal pain upper	1 (1.0%)	3 (3.1%)
Nausea	5 (5.1%)	5 (5.2%)
Nervous system disorders	11 (11.2%)	4 (4.2%)
Headache	5 (5.1%)	0
Musculoskeletal and connective tissue disorders	19 (19.4%)	15 (15.6%)
Rheumatoid arthritis	5 (5.1%)	3 (3.1%)
Cardiac disorders	1 (1.0%)	6 (6.3%)
Tachycardia	0	3 (3.1%)
Ear and labyrinth disorders	3 (3.1%)	1 (1.0%)
Vertigo	3 (3.1%)	0
Vascular disorders	4 (4.1%)	3 (3.1%)
Hypertension	2 (2.0%)	3 (3.1%)

Results are shown as n (%) of patients.
*Temporary or permanent discontinuation of the drug.
†Treatment-emergent adverse events occurring in >3% (by preferred term) of the safety population in the specified period (in either certolizumab pegol or placebo group).
AE, Adverse event.

DISCUSSION

In the CERTAIN study of RA patients with mostly MDA, addition of CZP, compared with addition of placebo, to non-biologic DMARDs led to significantly higher rates of sustained remission or LDA as assessed by CDAI (almost two-thirds of patients) and other scores. In CERTAIN, the CDAI remission rates at weeks 20 and 24 (the primary endpoint) were similar to SDAI/CDAI remission rates at a comparable time point in the Prospective, Randomized Etanercept Study to Evaluate Reduced dose Etanercept + MTX v. full dose Etanercept + MTX v. MTX alone for efficacy and radiographic endpoints in a moderate RA population (PRESERVE) study, which indicates that in patients with long-standing disease duration achievement of stringent remission is difficult. Indeed, this finding supports the notion of the Treat-to-Target and EULAR recommendations that suggest use of LDA rather than remission as a treatment target in patients with established disease.[10 11] Disease activity in patients receiving placebo (continuing non-biologic DMARDs) increased to week 24 by CDAI and SDAI, with over one-third of patients moving to an HDA state. This contrasts with decreases in disease activity in placebo-treated patients usually seen in clinical trials as a consequence of the 'placebo effect'. Thus, in these patients, CZP addition not only led to more frequent good clinical states but also prevented disease worsening by inhibiting progression to HDA. This novel finding is aligned with observations that early RA patients with persistent MDA experience functional deterioration.[2]

Rapid and sustained improvements in CDAI, SDAI and DAS28(ESR), from the first time point at 4 weeks, were observed following CZP initiation, with the majority of response observed within 12 weeks.

Results were consistent across secondary endpoints, including SDAI and DAS28(ESR) remission, ACR20, ACR50 and ACR70 response rates, CDAI, SDAI and DAS28(ESR) values and patient-reported outcomes over the entire 24-week treatment period. The low number of baseline tender and swollen joints may have contributed to lower ACR responses than observed in other CZP studies: 79% of CZP-treated and 86% of placebo-treated patients had baseline TJC or SJC≤3 and therefore could not achieve an ACR70 unless having 0 TJC and SJC by week 24.

CDAI and SDAI are considered the appropriate composite measures for definition of remission by ACR and EULAR.[24]] The primary endpoint of CERTAIN was CDAI remission at two consecutive time points at the end of the initial observation period, a stringent definition of remission. As CDAI does not include measures of acute phase reactants (APR), it is often more useful in routine clinical care.[25 26] Unlike CDAI and SDAI, DAS28(ESR) is strongly influenced by absolute values and changes of APR levels,[27 28] which are often profoundly affected by anticytokine agents.[29]

CERTAIN is a unique study, with the vast majority of included patients having MDA at baseline. Patients with LDA/MDA represent the largest RA subsets in routine clinical care,[1 4 30] who generally have disease activity that is lower than the entry criteria for most clinical studies.[31] This population accounts for a substantial economic burden, especially when considering impairments of physical function, work and daily activities.[32 33] The economic burden of patients with low to moderate disease activity is supported in the CERTAIN study by the substantial impairment in work productivity observed at baseline. Furthermore, such patients continue to have progressive joint damage and functional impairment[2 3 5] and the improvement in physical function and productivity, both in absenteeism, impairment in work-related productivity and impairment in

daily activities, noted with CZP here, suggests substantial benefit in treating patients with this mostly moderate level of disease activity.

The Treat-to-Target concept, which has been used successfully in other therapeutic areas such as diabetes for many years, has become increasingly adopted in RA. Remission is recommended as the primary therapeutic aim, although LDA is an acceptable alternative particularly in patients with long-standing disease for whom remission may not be realistic[10]; however, this latter recommendation was not based on primary evidence from controlled trials. Here we show that, in patients with established disease, stringent remission is difficult to achieve despite optimal therapy, even if patients have MDA at baseline, consistent with other studies including PRESERVE.[14 34 35] The alternative target of LDA was attained in almost two-thirds of CZP patients at 6 months in the CERTAIN study. Interestingly, patients achieving remission had shorter disease duration and fewer prior DMARD therapies, indicating that remission is more difficult to achieve in patients with more refractory disease. Also, baseline HAQ-DI scores tended to be lower among remitters despite similar SDAI, CDAI and DAS28 values, in patients assigned to both CZP and placebo, consistent with the PRESERVE study.[14 34 35] These may represent potential predictors for achievement of remission.

Current EULAR recommendations suggest considering withdrawal of biologic DMARDs in patients in stable remission.[11] However, this study reveals that, upon stopping CZP therapy, most patients were unable to maintain remission, in line with observational studies in established RA[36–38] and from the PRESERVE trial, where termination of etanercept in stable LDA resulted in a lower likelihood of maintaining LDA than continuing etanercept.[14] However, unlike in CERTAIN, comparisons between patients receiving etanercept and those who only continued prior non-biologic DMARD treatment could not be ascertained in PRESERVE due to the open-label nature of the run-in period that only included etanercept therapy and no placebo control.[14] In the CERTAIN study, somewhat more frequent flares were seen after anti-TNF withdrawal than in the PRESERVE study; this is likely a consequence of the requirement of achieving the clinical target for at least 6 months before withdrawal in the PRESERVE study compared with at least 4 weeks in the CERTAIN study; moreover, the treatment target was more stringent in the CERTAIn study (CDAI remission vs DAS28 LDA). In contrast to CERTAIN and PRESERVE studies, the Optimal Protocol for Treatment Initiation With Methotrexate and Adalimumab Combination Therapy in Patients With Early Rheumatoid Arthritis (OPTIMA) study assessed early RA patients and revealed that most of them were able to maintain DAS28 LDA upon stopping adalimumab and continuing MTX; only a relatively small number of patients would have benefited from continuing or reinstituting adalimumab.[39] This difference suggests that, contrasting with early disease, biological therapy should not be stopped in established disease once an acceptable disease activity state has been attained, in agreement with observational studies.[36 38] Alternatively, a longer remission state may be necessary prior to stopping biological therapy.

In line with observational studies on retreatment with biologics[36 37] and contrasting with DMARD retreatment,[40] among patients receiving CZP retreatment after flaring to MDA/HDA, almost half (4/10) of the prior CZP-treated patients re-achieved remission, and the remaining 6 LDA; thus, all these patients showed response to retreatment. Such retreatment was not assessed in PRESERVE or OPTIMA studies.

There are several limitations to this study. First, only a small number of patients were included in the follow-up since fewer patients than expected achieved remission, presumably a consequence of long-standing disease and stringent remission criteria. At the time of study design, there were no prior data available from patients with MDA or LDA and so the actual proportions of patients achieving sustained remission indicate that this trial was not adequately powered, which is a limitation of the study; however, despite this underpowering, the differences between the treatment arms were significant. Also, in a recent analysis from an observational prospective RA database, patient's global assessment of disease activity was often the limiting factor to reach remission;[41] this may also have contributed to the low CDAI remission rates in this study of patients with long-standing RA, and, indeed, the greatest mean contribution to the CDAI in patients not reaching remission at week 24 on certolizumab pegol came from the patient's global assessment (data not shown). Second, retreatment upon flaring was not performed in a placebo-controlled manner but as an open-label exploratory analysis; nevertheless, it is unlikely that we observed a placebo effect upon retreatment since disease activity increased also in the placebo arm and patients remained masked to the initial double-blind period. Third, we did not assess dose reduction or interval increase once patients achieved remission, a strategy reported effective in maintaining LDA in the PRESERVE trial.[14]

The results presented here reveal that CZP addition to non-biologic DMARDs in patients with long-standing, mostly MDA is associated with increased remission and LDA rates, prevention of worsening and improvements in physical function, quality of life, work productivity and daily activities. Remission was lost upon discontinuation of CZP treatment, although response was regained by reinstitution of CZP. Taken alongside the level of overall impairment in persistent MDA[2] and the low likelihood of these patients achieving LDA/remission with DMARD treatment alone,[3] the data suggest that RA patients with LDA/MDA are a relevant population to treat with TNF inhibitors.

Author affiliations
[1]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, and 2nd Department of Medicine, Hietzing Hospital, Vienna, Austria
[2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Leeds, UK
[3]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[4]Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy
[5]University of Medical Sciences, Poznan, Poland
[6]Department of Rheumatology, DHU i2B, INSERM UMR-S938, Pierre & Marie Curie University Paris 06, Saint-Antoine hospital, AP-HP, Paris, France
[7]UCB Pharma, Brussels, Belgium
[8]UCB Pharma, Raleigh, North Carolina, USA
[9]BABennett Consulting, Marietta, USA
[10]CIRI/Division of Rheumatology and Fraunhofer TMP, Goethe-University, Frankfurt am Main, Germany

Acknowledgements The authors acknowledge 'Matladi Ndlovu, PhD, UCB Pharma, Brussels, Belgium, for publication management and Costello Medical Consulting for editorial and administrative support.

Contributors JSS has received grants from and provided expert advice to UCB Pharma. PE has received grants from and is a consultant for UCB Pharma. GFF has received speaking fees from UCB Pharma. WS, FB and HB are consultants for UCB Pharma. ORD is a shareholder and employee of UCB Pharma. WK and OP are employees of UCB Pharma. BB is a former employee of UCB Pharma.

Funding This study was funded by UCB Pharma.

Competing interests JS has received grants from and provided expert advice to UCB Pharma. PE has received grants and consultancy fees from UCB Pharma, Pfizer, Merck, Abbott, Roche and BMS. GF has received speaking fees from UCB Pharma.

WS has acted as a consultant for UCB Pharma. FB has received consultancy fees for UCB Pharma. HB is a consultant for UCB Pharma. OD is an employee and a shareholder for UCB Pharma. WK and OP are employees of UCB Pharma. BB is a former employee of UCB Pharma and also holds stock options with UCB Pharma.

Ethics approval The study protocol was approved by an Ethics Committee at each of the participating sites.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Montag K, Gingold M, Boers A, *et al*. Disease-modifying anti-rheumatic drug usage, prescribing patterns and disease activity in rheumatoid arthritis patients in community-based practice. *Intern Med J* 2011;41:450–5.
2 Conaghan PG, Hensor EM, Keenan AM, *et al*. Persistently moderate DAS-28 is not benign: loss of function occurs in early RA despite step-up DMARD therapy. *Rheumatology (Oxford)* 2010;49:1894–9.
3 Kiely P, Walsh D, Williams R, *et al*. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity—the early RA network (ERAN). *Rheumatology (Oxford)* 2011;50:926–31.
4 Mierau M, Schoels M, Gonda G, *et al*. Assessing remission in clinical practice. *Rheumatology (Oxford)* 2007;46:975–9.
5 Macedo A, Oakley S, Gullick N, *et al*. An examination of work instability, functional impairment, and disease activity in employed patients with rheumatoid arthritis. *J Rheumatol* 2009;36:225–30.
6 Puolakka K, Kautiainen H, Mottonen T, *et al*. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. *Arthritis Rheum* 2005;52:36–41.
7 Roy S, Forster F, Hayes OA, *et al*. Do Patients with Moderate Rheumatoid Arthritis Experience As Much Disability and Benefit from Anti-TNF Treatment As Much As Patients with Severe Rheumatoid Arthritis?. *Ann Rheum Dis* 2012;69(Suppl 3):679.
8 Smolen JS, Han C, van der Heijde DM, *et al*. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. *Ann Rheum Dis* 2009;68:823–7.
9 Aletaha D, Funovits J, Smolen JS. The importance of reporting disease activity states in rheumatoid arthritis clinical trials. *Arthritis Rheum* 2008;58:2622–31.
10 Smolen JS, Aletaha D, Bijlsma JW, *et al*. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;69:631–7.
11 Smolen JS, Landewe R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492–509.
12 Hyrich KL, Deighton C, Watson KD, *et al*. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. *Rheumatology (Oxford)* 2009;48:1323–7.
13 Keystone E, Freundlich B, Schiff M, *et al*. Patients with moderate rheumatoid arthritis (RA) achieve better disease activity states with etanercept treatment than patients with severe RA. *J Rheumatol* 2009;36:522–31.
14 Smolen JS, Nash P, Durez P, *et al*. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013;381:918–29.
15 Keystone E, Heijde D, Mason D Jr., *et al*. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008;58:3319–29.
16 Fleischmann R, Vencovsky J, van Vollenhoven RF, *et al*. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis* 2009;68:805–11.
17 Weinblatt ME, Fleischmann R, Huizinga TW, *et al*. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. *Rheumatology (Oxford)* 2012;51:2204–14.
18 Kavanaugh A, Smolen JS, Emery P, *et al*. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. *Arthritis Rheum* 2009;61:1592–600.
19 Strand V, Mease P, Burmester GR, *et al*. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. *Arthritis Res Ther* 2009;11:R170.
20 Hazes JM, Taylor P, Strand V, *et al*. Physical function improvements and relief from fatigue and pain are associated with increased productivity at work and at home in rheumatoid arthritis patients treated with certolizumab pegol. *Rheumatology (Oxford)* 2010;49:1900–10.
21 Strand V, Smolen JS, van Vollenhoven RF, *et al*. Certolizumab pegol plus methotrexate provides broad relief from the burden of rheumatoid arthritis: analysis of patient-reported outcomes from the RAPID 2 trial. *Ann Rheum Dis* 2011;70:996–1002.
22 Smolen J, Landewe RB, Mease P, *et al*. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009;68:797–804.
23 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
24 Felson DT, Smolen JS, Wells G, *et al*. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;70:404–13.
25 Aletaha D, Nell VP, Stamm T, *et al*. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther* 2005;7:R796–806.
26 Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005;23:S100–8.
27 Smolen JS, Aletaha D. Interleukin-6 receptor inhibition with tocilizumab and attainment of disease remission in rheumatoid arthritis: the role of acute-phase reactants. *Arthritis Rheum* 2011;63:43–52.
28 Bakker MF, Cavet G, Jacobs JW, *et al*. Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. *Ann Rheum Dis* 2012;71:1692–7.
29 Charles P, Elliott MJ, Davis D, *et al*. Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-alpha therapy in rheumatoid arthritis. *J Immunol* 1999;163:1521–8.
30 Ziegler S, Huscher D, Karberg K, *et al*. Trends in treatment and outcomes of rheumatoid arthritis in Germany 1997–2007: results from the National Database of the German Collaborative Arthritis Centres. *Ann Rheum Dis* 2010;69:1803–8.
31 Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission. *J Rheumatol* 2003;30:1138–46.
32 Augustsson J, Neovius M, Cullinane-Carli C, *et al*. Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). *Ann Rheum Dis* 2010;69:126–31.
33 Radner H, Aletaha D, Smolen JS. Work Productivity, Quality of Life, and Health States of Different Disease Activity States in Patients with Rheumatoid Arthritis (RA). *Ann Rheum Dis 2009* 2009;68(Suppl 3):396.
34 Anderson JJ, Wells G, Verhoeven AC, *et al*. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. *Arthritis Rheum* 2000;43:22–9.
35 Yazici Y, Moniz Reed D, Klem C, *et al*. Greater remission rates in patients with early versus long-standing disease in biologic-naive rheumatoid arthritis patients treated with abatacept: a post hoc analysis of randomized clinical trial data. *Clin Exp Rheumatol* 2011;29:494–9.
36 Tanaka Y, Takeuchi T, Mimori T, *et al*. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. *Ann Rheum Dis* 2010;69:1286–91.
37 Brocq O, Millasseau E, Albert C, *et al*. Effect of discontinuing TNFalpha antagonist therapy in patients with remission of rheumatoid arthritis. *Joint Bone Spine* 2009;76:350–5.
38 Saleem B, Keen H, Goeb V, *et al*. Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped?. *Ann Rheum Dis* 2010;69:1636–42.
39 Smolen JS, Emery P, Fleischmann R, *et al*. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. *Lancet* 2013. Epub ahead of print. doi:10.1016/S0140–6736(13)61751-1
40 ten Wolde S, Hermans J, Breedveld FC, *et al*. Effect of resumption of second line drugs in patients with rheumatoid arthritis that flared up after treatment discontinuation. *Ann Rheum Dis* 1997;56:235–9.
41 Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. *Ann Rheum Dis* 2012;71:1702–5.

SUPPLEMENTARY INFORMATION

METHODS

Exclusion Criteria

Exclusion criteria included a history of a non-inflammatory type of joint disease that may interfere with evaluation of the study drug on RA, chronic infections or recent serious infections, concurrent malignancy or demyelinating disorder. Patients with active or latent tuberculosis, or a positive purified protein derivative (PPD) test, were also excluded. In addition, patients were excluded if they had previously received any biologic therapy for RA.

Study Design

During the OLE study, patients received CZP 400 mg at Weeks 0, 2 and 4, unless they had received this loading dose following a flare between Weeks 24 and 50, and CZP 200 mg Q2W thereafter (Figure 1A).

Efficacy evaluations

The exploratory objective of impact of patients' disease activity on work productivity and regular activities was investigated using the WPAI-RA questionnaire[1] and was measured at Weeks 0, 24 and 52. This assessed the impact of RA on 4 dimensions: work absenteeism (sick leave), work presenteeism (work impairment whilst working), overall work impairment and daily activity impairment over the 7 days prior to the respective study visit. WPAI-RA results are presented as observed data on which no statistical analyses were conducted.

Safety evaluations

Safety analysis comprised of physical examinations (including monitoring for any signs or symptoms of tuberculosis), measurement of vital signs and clinical laboratory values, and assessment of all AEs, serious AEs (SAEs), injection-site reactions and serious infections.

RESULTS

Safety

The frequency of injection site reactions was 3.1% and 2.0% in CZP and placebo groups, respectively. There was only one case of injection site pain (1.0%), in the placebo group. In the 27 patients who continued in the follow-up period, the most frequently reported AEs included infections and infestations, gastrointestinal disorders and nervous system disorders (Table S2). The only SAE was one event of cerebrovascular accident (in the prior CZP group).

REFERENCES

1. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics*. 1993 Nov;**4**(5):353-65.

Table S1. ACR core components and patient-reported outcomes at Baseline and Week 24 (LOCF).

Mean (SD)	Baseline		Week 24		Change from Baseline	
	Placebo (n=98)	CZP (n=96)	Placebo (n=98)	CZP (n=96)	Placebo (n=98)	CZP (n=96)
ACR Core Components						
TJC	3.9 (1.6)	3.7 (1.5)	5.7 (5.4)	3.1 (3.8)	1.8 (5.5)	-0.6 (3.8)
SJC	3.2 (1.3)	3.4 (1.5)	4.1 (3.6)	1.7 (2.1)	0.9 (3.2)	-1.6 (2.4)
Patient's global assessment of pain (VAS)	36.8 (19.1)	36.9 (20.8)	37.1 (26.3)	27.5 (23.6)	1.0 (24.3)	-12.4 (25.5)***
Patient's global assessment of disease activity (VAS)	35.6 (16.7)	36.7 (18.5)	38.3 (25.0)	28.8 (23.5)	2.9 (25.4)	-7.6 (28.7)**
Physician's global assessment of disease activity (VAS)	27.2 (10.7)	26.9 (10.5)	30.4 (20.1)	17.1 (14.9)	3.4 (20.7)	-9.7 (17.2)
HAQ-DI	1.04 (0.60)	1.11 (0.62)	1.00 (0.68)	0.86 (0.63)	-0.03 (0.49)	-0.25 (0.46)**
CRP geometric mean (CV) – ratio to Baseline	8.6 (116.6)	7.2 (114.2)	8.4 (125.0)	4.9 (93.8)	1.0 (108.9)	0.69 (122.6)
ESR geometric mean (CV) – ratio to Baseline	31.5 (38.6)	32.1 (40.1)	22.4 (77.5)	15.2 (72.8)	0.72 (72.8)	0.48 (68.1)
Other Patient Reported Outcomes						
FAS	4.3 (2.0)	4.9 (2.4)	4.3 (2.4)	3.7 (2.2)	0.1 (2.1)	-1.2 (2.2)**
SF-36† PCS	36.9 (7.2)	35.2 (7.2)	38.0 (7.8)	40.8 (8.5)	1.7 (7.6)	6.0 (7.5)**
MCS	44.3 (11.2)	42.1 (10.2)	44.7 (11.3)	46.1 (11.4)	0.5 (9.3)	4.0 (9.8)*

*p≤0.05 (CZP – placebo LS mean difference in change from Baseline); **p≤0.01 (CZP – placebo LS mean difference in change from Baseline); ***p≤0.001 (CZP – placebo LS mean difference in change from Baseline); †Values are reported for the observed set, with no imputation method. There were no statistical comparisons for TJC, SJC, CRP and ESR. HAQ-DI, Health assessment questionnaire–disability index; TJC, Tender joint count; SJC, Swollen joint count; VAS, Visual analog scale; CV, Coefficient of variation; FAS, Fatigue assessment scale; SF-36, Short form health survey with 36 questions; PCS, Physical component summary; MCS, Mental component summary.

Table S2: Treatment-emergent adverse events in the safety population during the open-label follow-up period.

	Open-label follow-up period	
	Prior placebo (n=7)	Prior CZP (n=20)
Any AE, n (%)	0	7 (35.0%)
Drug related, n (%)	0	1 (5.0%)
Infections and infestations	0	4 (20.0%)
Serious AEs, n (%)	0	1 (5.0%)
Serious infections, n (%)	0	0
Malignancies	0	0
AE leading to death, n (%)	0	0
AE leading to withdrawal*	0	1 (5.0%)
Most common AE**		
System order class		
Preferred term		
Gastrointestinal disorders	0	2 (10.0%)
Nausea	0	2 (10.0%)
General disorders and administration site conditions	0	1 (5.0%)
Influenza-like illness	0	1 (5.0%)
Infections and infestations	0	4 (20.0%)
Bronchitis	0	2 (10.0%)
Laryngitis	0	1 (5.0%)
Rhinitis	0	1 (5.0%)
Nervous system disorders	0	2 (10.0%)
Cerebrovascular accident	0	1 (5.0%)
Syncope vasovagal	0	1 (5.0%)
Psychiatric disorders	0	1 (5.0%)
Depression	0	1 (5.0%)
Respiratory, thoracic and mediastinal disorders	0	2 (10.0%)
Cough	0	1 (5.0%)
Rhinorrhoea	0	1 (5.0%)
Skin and subcutaneous tissue disorders	0	1 (5.0%)
Hyperhidrosis	0	1 (5.0%)

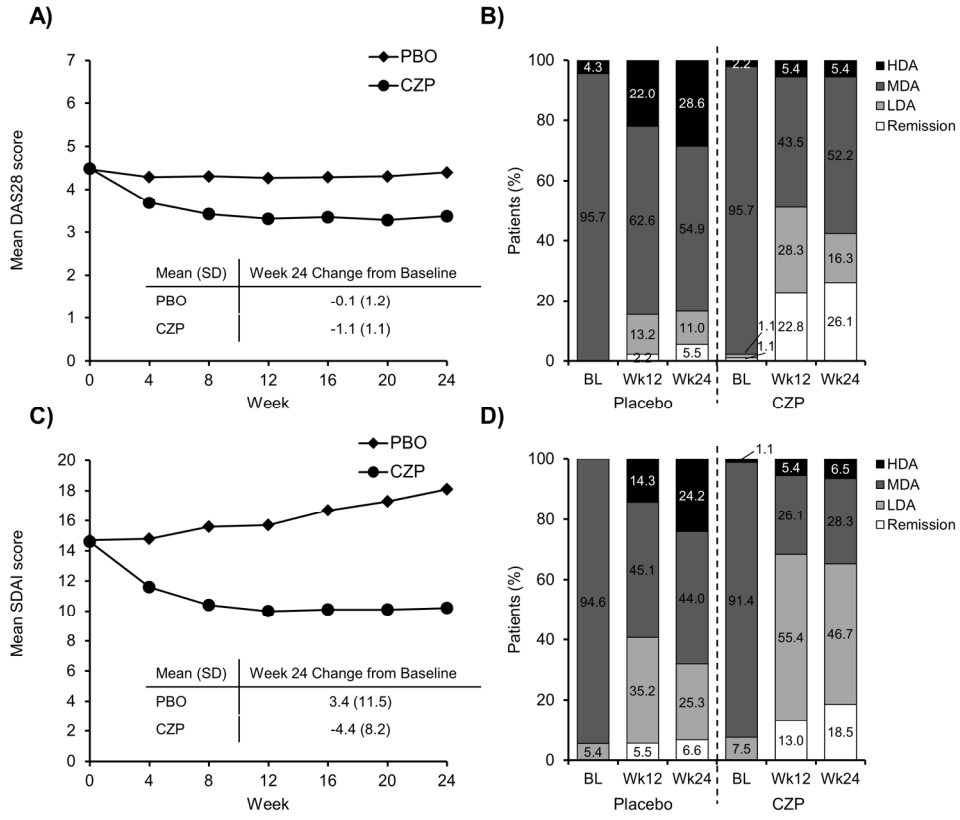
Results are shown as n (%) of patients. *Temporary or permanent discontinuation of the drug. **Treatment-emergent adverse events occurring in >3% of the safety population in the specified period (in either CZP or placebo group). AE, Adverse event.

SUPPLEMENTARY FIGURE TITLES AND LEGENDS

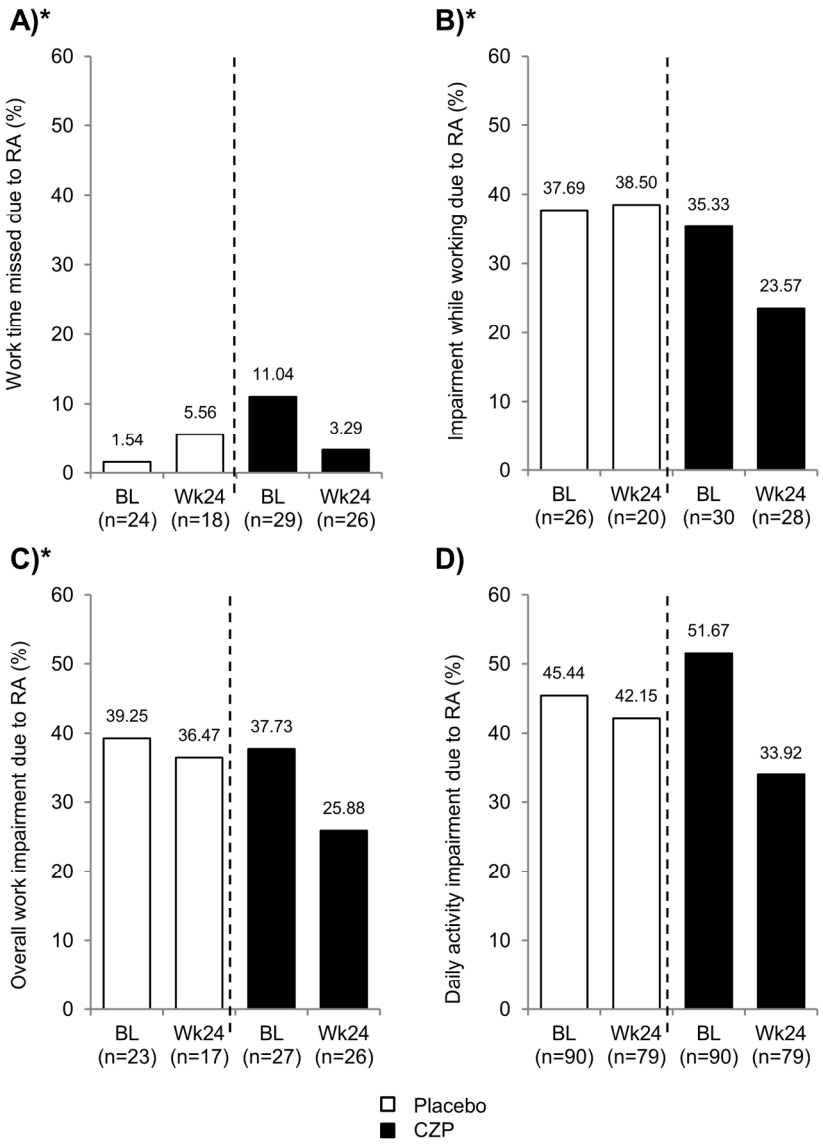
Figure S1. (A) Mean DAS28(ESR) scores up to Week 24 (LOCF); (B) DAS28(ESR) disease state at Baseline, Week 12 and Week 24 (LOCF); (C) Mean SDAI scores up to Week 24 (LOCF); (D) SDAI disease state at Baseline, Week 12 and Week 24 (LOCF).

Figure S2. Effect of CZP on work productivity and daily activities. (A) Absenteeism (% work time missed due to RA); (B) Presenteeism (% impairment while working due to RA); (C) Overall work impairment due to RA (%); (D) Daily activity impairment due to RA (%) (ITT population, observed data).

Figure S3. Kaplan-Meier curve for loss of CDAI remission (CDAI score >2.8 at 2 consecutive visits) after Week 24 (W24 Remitter Set, n=24).

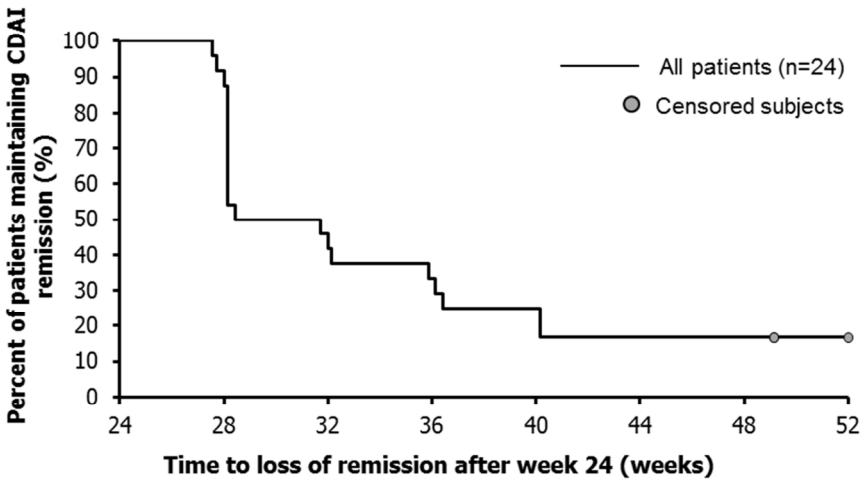


180x150mm (300 x 300 DPI)



* Based on employed patients only.

180x228mm (300 x 300 DPI)



Patients who completed the Week 52 visit or withdrew after Week 24 visit without losing remission were censored in analysis at the time of completion or withdrawal

180x116mm (300 x 300 DPI)