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ORIGINAL ARTICLE

Effect of Certolizumab Pegol on Multiple Facets of Psoriatic Arthritis as Reported by Patients: 24-Week Patient-Reported Outcome Results of a Phase III, Multicenter Study

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Objective. **To examine the effect of certolizumab pegol (CZP) on patient-reported outcomes (PROs) in psoriatic arthritis (PsA) patients with and without prior tumor necrosis factor (TNF) inhibitor exposure.**

Methods. **The ongoing phase III RAPID-PsA trial was double blind and placebo controlled to week 24. Patients were randomized 1:1:1 to placebo every 2 weeks or CZP 400 mg at weeks 0, 2, and 4, followed by either CZP 200 mg every 2 weeks or CZP 400 mg every 4 weeks. PRO measures evaluated were the Health Assessment Questionnaire (HAQ) disability index (DI), health status (measured by the Short Form 36 [SF-36] health survey), Psoriatic Arthritis Quality of Life (PsAQOL), Fatigue Assessment Scale, patient assessment of pain (visual analog scale), and Dermatology Life Quality Index (DLQI). Post hoc analyses of PROs in patients with and without prior TNF inhibitor exposure were conducted. Change from baseline for all PROs was analyzed for the randomized population using analysis of covariance with last observation carried forward imputation.**

Results. **A total of 409 patients were randomized. Twenty percent had received a prior TNF inhibitor. Baseline demographics were similar between the treatment groups. At week 24, clinically meaningful differences in HAQ DI, SF-36, PsAQOL, fatigue, pain, and DLQI were observed in both CZP arms versus placebo ($P < 0.001$), irrespective of prior TNF inhibitor exposure. More CZP-treated patients reached SF-36 general population norms than placebo-treated patients.**

Conclusion. **Both CZP dosing schedules provided rapid improvements in PROs across multiple disease aspects in patients with PsA. The benefits of CZP treatment for health-related quality of life were seen across generic, PsA-specific, and dermatology-specific measures and were observed in patients regardless of prior TNF inhibitor exposure.**

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that affects up to 30% of patients with psoriasis (1,2), with more than half of patients exhibiting progressive, erosive, functionally impairing (3,4), and rapidly progressing joint damage (3,5). PsA has a considerable negative impact on multiple physical and emotional aspects of patients' lives (6,7). Patients with PsA have reported poorer health-related quality of life (HRQOL) compared to the general population and to psoriasis patients (6,8), and experience a level of functional impairment similar to patients with rheumatoid arthritis (RA) (9).

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Significance & Innovations

- This is the first study to investigate the impact of certolizumab pegol (CZP) treatment on patient-reported outcomes in psoriatic arthritis (PsA).
- We demonstrated the efficacy of CZP in improving patient-relevant outcomes across various aspects of patients' lives that are impacted by PsA.
- The treatment benefits were observed both in patients who were naive to tumor necrosis factor (TNF) inhibitor therapy and in those who had previously received treatment with a TNF inhibitor.

Possibly due to the complex presentation of PsA, several distinct clinical domains have been recommended to be assessed in clinical trials, including joint counts, skin, enthesitis, dactylitis, patient global assessments, function, pain, and quality of life (10). A variety of measures for these domains have been developed and utilized in PsA clinical trials (11,12). Furthermore, both generic and PsA-specific HRQOL measures have been used to assess HRQOL in PsA patients, although the degree to which these measures quantify the same concepts, and their relationship to clinical outcomes, have not been extensively reported (12).

Certolizumab pegol (CZP) is a PEGylated Fc-free anti–tumor necrosis factor (anti-TNF) that was shown to improve patient-reported outcomes (PROs) in RA (13) and plaque psoriasis (14). The efficacy and safety of CZP in PsA have been investigated in RAPID-PsA, which is the first published trial in PsA to include patients with prior exposure to TNF inhibitors (15). A detailed description of the methods and results for the efficacy and safety outcomes of the RAPID-PsA study has been published previously (15).

MATERIALS AND METHODS

Patients. Patients were ages ≥18 years and had a diagnosis of adult-onset active PsA of ≥6 months' duration, as defined by the criteria of the Classification of Psoriatic Arthritis Study Group (16). Patients had to have active psoriatic skin lesions or a documented history of psoriasis, active arthritis (≥3 tender joints and ≥3 swollen joints at screening and baseline), an erythrocyte sedimentation rate ≥28 mm/hour (Westergren method) and/or a C-reactive protein (CRP) concentration greater than the upper limit of normal, and failed treatment with, or been resistant to, ≥1 disease-modifying antirheumatic drug (DMARD). Up to 40% of patients could have previously been treated with 1 TNF inhibitor.

Patients were excluded if they had a form of inflammatory arthritis other than PsA or a secondary, noninflammatory condition symptomatic enough to interfere with evaluation of CZP for PsA; had received previous treatment for PsA or psoriasis with >2 biologic agents or previous treatment with ≥2 TNF inhibitors; or had a primary failure to respond to TNF inhibitor therapy.

Study design. RAPID-PsA is an ongoing, phase III, multicenter study in PsA patients. The trial is double blind and placebo controlled to week 24, dose blind to week 48, and then open label to study closure. Patients were randomized 1:1:1 to placebo or subcutaneous CZP 400 mg at weeks 0, 2, and 4 (loading dose), followed by either CZP 200 mg every 2 weeks or CZP 400 mg every 4 weeks (15). Randomization was stratified per protocol, according to investigator site and prior TNF inhibitor exposure. Those patients who were receiving DMARDs at baseline continued with their DMARD medication during the study. Patients receiving placebo who failed to achieve a ≥10% decrease in tender and swollen joint counts at weeks 14 and 16 underwent a mandatory escape to active treatment in a blinded manner and were re-randomized at week 16 to receive CZP 200 mg every 2 weeks or CZP 400 mg every 4 weeks, following the loading dose at weeks 16, 18, and 20. All patients remained in the trial, and blinding was maintained for all patients to week 24.

The primary clinical end point was the American College of Rheumatology criteria for ≥20% improvement (17) at week 12; the primary radiographic end point (reported separately) was the change from baseline in the modified total Sharp score at week 24 (15,18). Safety data are reported in the primary publication for this trial (15).

PROs. Secondary end points included change from baseline in Health Assessment Questionnaire (HAQ) disability index (DI) score at weeks 12 and 24, Short Form 36 (SF-36) health survey–derived variables at week 24, Psoriatic Arthritis Quality of Life (PsAQOL) at week 24, Fatigue Assessment Scale (FAS) at week 24, and patient assessment of arthritis pain at week 24. Other end points included change from baseline in the Dermatology Life Quality Index (DLQI) at week 24 for both the overall population and the subpopulation of patients with ≥3% body surface area (BSA) skin involvement at baseline.

Improvements in PROs were also measured using minimum clinically important differences (MCIDs). An MCID is a clinically relevant change in a patient's status. These were defined as a ≥10-point decrease from baseline for pain (19), a ≥1-point decrease from baseline for the FAS, and a ≥2.5-point increase from baseline in the physical component summary (PCS) and mental component summary (MCS) of health status by the SF-36 (20). Improvements in HAQ DI score were assessed using 2 values for

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Table 1. Baseline demographics and disease severity characteristics*

	Placebo (n = 136)	CZP 200 mg every 2 weeks (n = 138)	CZP 400 mg every 4 weeks (n = 135)
Demographic characteristics			
Age, years	47.3 ± 11.1	48.2 ± 12.3	47.1 ± 10.8
Sex, % female	58.1	53.6	54.1
Weight, kg	82.6 ± 19.9†	85.8 ± 17.7	84.8 ± 18.7
BMI, kg/m^2	29.2 ± 6.7†	30.5 ± 6.2	29.6 ± 6.6
Arthritis characteristics			
CRP, median (range) mg/liter‡	9.0 (0.2–131.0)	7.0 (0.2–238.0)	8.7 (0.1–87.0)
ESR, median (range) mm/hour	34.0 (6.0–125.0)	35.0 (5.0–125.0)	33.0 (4.0–120.0)
Tender joint count (range 0–68 joints)	19.9 ± 14.7	21.5 ± 15.3	19.6 ± 14.8
Swollen joint count (range 0–66 joints)	10.4 ± 7.6	11.0 ± 8.8	10.5 ± 7.5
Modified total Sharp score	24.4 ± 49.7	18.0 ± 30.6	22.8 ± 46.5
Erosion score	14.0 ± 27.0	10.3 ± 17.3	13.4 ± 25.2
Joint space narrowing score	10.4 ± 23.3	7.7 ± 14.5	9.4 ± 22.1
Physician's assessment of disease activity (VAS), mm	58.7 ± 18.7	56.8 ± 18.2	58.2 ± 18.9
Enthesitis, %§	66.9	63.8	62.2
LEI¶	2.9 ± 1.6	3.1 ± 1.7	2.9 ± 1.6
Dactylitis, %#	25.7	25.4	28.1
LDI¶	65.6 ± 90.4	45.3 ± 36.0	56.8 ± 75.9
Psoriasis characteristics			
≥3% BSA psoriasis, no. (%)	86 (63.2)	90 (65.2)	76 (56.3)
PASI, median (range)**	7.1 (0.3–55.2)	7.0 (0.6–72.0)	8.1 (0.6–51.8)
Nail involvement, %	75.7	66.7	77.8
mNAPSI	3.4 ± 2.2	3.1 ± 1.8	3.4 ± 2.2
Patient-reported outcomes			
Patient assessment of disease activity, mm	57.0 ± 22.4	60.2 ± 21.0	60.2 ± 18.4
Patient assessment of arthritis pain, mm	60.0 ± 22.0	59.7 ± 20.7	61.1 ± 18.5
Fatigue (range 0–10)	5.8 ± 2.0	6.3 ± 2.0	6.2 ± 2.1
HAQ DI (range 0–3)	1.3 ± 0.7	1.3 ± 0.7	1.3 ± 0.6
SF-36 PCS	33.8 ± 7.9	33.1 ± 7.7	33.2 ± 7.5
SF-36 MCS	42.4 ± 12.5	40.7 ± 11.2	41.9 ± 12.5
PsAQOL	10.9 ± 5.6	11.1 ± 5.5	11.3 ± 5.6
DLQI	7.9 ± 6.8	9.2 ± 7.4	8.5 ± 7.3
DLQI (patients with ≥3% BSA psoriasis)	9.8 ± 6.9	11.7 ± 7.3	10.7 ± 7.6
Prior TNF inhibitor exposure, no. (%)	26 (19.1)	31 (22.5)	23 (17.0)
Adalimumab	13 (9.6)	10 (7.2)	10 (7.4)
Etanercept	9 (6.6)	15 (10.9)	8 (5.9)
Infliximab	2 (1.5)	5 (3.6)	5 (3.7)
Golimumab	2 (1.5)	1 (0.7)	1 (0.7)

* Values are the mean ± SD unless indicated otherwise. CZP = certolizumab pegol; BMI = body mass index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VAS = visual analog scale; LEI = Leeds Enthesitis Index; LDI = Leeds Dactylitis Index; BSA = body surface area; PASI = Psoriasis Area and Severity Index; mNAPSI = modified Nail Psoriasis Severity Index; HAQ = Health Assessment Questionnaire; DI = disability index; SF-36 = Short Form 36; PCS = physical component summary; MCS = mental component summary; PsAQOL = Psoriatic Arthritis Quality of Life; DLQI = Dermatology Life Quality Index; TNF = tumor necrosis factor.
† N = 135.
‡ Normal range of CRP <8.0 mg/liter.
§ Presence of enthesitis at baseline was defined as a baseline LEI score of >0.
¶ LDI and LEI reported for patients with dactylitis and enthesitis, respectively, at baseline.
# Presence of dactylitis at baseline was assessed using the LDI.
** PASI for patients with ≥3% BSA psoriatic skin involvement at baseline.

the MCID: the prespecified value of a ≥0.3-point decrease from baseline (21) and the most recently accepted estimate for the MCID of the HAQ DI (a ≥0.35-point decrease from baseline) (22).

Statistical analysis. All end point analyses were conducted in the randomized set of patients using an intent-to-treat analysis (i.e., based on all patients randomized to CZP or placebo in the study, regardless of their subsequent disposition). Adjusted mean changes from baseline in all PROs were obtained using analyses of covariance with treatment, region, and prior TNF inhibitor exposure as model factors and baseline score as a covariate. Missing data were imputed by the last observation carried forward method.

Spearman's rank correlation analyses at baseline and week 12 were conducted to assess the overlap in concepts addressed by the health status/HRQOL measures (SF-36 PCS, SF-36 MCS, PsAQOL, and DLQI), as well as the correlation between improvements in HRQOL measures and in clinical outcomes of PsA (Disease Activity Score in

Table 2. Mean baseline scores and mean changes from baseline at week 24 in patient-reported outcomes in patients with and without prior TNF inhibitor exposure*

	No prior TNF inhibitor exposure		Prior TNF inhibitor exposure	
	Placebo (n = 110)	CZP combined arms (n = 219)	Placebo (n = 26)	CZP combined arms (n = 54)
Pain, mm				
Baseline	59.3	58.8	63.2	67.0
Change	−11.8	−27.3†	−8.8	−33.3†
Fatigue				
Baseline	5.7	6.2	6.4	6.5
Change	−0.7	−2.0†	−0.5	−2.1‡
HAQ DI				
Baseline	1.29	1.29	1.37	1.37
Change	−0.20	−0.45†	−0.04	−0.60†
SF-36 PCS				
Baseline	33.8	33.5	33.9	31.9
Change	2.9	7.9†	−1.2	8.4†
SF-36 MCS				
Baseline	42.5	41.1	41.7	42.3
Change	0.8	4.5‡	0.5	4.6
PsAQOL				
Baseline	10.7	11.2	11.6	11.4
Change	−1.5	−3.8†	−0.4	−4.1‡
DLQI§				
Baseline	9.0	11.1	12.6	11.7
Change	−1.3	−7.2†	−2.0	−9.0†

* TNF = tumor necrosis factor; CZP = certolizumab pegol; HAQ = Health Assessment Questionnaire; DI = disability index; SF-36 = Short Form 36; PCS = physical component summary; MCS = mental component summary; PsAQOL = Psoriatic Arthritis Quality of Life; DLQI = Dermatology Life Quality Index.
† $P < 0.001$ for CZP vs. placebo.
‡ $P < 0.05$ for CZP vs. placebo.
§ DLQI for patients with ≥3% body surface area psoriatic skin involvement at baseline.

28 joints using the CRP level, tender joint count, swollen joint count, and the Psoriasis Area and Severity Index).

RESULTS

Patient disposition. A total of 409 patients were randomized; 368 patients (90%) completed the 24-week, double-blind phase of the RAPID-PsA study. There were 59 patients from the placebo group who underwent mandatory withdrawal and were randomized in a blinded manner to escape treatment from week 16. Patient disposition is reported elsewhere (15). Baseline characteristics were similar between the groups (Table 1). Patients with and without prior exposure to TNF inhibitors had similar baseline characteristics (see Supplementary Table 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22256/abstract). Those patients with prior exposure to a TNF inhibitor had withdrawn from previous treatment primarily due to a lack of response (see Supplementary Table 2, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22256/abstract).

PRO burden of disease at baseline. At baseline, patients reported moderate to severe impairment in physical function and HRQOL (Table 1). The mean HAQ DI score at baseline was 1.3 in both placebo patients and patients randomized to CZP. At baseline, 6.5%, 6.7%, and 5.1% of CZP 200 mg every 2 weeks, CZP 400 mg every 4 weeks, and placebo patients, respectively, reported SF-36 PCS values above the first quartile of the age- and sex-matched population normal values; for the mental components, 31.2%, 40.0%, and 40.4% of patients were above the first quartile of the SF-36 MCS population norms for the CZP 200 mg every 2 weeks, CZP 400 mg every 4 weeks, and placebo groups, respectively. Patients who had previously been treated with a TNF inhibitor had a slightly higher PRO burden of disease at baseline (Table 2).

CZP impact on PROs. Physical function, as measured by the HAQ DI, was improved in the CZP groups compared to placebo from as early as week 2 ($P < 0.01$). Statistically significant improvements were observed in both the CZP 200 mg every 2 weeks and CZP 400 mg every 4 weeks treatment arms at week 24 (−0.52 and −0.43, respectively, versus −0.17 for placebo; $P < 0.001$ for both doses) (Table 3).

At week 24, substantially more CZP-treated patients reported improvements greater than the MCID for the HAQ

Table 3. Mean changes from baseline in patient-reported outcomes in RAPID-PsA*

	Week 4			Week 12			Week 24		
	Placebo (n = 136)	CZP 200 mg every 2 weeks (n = 138)	CZP 400 mg every 4 weeks (n = 135)	Placebo (n = 136)	CZP 200 mg every 2 weeks (n = 138)	CZP 400 mg every 4 weeks (n = 135)	Placebo (n = 136)	CZP 200 mg every 2 weeks (n = 138)	CZP 400 mg every 4 weeks (n = 135)
Pain, mm	−5.4 ± 18.3	−16.0 ± 24.0†	−18.6 ± 22.8†	−9.9 ± 21.0	−26.9 ± 28.7†	−22.5 ± 23.4†	−11.2 ± 21.8	−28.6 ± 28.8†	−28.4 ± 25.5†
Fatigue	−0.2 ± 2.1	−1.2 ± 2.1†	−1.3 ± 2.2†	−0.3 ± 2.2	−2.1 ± 2.3†	−1.4 ± 2.1†	−0.6 ± 2.3	−2.2 ± 2.6†	−1.9 ± 2.3†
HAQ DI	−0.13 ± 0.31	−0.30 ± 0.48†	−0.33 ± 0.44†	−0.16 ± 0.36	−0.45 ± 0.56†	−0.39 ± 0.47†	−0.17 ± 0.43	−0.52 ± 0.66†	−0.43 ± 0.54†
SF-36 PCS	1.5 ± 5.3	4.5 ± 7.0†	4.9 ± 7.1†	1.8 ± 6.1	7.5 ± 9.1†	6.7 ± 7.7†	2.1 ± 7.2	8.4 ± 10.1†	7.6 ± 8.1†
SF-36 MCS	0.2 ± 7.1	3.1 ± 9.2‡	2.4 ± 8.4‡	1.4 ± 8.6	4.9 ± 10.0‡	2.4 ± 8.7	0.7 ± 9.9	5.5 ± 10.2†	3.5 ± 9.6‡
PsAQOL	−0.8 ± 3.7	−2.4 ± 3.9†	−2.5 ± 4.5†	−1.0 ± 4.1	−3.6 ± 4.6†	−2.8 ± 4.9†	−1.3 ± 4.7	−4.4 ± 5.1†	−3.3 ± 5.1†
DLQI	−1.7 ± 4.3	−3.9 ± 5.7†	−3.2 ± 4.9‡	−1.1 ± 5.4	−5.8 ± 6.9†	−4.5 ± 6.2†	−1.4 ± 5.2	−6.3 ± 7.5†	−5.2 ± 6.2†
DLQI (patients with ≥3% BSA psoriasis at baseline)	−2.1 ± 4.5	−5.0 ± 6.1‡	−4.0 ± 5.1‡	−1.0 ± 5.8	−7.8 ± 7.1†	−5.9 ± 6.8†	−1.5 ± 5.6	−8.6 ± 7.8†	−6.4 ± 6.8†

* Values are the mean ± SD. CZP = certolizumab pegol; HAQ = Health Assessment Questionnaire; DI = disability index; SF-36 = Short Form 36; PCS = physical component summary; MCS = mental component summary; PsAQOL = Psoriatic Arthritis Quality of Life; DLQI = Dermatology Life Quality Index; BSA = body surface area.
† $P < 0.001$ for CZP vs. placebo.
‡ $P < 0.05$ for CZP vs. placebo.

Table 4. Proportion of patients achieving an MCID at week 24 for pain, fatigue, HAQ DI (both 0.3 and 0.35 thresholds), SF-36 PCS, and SF-36 MCS*

	Placebo (n = 136)	CZP 200 mg every 2 weeks (n = 138)	CZP 400 mg every 4 weeks (n = 135)
Pain	29.4	69.6	68.9
Fatigue	28.7	65.9	63.0
HAQ DI (MCID 0.3) (20)	15.4	49.3	48.1
HAQ DI (MCID 0.35) (21)	15.4	49.3	48.1
SF-36 PCS†	30.1 (11.0)	63.8 (33.3)	71.9 (29.6)
SF-36 MCS†	22.8 (26.5)	54.3 (47.1)	48.9 (51.1)

* Values are the percentage. $P < 0.001$ for all certolizumab pegol (CZP) groups vs. placebo. MCID = minimum clinically important difference; HAQ = Health Assessment Questionnaire; DI = disability index; SF-36 = Short Form 36; PCS = physical component summary; MCS = mental component summary.
† Values in parentheses represent the percentage of patients within the first quartile of the population norm.

DI than those treated with placebo ($P < 0.001$) (Table 4). The same improvement was observed with both the 0.3 and 0.35 MCID values. These improvements were seen for both MCID values from week 4 onward ($P < 0.001$).

Patients receiving CZP reported greater improvements in pain compared to placebo patients from week 1 ($P < 0.001$) to week 24 ($P < 0.001$) (Table 3), and at week 24, more CZP-treated patients reported improvements greater than or equal to the MCID for pain compared to the placebo group ($P < 0.001$) (Table 4). The proportion of patients reporting an improvement greater than or equal to the MCID was markedly higher in the CZP groups from week 1 onward (44.9% for CZP 200 mg every 2 weeks and 43.7% for CZP 400 mg every 4 weeks versus 26.5% for placebo; $P < 0.005$ for both doses).

Fatigue was substantially reduced in the CZP groups compared to placebo from week 2 ($P \leq 0.05$) to week 24 ($P < 0.001$) (Table 3). At week 24, more CZP-treated patients reported improvements greater than or equal to the MCID for fatigue compared to the placebo group ($P < 0.001$) (Table 4), with differences observed between CZP 200 mg every 2 weeks and CZP 400 mg every 4 weeks patients versus placebo patients from week 1 onward (50.7% and 42.2% versus 33.8%, respectively).

HRQOL. Patients receiving CZP experienced a rapid, clinically relevant improvement in PsAQOL compared to those receiving placebo from week 1 (CZP 200 mg every 2 weeks: −1.17, CZP 400 mg every 4 weeks: −1.40, placebo: −0.58) to week 24 ($P < 0.001$) (Table 3). Patients in the CZP groups also reported a rapid and sustained improvement in the DLQI compared to placebo patients (Table 3), with those who had ≥3% BSA psoriasis involvement at baseline experiencing greater improvements in the DLQI (Table 3).

Substantial improvements compared to placebo were seen in all domains of the SF-36 from the first assessment (week 4; $P < 0.05$) to week 24 (Figure 1). At week 24, more

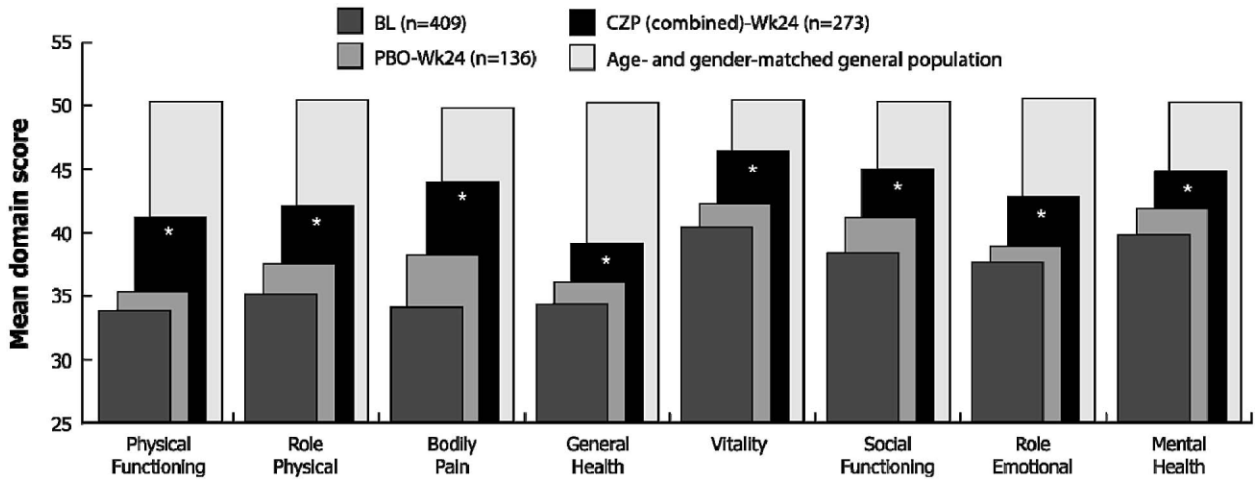

Figure 1. Improvements in Short Form 36 domains at week 24. BL = baseline; CZP = certolizumab pegol; PBO = placebo; * = $P < 0.001$ for CZP vs. PBO.

CZP-treated patients reported improvements greater than or equal to the MCID for the SF-36 PCS and SF-36 MCS compared to the placebo group ($P < 0.001$ for all) (Table 4).

At week 24, 33.3% and 29.6% of patients in the CZP 200 mg every 2 weeks and CZP 400 mg every 4 weeks groups reported higher SF-36 scores than the first quartile of population norms in terms of the PCS, compared to 11.0% of placebo patients. The proportion of patients above the first quartile of population norms for the MCS was also higher in the CZP groups compared to placebo at week 24 (47.1% and 51.1% versus 26.5% for CZP 200 mg every 2 weeks and CZP 400 mg every 4 weeks versus placebo, respectively).

Moderate to high correlations (−0.48 to −0.76) were observed between SF-36 and PsAQOL outcomes at baseline and week 12; conversely, poor correlations (−0.18 to 0.46) were calculated between the DLQI and other health status/HRQOL measures (see Supplementary Table 3, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22256/abstract). Poor correlations were observed between improvements in clinical outcomes and in HRQOL outcomes (see Supplementary Table 3, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22256/abstract).

Prior TNF inhibitor exposure. The treatment effect of CZP versus placebo on pain, physical function, and PsAQOL was slightly larger in patients who had prior TNF inhibitor exposure compared to TNF inhibitor–naive patients. However, similar treatment responses in fatigue, SF-36 PCS and MCS, and DLQI were reported in patients with and without prior exposure to TNF inhibitors (Table 2).

DISCUSSION

At trial baseline, patients in each treatment group were observed to have significant impairments in physical function and HRQOL as measured by PROs. CZP rapidly improved multiple PROs when compared to placebo. This included improvements from week 1 in pain and week 2 in fatigue and physical function, both in population means and in the proportion of patients achieving the MCID. Furthermore, CZP treatment provided rapid benefits in both physical and emotional components of health status and HRQOL across generic (SF-36 domains from week 4), PsA-specific (PsAQOL from week 1), and dermatology-specific (DLQI from week 2) measures, indicating that CZP can act simultaneously on multiple disease components to provide comprehensive disease control. This diverse improvement has not been observed for other TNF inhibitors in the treatment of patients with PsA (23), although care should be taken when making direct comparisons between studies (24).

Improvements in SF-36 domains were clinically relevant from week 4 through to week 24, with improvements in the physical components of SF-36 being slightly greater than the mental components, possibly because these outcomes were less severely affected by PsA prior to treatment (as demonstrated by the greater impairment in the PCS compared to the MCS at baseline). There was also a substantial increase in the proportion of patients who reported SF-36 scores greater than the first quartile of population norms, and whose self-reported health status might therefore be considered "normal" (based on their age and sex). These improvements demonstrate that treatment with CZP may help patients to achieve a similar health status to that of the general population.

This study revealed that, at week 24, substantially more CZP patients achieved the MCID in pain, fatigue, physical function, and physical and mental component scores of the SF-36. Additionally, a rapid and sustained improvement in DLQI was observed, particularly in patients with ≥3% BSA skin involvement at baseline.

Although the PRO burden of disease at baseline was higher in patients who had previously received TNF inhibitors, these patients experienced a similar response to CZP compared to those who were TNF inhibitor naive.

Correlation analyses demonstrated overlap between the generic SF-36 and the PsA-specific PsAQOL tool, possibly

indicating that measuring both of these outcomes in a single trial may provide limited additional information on treatment effect. Conversely, there was minimal correlation between the skin-specific DLQI measure and the SF-36, which supports the use of this disease aspect–specific instrument in combination with more general measures of HRQOL.

In contrast to other TNF inhibitor studies, where moderate correlations were observed between PROs and clinical outcomes (25), in this study it was observed that PROs correlate very poorly with clinical outcomes in PsA, indicating that patients who respond clinically do not necessarily report improvements to their HRQOL and vice versa. This also indicates that, although HRQOL measures may provide valuable information about treatment benefits in patient well-being, they are an independent domain in PsA, and should not be considered in isolation from clinical outcomes.

There were a number of limitations to this study, including the short duration of treatment (24 weeks) and the per-protocol escape at week 16, which resulted in approximately half of the placebo group being re-randomized to active treatment, which led to substantial imputation at week 24 for this group. Furthermore, due to the study design, the number of patients with prior TNF inhibitor exposure was relatively low, making it difficult to make unequivocal comparisons between TNF inhibitor–experienced and TNF inhibitor–naive patients.

In conclusion, CZP was shown to rapidly improve multiple PROs in PsA patients across many disease aspects, including physical and emotional aspects of health status, and generic, PsA-specific, and dermatology-specific measures. Patients with prior TNF inhibitor exposure demonstrated a similar response to CZP compared to TNF inhibitor–naive patients, despite having a higher burden of disease at baseline. The outcomes of CZP treatment over an extended duration will be assessed in the week 48 dose-blind and longer-term open-label phases of the RAPID-PsA trial.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gladman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Woltering, Mease.

Acquisition of data. Gladman, Fleischmann, Mease.

Analysis and interpretation of data. Coteur, Woltering, Mease.

ROLE OF THE STUDY SPONSOR

UCB Pharma employees were involved in the design of the study and in analysis and interpretation of the data. Collection of the data was facilitated by UCB Pharma, but carried out by study investigators. UCB Pharma also funded writing and editorial assistance for the publication of this article. The decision to submit this article for publication involved all authors, including those employed by UCB Pharma.

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