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%)

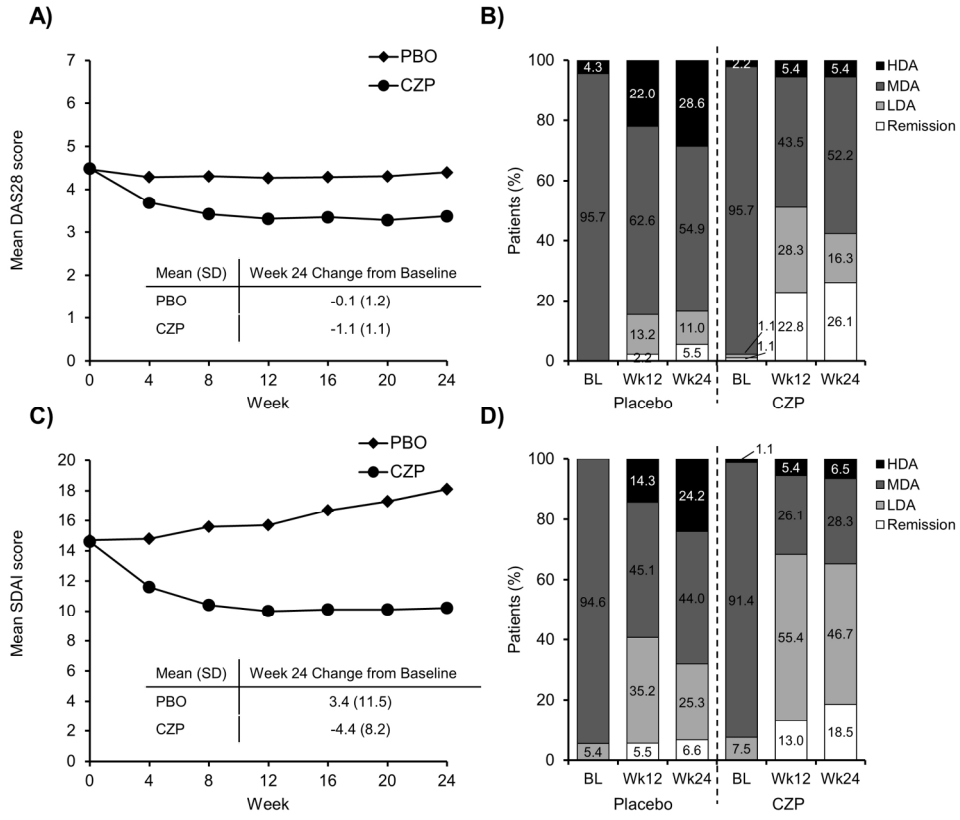
Results are shown as n (%) of patients. *Temporary or permanent discontinuation of the drug. **Treatment-emergent adverse events occurring in >3% of the safety population in the specified period (in either CZP or placebo group). AE, Adverse event.

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).



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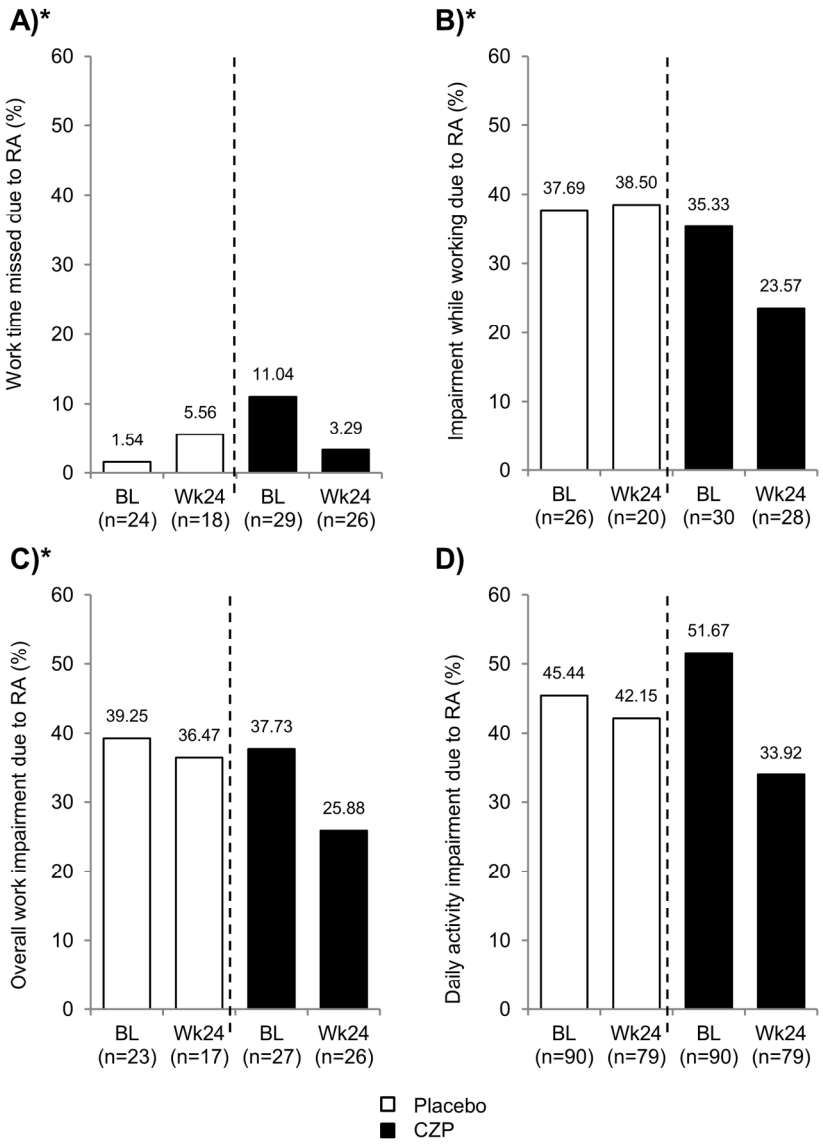

* Based on employed patients only.

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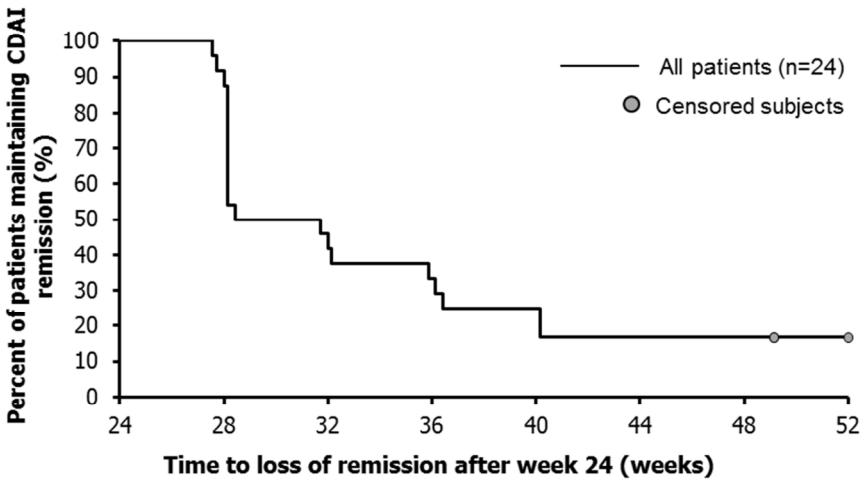

Patients who completed the Week 52 visit or withdrew after Week 24 visit without losing remission were censored in analysis at the time of completion or withdrawal

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