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Original article

Sustained efficacy of certolizumab pegol added to methotrexate in the treatment of rheumatoid arthritis: 2-year results from the RAPID 1 trial

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Abstract

Objective. To evaluate the safety and efficacy of 2-year administration of certolizumab pegol (CZP) + MTX in patients with active RA.

Methods. Patients completing 52 weeks in the Rheumatoid Arthritis Prevention of Structural Damage (RAPID) 1 trial (52-week completers), or withdrawing at week 16 due to lack of ACR20 response were eligible for open-label treatment (CZP 400 mg every other week + MTX). After 2 years' treatment, HAQ-Disability Index response, ACR20/50/70 responses, DAS-28 and radiographic progression were assessed in 52-week completers. ACR20/50/70 and DAS-28 were also calculated for the intent-to-treat (ITT) population. Adverse events were assessed in patients who received one or more CZP doses during the study.

Results. At week 100, 88.9% ($n = 216$) of 52-week completers who originally received CZP 200 mg + MTX and open-label treatment remained in the study. In this group, ACR20/50/70 at week 100 were 68.2, 55.2 and 35.6%, respectively. HAQ-DI and DAS-28 improvements were sustained throughout the open-label extension (mean change −0.79 and −3.5 at week 100, respectively). A total of 46.7% ($n = 113$) of CZP 200 mg + MTX 52-week completers achieved low disease activity by week 100. Inhibition of radiographic progression was maintained. Similar findings were observed in 52-week completers who originally received CZP 400 mg + MTX and in the ITT population. Rates of serious infection or malignancies did not increase over time and no new safety signals were observed.

Conclusion. CZP + MTX provided sustained, 2-year inhibition of radiographic progression and sustained improvements in RA clinical signs and symptoms, with no new safety signals observed in patients who completed 2 years of treatment.

Trial registration: clinicaltrials.gov, http://www.clinicaltrials.gov, NCT00175877.

Key words: certolizumab pegol, rheumatoid arthritis, efficacy, RAPID 1, ACR.

CLINICAL SCIENCE

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Introduction

It is important in chronic diseases such as RA that treatment regimens provide sustained efficacy, good tolerability and long-term improvements in patient-reported outcomes, e.g. physical function and health-related quality of life. The combination of TNF inhibitors with MTX has provided a major advance in treating signs and symptoms of RA [1–4] and inhibiting progression of joint damage [4–9].

Certolizumab pegol (CZP) is a PEGylated Fab′ anti-TNF approved for treatment of adults with moderately to severely active RA. In the 52-week phase III, double-blind, randomized, placebo-controlled, multi-centre Rheumatoid Arthritis Prevention of Structural Damage (RAPID) 1 trial, CZP 200 or 400 mg every other week (EOW) + MTX provided rapid and sustained improvements in signs and symptoms and inhibition of radiographic damage in subjects with active RA despite $\geqslant$6 months' treatment with MTX [10]. An open-label extension (OLE) study to RAPID 1 was designed to investigate long-term efficacy and safety of s.c. CZP 400 mg EOW + MTX in patients who completed RAPID 1. Patients who failed to achieve ACR20 responses were withdrawn at week 16 and could also enter the OLE. Here, we report efficacy (ACR20/50/70 response rates, DAS-28, physical function and radiographic progression) and safety of CZP 400 mg EOW + MTX over 2 years.

Patients and methods

Patient populations in the OLE study: 52-week completers and withdrawers

The inclusion criteria for RAPID 1 were previously reported [10]. Two RAPID 1 populations were eligible to enter the OLE study: (i) patients who completed the 52-week RAPID 1 study (52-week completers) and (ii) patients who were ACR20 non-responders at both weeks 12 and 14 in RAPID 1 and had withdrawn at week 16 (upon re-consenting, these patients received open-label (OL) CZP EOW + MTX from week 16 onward) (per study protocol) [10].

Study protocol

The study protocol for RAPID 1 has been described previously [10]. Eligible patients were randomized to either s.c. CZP 400 mg at weeks 0, 2 and 4 followed by 200 or 400 mg EOW thereafter + MTX or placebo CZP + MTX. During the OLE, all patients received CZP 400 mg EOW + MTX. The study was approved by all local independent ethics committees or institutional review boards, and informed and written consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) guidelines. The trial was registered at clinicaltrials.gov (NCT00175877).

Efficacy analyses

In the OLE, efficacy assessments were performed every 12 weeks. The results reported herein are shown by treatment group to which patients were originally randomized in RAPID 1. This interim analysis reports assessments from RAPID 1 baseline through week 100.

Efficacy analyses included mean DAS-28-joint score (ESR) (DAS-28) over 100 weeks, ACR20/50/70 responder rates [11] and mean changes from baseline in individual ACR core components: swollen (66) and tender (68) joint counts, Physician's and Patient's Global Assessments of Disease Activity [100 mm visual analogue scales (VASs)], Patient's Assessment of Arthritis Pain (100 mm VAS), HAQ-Disability Index (HAQ-DI) and CRP. A patient was defined as having low disease activity (LDA) if DAS-28 was $\leqslant$3.2 and in remission if DAS-28 was $\leqslant$2.6 [12].

ACR20/50/70 response rates are presented for 52-week completers entering the OLE. Patients who used rescue medication or withdrew for any reason were considered non-responders (NRs) [NR imputation (NRI)]. For continuous measures, e.g. mean DAS-28 and individual ACR core components, last observations carried forward (LOCF) were used. As a sensitivity analysis, observed ACR response rates, DAS-28 LDA and remission rates are presented for 52-week completers, i.e. rates based on available data at each time point up to week 100. To provide a conservative estimate of clinical response and in line with recent suggestions on OLE [13], DAS-28 values and ACR20/50/70 responder rates were calculated through 2 years for the RAPID 1 intent-to-treat (ITT) population using LOCF and NRI, respectively.

Radiographs of hands, wrists and feet were assessed for joint damage progression using change from baseline in van der Heijde modified total Sharp score (mTSS) [14, 15]; they were obtained at baseline, weeks 24 and 52 in the double-blind phase, and week 100 in OLE for 52-week completers. Radiographs were blinded for patient identity, clinical data, treatment and chronology, and scored simultaneously for all time points per patient by two readers and analysed for mean mTSS, joint space narrowing scores and erosion scores. Change from baseline mTSS was the main radiographic outcome. Missing baseline values in mTSS were not imputed. Missing values for mTSS change from baseline were imputed using linear extrapolation (LinExt), i.e. where data were missing, the last two recorded values were used to extrapolate data of interest. Denominators therefore deviate slightly from ITT population numbers due to non-imputable missing data. Non-progression was defined as a change of $\leqslant$0.5 U from baseline in mTSS.

Safety

Adverse events (AEs) were assessed at each visit; rates are presented with a cut-off at week 100 after baseline calculated from time of first exposure to CZP for all patients who received one or more doses either in RAPID 1 or the OLE (safety population). AEs and serious AEs (SAEs) are presented as cases per 100 patient-years, with exposure censored at the first experience of the

AE. The most frequent AEs and SAEs (i.e. all AEs occurring at ⩾4.0 cases/100 patient-years and all SAEs occurring at ⩾1.0 cases/100 patient-years) are reported herein. AEs and SAEs were presented by system organ class and preferred term, as per the Medical Dictionary for Regulatory Activities (MedDRA version 9.0). Tuberculosis (TB), headache, injection site reactions, lower respiratory tract and lung infections and RA flare were presented according to the MedDRA high-level term. According to the study sponsor, all opportunistic infections, including tuberculosis (TB), were considered SAEs.

Results

Patient disposition

Of the 982 randomized patients in RAPID 1 (ITT population), 572 patients completed 52 weeks of blinded treatment [21.6% ($n = 43$), 64.9% ($n = 255$) and 70.3% ($n = 274$) of patients in the placebo + MTX group, CZP 200 mg + MTX group and CZP 400 mg + MTX group, respectively] (Fig. 1). Of these, 549 [95.3% ($n = 41$), 95.3% ($n = 243$) and 96.4% ($n = 265$)] re-consented and received open-label CZP 400 mg EOW + MTX. At week 100, 500 52-week completers remained in the OLE, consisting of 92.7% ($n = 38$), 88.9% ($n = 216$) and 92.8% ($n = 246$) of those originally receiving placebo + MTX, CZP 200 mg + MTX and CZP 400 mg + MTX, respectively.

Overall, at week 100, 718 (73.1%) patients of the ITT population remained in the study; these comprised 500 52-week completers and 218 patients who withdrew from RAPID 1 at week 16 due to lack of efficacy and re-consented into the OLE from week 16 onwards: 70.5% ($n = 277$), 76.2% ($n = 297$) and 72.4% ($n = 144$) of patients originally receiving CZP 200 mg, CZP 400 mg and placebo, respectively, and who all received CZP 400 mg EOW + MTX in the OLE.

During the OLE, 23 (9.5%), 15 (5.7%) and 4 (9.8%) of 52-week completers originally receiving CZP 200 mg, CZP 400 mg and placebo, respectively, withdrew due to AEs. Meanwhile, 2 (0.8%), 0 (0.0%) and 2 (4.9%) 52-week completers originally receiving CZP 200 mg, CZP 400 mg and placebo, respectively, withdrew due to lack of efficacy.

Baseline demographics and disease characteristics

Patient baseline demographics and disease characteristics were similar for 52-week completers originally receiving CZP 200 or 400 mg + MTX *vs* placebo + MTX, and for 52-week completers entering the OLE *vs* safety population (Table 1).

Efficacy

DAS-28

Improvements in DAS-28 occurring during RAPID 1 in patients treated with CZP + MTX were sustained over 2 years in the OLE. At week 100, among 52-week completers originally receiving CZP 200 or 400 mg + MTX who entered the OLE, mean changes from baseline in DAS-28 (ESR) were −3.5 and −3.5, respectively, and mean DAS-28 (ESR) achieved was 3.4 and 3.4, respectively (Fig. 2A). At week 52, 43.4% ($n = 105$) and 41.1% ($n = 109$) had LDA and 23.5% ($n = 57$) and 25.3% ($n = 67$) were in remission. At week 100, 46.7% ($n = 113$) and 42.6% ($n = 113$) had LDA and 29.2% ($n = 71$) and 29.4% ($n = 78$) were in remission. Furthermore, 82.9% ($n = 87$) and 77.1% ($n = 84$) of those patients who achieved LDA at week 52 also had LDA at week 100. Of the CZP 200 and 400 mg 52-week completers who failed to achieve LDA at week 52, 18.9% ($n = 26$) and 18.6% ($n = 29$) achieved LDA by week 100, and 8.0% ($n = 5$) and 10.3% ($n = 7$) were in remission. Moreover, of those who achieved LDA at week 52, 39.6% ($n = 42$) and 40.5% ($n = 44$) were in remission by week 100. As a sensitivity analysis, observed LDA and remission rates at week 100 were calculated in 52-week completers; LDA and remission rates were 52.6% ($n = 90$) and 34.5% ($n = 59$) in those originally receiving 200 mg, and 47.4% ($n = 90$) and 33.7% ($n = 64$) in those originally receiving 400 mg.

In placebo 52-week completers, reductions in disease activity were observed at week 52. These patients had additional improvements in DAS-28 with the addition of CZP 400 mg in the OLE: mean changes from RAPID 1 baseline were −2.3 and −3.3 at weeks 52 and 100, respectively. Furthermore, these patients achieved a mean DAS-28 at weeks 52 and 100 of 4.6 and 3.6, respectively.

DAS-28 was assessed from RAPID 1 baseline through week 100 in the ITT population. DAS-28 rapidly declined with CZP + MTX treatment and this result was sustained (Fig. 2B) with a mean DAS-28 of 3.9 at week 100. The proportion of patients in CZP (+ MTX) groups achieving LDA and remission at weeks 52 and 100 was similar. At week 52, 32.0% ($n = 125$) and 32.8% ($n = 127$) of patients originally randomized to 200 and 400 mg CZP achieved LDA, and 17.6% ($n = 69$) and 19.6% ($n = 76$) achieved remission. By week 100, 36.1% ($n = 141$) and 34.4% ($n = 133$) achieved LDA and 23.0% in both groups ($n = 90$ and $n = 89$) achieved remission.

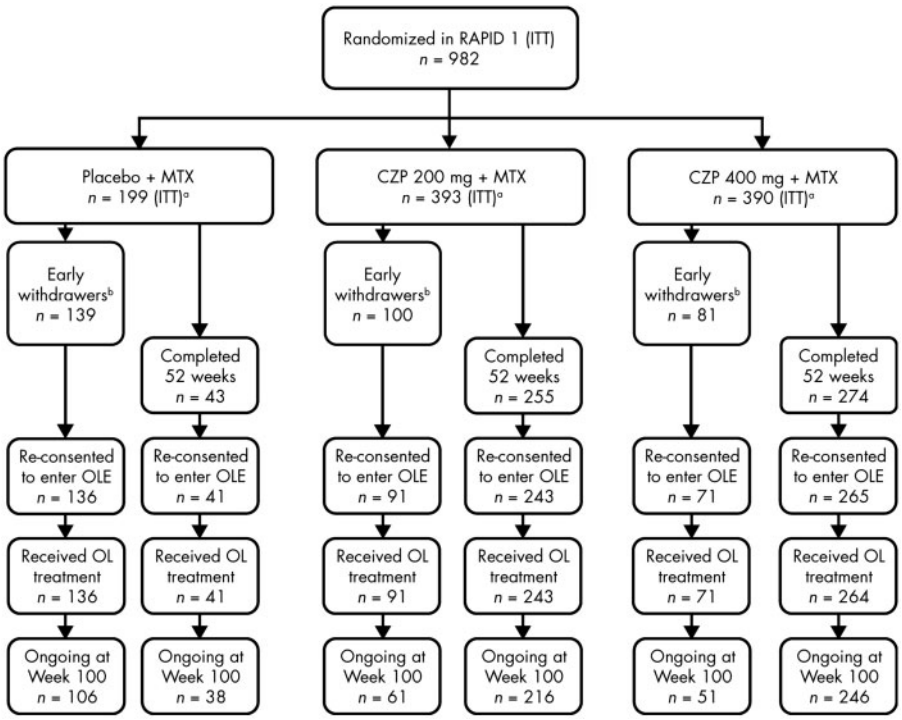
ACR responses and HAQ-DI (physical function)

ACR responses were sustained through 2 years in patients treated with CZP + MTX (Fig. 3). In CZP 200 mg + MTX 52-week completers, ACR20/50/70 response rates using NRI were 68.2% ($n = 163$), 55.2% ($n = 132$) and 35.6% ($n = 85$), respectively, at week 100 (Fig. 3A).

Observed analysis revealed that among CZP 52-week completers, ACR 20/50/70 response rates in those originally receiving 200 mg were 94.2% ($n = 163$), 76.3% ($n = 132$) and 49.1% ($n = 85$), respectively, and 94.8% ($n = 182$), 70.3% ($n = 135$) and 47.4% ($n = 91$), respectively, in those originally receiving 400 mg. Analyses performed using the ITT population (NRI analysis) showed rapid increases in ACR20/50/70 responses following treatment with CZP + MTX; these responses were sustained to week 100 (Fig. 3B).

Improvement in physical function in CZP 52-week completers was sustained to week 100 (Table 2). In placebo 52-week completers, physical function improvements

FIG. 1 Patient disposition.



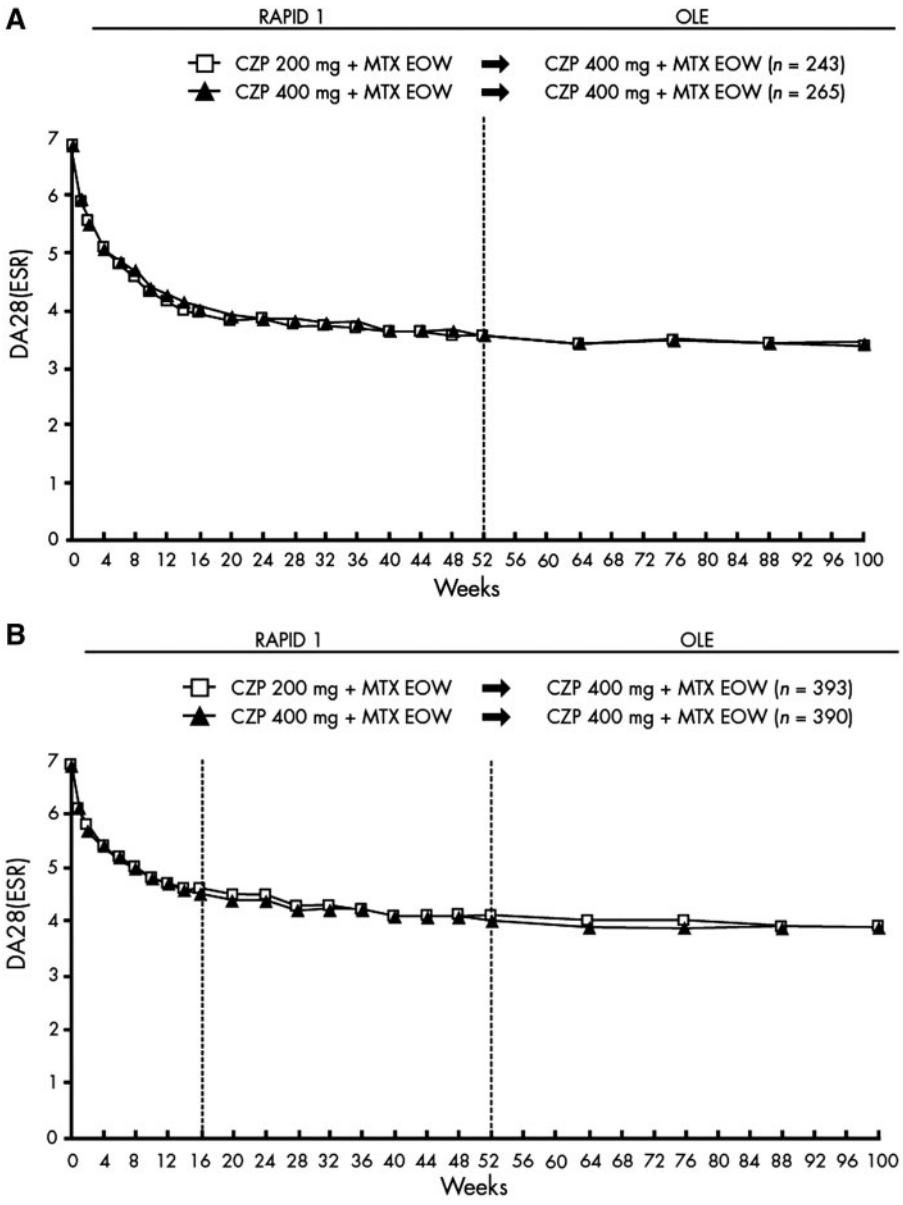
[a]RAPID 1 safety population consisted of 199, 392 and 389 patients in the placebo (PBO) + MTX, CZP 200 mg + MTX and CZP 400 mg + MTX groups, respectively; the safety population in this report consisted of 392 and 389 patients from the RAPID 1 safety population originally receiving CZP 200 and 400 mg, respectively, plus 177 patients who received placebo in RAPID 1 and who re-consented and received one or more doses of CZP in the OLE. [b]Had to leave the study at week 16 per protocol and were eligible for entry into the OLE.

TABLE 1 Baseline demographics and patient characteristics for 52-week completers who entered the OLE and for all patients who received at least one dose of CZP (safety population)

Baseline and patient characteristics	52-week completer population entering OLE			Safety population
	Placebo + MTX ($n = 41$)	CZP 200 mg + MTX ($n = 243$)	CZP 400 mg + MTX ($n = 265$)	All CZP doses[a] ($n = 958$)
Age, mean (S.D.), years	50.2 (11.3)	51.4 (11.6)	51.7 (11.2)	51.8 (11.6)
Gender, female, %	90.2	81.5	84.5	83.1
Duration of disease, mean (S.D.), years	6.2 (4.9)	6.1 (4.1)	6.1 (4.1)	6.2 (4.3)
MTX dose, mean (S.D.), mg/week	14.9 (4.4)	13.5 (4.1)	13.6 (4.0)	13.6 (4.2)
Number of prior DMARDs except MTX, mean (S.D.)	1.0 (1.1)	1.3 (1.3)	1.4 (1.3)	1.3 (1.3)
RF positive ($\geqslant$14 IU/ml), %	78.0	83.5	86.0	81.9
Tender/painful joint count, mean (S.D.)	29.3 (13.5)	30.5 (12.1)	31.4 (13.3)	30.8 (12.9)
Swollen joint count, mean (S.D.)	20.9 (8.2)	22.2 (10.0)	22.2 (9.8)	21.9 (9.8)
HAQ-DI, mean (S.D.)	1.6 (0.72)	1.6 (0.63)	1.7 (0.59)	1.7 (0.60)
DAS-28 (ESR), median (min, max)	6.8 (5.0, 8.7)	7.0. (4.3, 8.6)	6.9 (4.8, 9.1)	7.0 (4.3, 9.1)
CRP[b] (mg/l), median (min, max)	13.0 (3, 152)	15.0 (1, 191)	14.0 (2, 273)	15.0 (1, 273)
ESR (mm/h), median (min, max)	45.0 (25, 118)	44.5 (5, 115)	43.0 (3, 141)	44.0 (3, 141)
mTSS, median (min, max)	27.0 (0.5, 254.0)	27.0 (0.0, 313.5)	27.5 (0.0, 267.0)	20.0 (0.0, 308.2)

[a]Safety population (392 and 389 patients from the RAPID 1 safety population originally receiving CZP 200 and 400 mg, respectively) plus 177 patients who received placebo in RAPID 1 and who re-consented and received one or more doses of CZP in the OLE. [b]Normal CRP 0–6 mg/l.

Fig. 2 DAS-28 (ESR) over 100 weeks (LOCF).



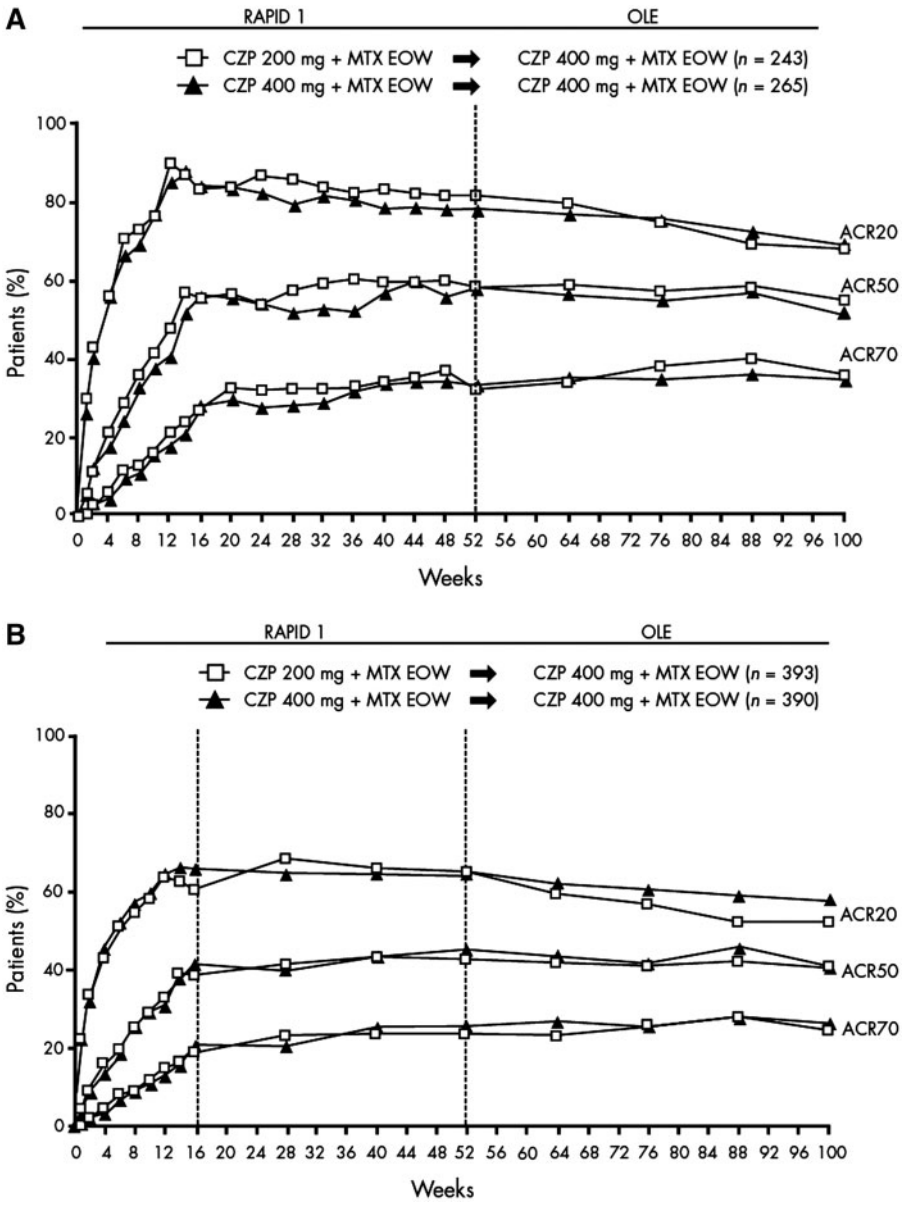
(**A**) The 52-week completers originally receiving CZP 200 or 400 mg + MTX. (**B**) The CZP ITT population (the CZP RAPID 1 ITT population consisted of CZP 52-week completers who entered the OLE, CZP patients who withdrew from RAPID 1 at week 16 and who entered the OLE, CZP patients who withdrew from the double-blind phase at any other time point and CZP patients who did not consent to continue into the OLE).

observed at the end of the double-blind phase were further improved upon receiving CZP 400 mg + MTX in the OLE.

Inhibition of radiographic progression

In CZP 52-week completers entering the OLE, inhibition of radiographic progression observed at year 1 with CZP + MTX was sustained through year 2 (Table 2). Cumulative probability plots (Fig. 4) show comparison of mTSS changes from weeks 0–52 and 52–100 for individual patients originally randomized to either 200 or 400 mg CZP + MTX. In placebo 52-week completers who received OLE CZP in year 2 ($n = 41$), 11 (33.3%) had radiographic progression between weeks 0–52, of which 5 patients (45.5%) showed no radiographic progression between weeks 52–100 and the other 6 patients had less radiographic progression in the second year. Overall, at week 100, 72.4% ($n = 155$), 77.3% ($n = 180$) and 51.5% ($n = 17$) of CZP 200 mg, CZP 400 mg or placebo 52-week completers, respectively, did not have radiographic

FIG. 3 ACR20/50/70 responder rates over 100 weeks (NRI analysis).



(**A**) The 52-week completers initially receiving CZP 200 or 400 mg + MTX and (**B**) the CZP ITT population.

progression, as defined by a change from baseline in mTSS of $\leqslant 0.5$.

Safety

AEs were reported in 839 (87.6%) subjects in the safety population, representing 187.0 cases per 100 patient-years. The majority (96.4%) were mild to moderate and no new safety signals were observed (Table 3). The rate of AEs leading to withdrawal did not increase over time, with 7.3 and 5.6 cases per 100 patient-years reported between 0–12 and 12–24 months, respectively, from CZP initiation. Ninety-nine (10.3%) patients originally receiving placebo or CZP 200 or 400 mg + MTX discontinued treatment due to AEs during the double-blind study and OLE combined. Among 52-week completers, 15 of those originally receiving CZP 200 mg and nine of those originally receiving 400 mg withdrew from the OLE between 52 and 100 weeks due to AEs.

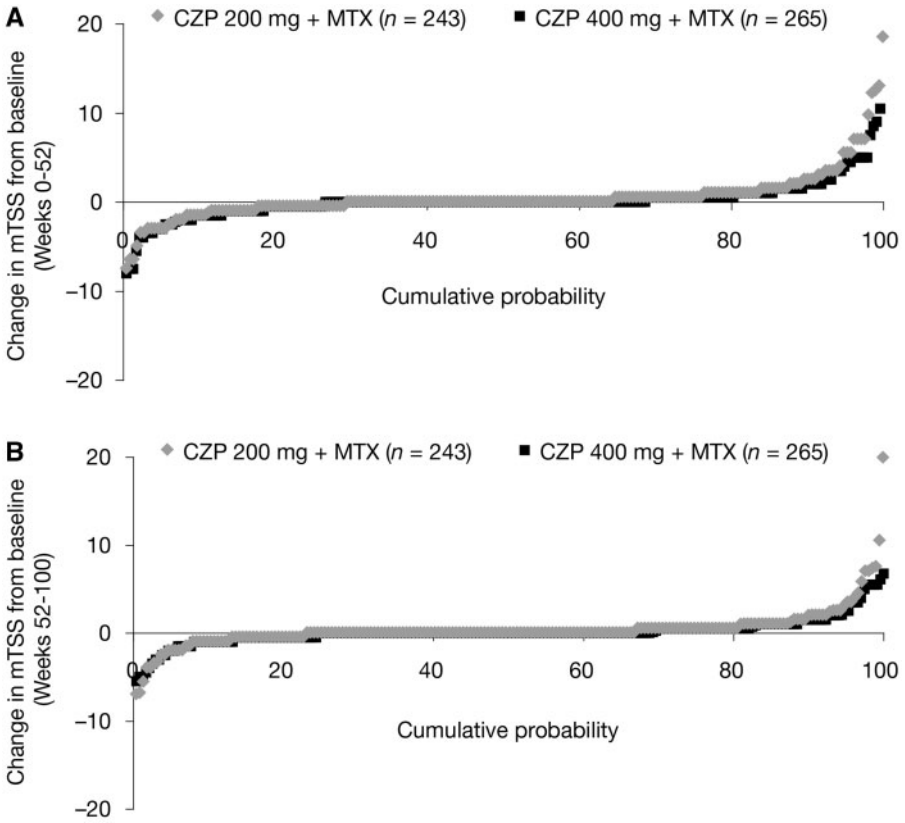
Of 958 patients in the safety population, 220 (23.0%) experienced an SAE (16.1 cases per 100 patient-years) (Table 3). The most commonly reported SAEs were presented under the heading infections and infestations (the vast majority being infections). The rate of serious infection did not increase over time, being 7.3 and 5.4 cases per 100 patient-years between 0–12 and 12–24 months from CZP initiation, respectively.

TABLE 2 Improvement in physical function [HAQ-DI (LOCF)] and inhibition of radiographic progression (LinExt) in 52-week completers

Measurement	Originally receiving CZP 200 mg ($n = 243$)		Originally receiving CZP 400 mg ($n = 265$)	
	Week 52	Week 100	Week 52	Week 100
HAQ-DI change from baseline, mean (S.D.)	−0.75 (0.58)	−0.79 (0.57)	−0.76 (0.58)	−0.78 (0.59)
HAQ-DI score[a], mean (S.D.)	0.89 (0.64)	0.85 (0.61)	0.94 (0.62)	0.92 (0.60)
Change from baseline in mTSS, mean (S.D.)	0.45 (2.8)	0.85 (3.8)	0.54 (4.7)	0.69 (5.3)

[a]In the ITT population, week 100 mean (S.D.) HAQ-DI scores were 1.00 (0.68) and 1.00 (0.66) in patients originally randomized to CZP 200 and 400 mg, respectively.

FIG. 4 Cumulative probability plot of change from baseline in mTSS from (**A**) weeks 0–52 and (**B**) weeks 52–100 in 52-week completers initially receiving 200 or 400 mg CZP + MTX who entered the OLE (LinExt used for missing data).



A total of 11 deaths (0.73 per 100 patient-years; 6 within 12 months of CZP initiation and 5 between 12–24 months) were reported in the safety population (Table 3). This mortality rate is comparable to other studies [16, 17].

Tuberculosis was reported in 15 (1.5%) patients in the safety population; 5 cases in the double-blind study and 10 cases in the OLE, with patients screened for TB according to individual country guidelines. The majority of cases (14/15; 93.3%) occurred in Eastern Europe, and the remaining case (6.7%) occurred in South America (Argentina), i.e. all cases occurred in countries with a high background risk of TB, with no cases in the USA, Canada or Western Europe. No increased risk over time was observed, with rates of 1.0 and 0.92 cases per 100 patient-years between

TABLE 3 AEs in all patients treated with CZP (safety population)[a]

Adverse event	CZP + MTX (*n* = 958)	
	All CZP dose groups, *n* (%)	Cases per 100 patient-years (95% CI)
Duration of exposure, mean (S.D.), days	575.4 (197.7)	
Total AEs	839 (87.6)	187.0 (174.6, 200.1)
AEs leading to withdrawal	99 (10.3)	6.6 (5.4, 8.1)
AEs leading to death[b]	11 (1.2)	0.73 (0.36, 1.3)
AEs due to infection	600 (62.6)	68.3 (63.0, 74.0)
Most frequent AEs due to infection[c]		
Urinary tract infection	97 (10.1)	6.9 (5.6, 8.4)
Nasopharyngitis	83 (8.7)	5.8 (4.6, 7.2)
Upper respiratory tract infection	97 (10.1)	6.8 (5.5, 8.3)
Most frequent non-infectious AEs[c]		
Hypertension	116 (12.1)	8.3 (6.9, 9.9)
Headache	74 (7.7)	5.2 (4.1, 6.5)
Back pain	71 (7.4)	4.9 (3.8, 6.2)
Rheumatoid arthropathies[d]	100 (10.4)	7.0 (5.7, 8.6)
Injection site reactions	92 (9.6)	6.7 (5.4, 8.2)
Rash	59 (6.2)	4.1 (3.1, 5.2)
All SAEs	220 (23.0)	16.1 (14.0, 18.4)
SAE due to infection	92 (9.6)	6.3 (5.1, 7.8)
Most frequent SAEs due to infection[e]		
Lower respiratory tract/lung infection	24 (2.5)	1.6 (1.0, 2.4)
Tuberculosis	15 (1.6)	1.0 (0.6, 1.6)
Most frequent non-infectious SAEs[e]		
Malignancies[f]	9.6 (1.0)	0.7 (0.3, 1.2)
Rheumatoid arthropathies[d]	15 (1.6)	1.0 (0.6, 1.7)

[a]The safety population consists of all patients who received one or more doses of CZP in the double-blind phase and/or the OLE and includes 392, 389 and 177 patients who originally received CZP 200 mg + MTX, CZP 400 mg + MTX or placebo + MTX in RAPID1, respectively. [b]Two deaths due to cardiac arrest, one case each of death due to pulmonary thromboembolism, occult cancer, stage IV cancer of the upper one-third of the stomach, liver tumour, arteriosclerosis, cerebral stroke, myocardial necrosis and purulent peritonitis. In one case the reported cause of death was unclear. [c]AEs occurring at a rate of $\geqslant 4.0$ cases/100 patient-years. [d]Rheumatoid arthropathies includes RA and rheumatoid nodule. [e]SAEs occurring at a rate of $\geqslant 1.0$ cases/100 patient-years. [f]One case each of hepatic neoplasm, oesophageal carcinoma, uterine cancer, breast cancer, colon cancer, endometrial cancer, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type, gastric cancer stage IV, malignant peritoneal neoplasm and metastatic neoplasm.

0–12 months (nine cases) and 12–24 months from CZP initiation (six cases), respectively.

Ten malignancies (automatically selected by MedDRA system organ class neoplasms as benign, malignant and unspecified including cysts and polyps, excluding cases where the high-level term contained benign) were medically confirmed and reported before the study cut-off period (week 100) in 10 patients (0.7 cases per 100 patient-years) during the double-blind study and OLE combined. Between 0–12 and 12–24 months from CZP initiation 0.6 and 0.8 cases per 100 patient-years, respectively, were reported (Table 3). Data from the Surveillance, Epidemiology and End Results (SEER) database indicate that the number of cases expected to be reported was 10.6, resulting in a standardized incidence ratio of 0.9 (95% CI 0.5, 1.7). GLOBOCAN [18] data estimate that the number of expected cases was 8.2, resulting in a standardized incidence ratio of 1.2 (95% CI 0.6, 2.2). No new lymphomas were reported in 52-week completers entering the OLE (one lymphoma was reported in the 12 months from CZP initiation).

The rate of injection site reactions was 9.6% in the OLE phase (6.7 cases per 100 patient-years), and of these AEs the overall rate of injection site pain was 1.8% in the OLE phase (1.1 cases per 100 patient-years): 1.5 cases per 100 patient-years between 0 and 12 months and 0.9 cases per 100 patient-years between 12 and 24 months from CZP initiation, respectively.

Discussion

Treatment with CZP 200 or 400 mg EOW + MTX was shown to provide rapid improvement in signs and symptoms of RA, inhibit radiographic progression and improve physical function over 52 weeks in patients with inadequate response to MTX in the RAPID 1 trial [10]. Results from CZP 52-week completers who entered the OLE demonstrate that CZP added to MTX provides sustained improvements and clinical benefits through 2 years in those patients who had previously responded. Comparable benefits were observed in 52-week completers from both CZP 200 and 400 mg EOW treatment arms.

Increasing the CZP dose from 200 to 400 mg (in the OLE) did not result in additional improvement in 52-week completers, evident by similar DAS-28, ACR20/50/70 response and improvements in HAQ-DI before and after dose escalation. Interestingly, ACR20 response rates dropped slightly between week 52 and 100, whereas ACR50/70 response rates remained stable throughout the second year, despite being very conservative assessments. This suggests that patients with profound responses felt much improved and remained in the study, whereas patients with lower degrees of response did not feel sufficiently improved and withdrew from the OLE partly because of insufficient efficacy. Furthermore, the majority of 52-week completers who re-consented and received open-label treatment remained on therapy at 2 years (91.1% overall; 92.7, 88.9 and 92.8% of those originally receiving placebo + MTX, CZP 200 mg + MTX and CZP 400 mg + MTX, respectively). These findings suggest that CZP added to MTX is an effective longer term treatment option for RA patients with an inadequate MTX response, providing both rapid and sustained efficacy up to 2 years.

Patients originally treated with CZP had sustained improvements in physical function with HAQ reduced from 1.6–1.7 on average at baseline to 0.9 at week 100. This is a key finding, as HAQ is a strong predictor of long-term morbidity and mortality [19, 20]. In established RA there is correlation between joint damage on X-ray and decline in physical function [21–23]. Importantly, radiographic progression was also inhibited over 2 years in patients originally randomized to CZP treatment. Radiographic progression was also inhibited in placebo patients who switched to CZP in the OLE.

A limitation associated with longer term studies is the method of analysis of the results [13]. Analyses focusing on patients completing the randomized phase of the study, or observed analyses focusing only on patients remaining in the study at each time point exclude patients withdrawing due to lack of efficacy or AEs in the double-blind phase. Patient retention rates are thus not taken into account. In order to provide a conservative estimate of efficacy, analyses were performed using the ITT population. These results, i.e. sustained clinical efficacy (ACR20/50/70, DAS-28) over 2 years of CZP treatment, confirmed the findings of the impact of CZP use observed in 52-week completers and were similar to results observed with other TNF-inhibitor studies [24, 25]. Importantly, even when a conservative analysis using NRI from the start of treatment to week 100 was applied, ACR response rates, especially profound ACR50/70 response rates, remained stable. Further to this, in a separate sensitivity analysis, observed data used to determine ACR response rates in CZP 52-week completers showed a mean rapid improvement and sustained results as shown in our initial analyses. In OLEs of RCTs, the efficacy of an agent is supported by the consistency of findings across different analyses populations.

OLE studies provide an opportunity to assess long-term safety. In this study, treatment with CZP 400 mg EOW over 2 years demonstrated an acceptable safety profile, and no new safety signals were observed in the OLE. However, it should be noted that rare events are seldom detected in OLEs due to sample size.

The incidence rates of serious infections did not increase over time (0–12 *vs* 12–24 months). All TB cases reported during the complete treatment period (RAPID 1 and OLE) occurred in Eastern Europe (14/15) and Argentina (1 case), where there is a high background incidence of this disease [10, 26]. No cases of TB were reported in areas of low risk such as the USA, Canada and Western Europe. Patients were permitted to enter RAPID 1 with a positive tuberculin skin test (>5 mm) if baseline chest radiograph was negative for signs of TB; 4 of the 15 reported cases of TB had a tuberculin skin test reading at entry of >5 mm. The incidence rate of malignancies occurring in the safety population did not increase with additional CZP exposure over time, and the number of confirmed cases based on medical review was similar to that expected according to the SEER database and GLOBOCAN estimates. Furthermore, malignancies occurred at a similar rate across all treatment groups (placebo and CZP 200 and 400 mg) in a previous CZP + MTX study (RAPID 2) [10, 27]. The incidence of injection site pain throughout the double-blind study and OLE was low in the safety population and there was a low incidence of treatment discontinuation due to AEs. Taken together, the low discontinuation rate due to AE or injection site pain may have important implications for adherence to CZP treatment.

These results demonstrate that CZP + MTX provides sustained, longer-term benefits in terms of improvement in clinical signs and symptoms of RA, inhibition of structural joint damage and improvement in physical function with a stable risk–benefit profile through 2 years of continued therapy. No new or increased safety signals and no increase in the rates of serious infection events or malignancies over time were observed.

Rheumatology key messages

- CZP + MTX provided sustained, 2-year inhibition of radiographic progression in RA patients.
- CZP + MTX provided sustained improvements in signs and symptoms of RA.
- No new safety signals were observed in RA patients treated over 2 years.

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