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ORIGINAL RESEARCH

Certolizumab Pegol for the Treatment of Moderate to Severe Plaque Psoriasis: 16-Week Results from a Phase 2/3 Japanese Study

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ABSTRACT

Introduction: Certolizumab pegol (CZP), the Fc-free, PEGylated anti-tumor necrosis factor, is approved for the treatment of moderate to severe plaque psoriasis (PSO) in Western countries and in Japan, among other indications.

Methods: We report results from the first 16 weeks of a 52-week phase 2/3 trial of CZP in Japanese patients with PSO. Patients ≥ 20 years with PSO ≥ 6 months (Psoriasis Area and Severity Index [PASI] ≥ 12, body surface area affected ≥ 10%, and Physician's Global Assessment [PGA] ≥ 3 on a 5-point scale) were randomized 2:2:1 to CZP 400 mg every 2 weeks (Q2W), CZP 200 mg Q2W (400 mg weeks 0/2/4), or placebo Q2W. Outcomes assessed to week 16: PASI 75, PASI 90, PGA 0/1 (Markov chain Monte Carlo), Dermatology Life Quality Index (DLQI 0/1) and Itch Numeric Rating Scale (INRS 0) (non-responder imputation), and DLQI and INRS change from baseline (last observation carried forward). Safety data were reported for patients receiving ≥ 1 dose of study medication through weeks 0–16; adverse events were evaluated using Medical Dictionary for Regulatory Activities version 18.1.

Results: A total of 127 patients were randomized to CZP 400 mg Q2W ($N = 53$), CZP 200 mg Q2W ($N = 48$), placebo ($N = 26$). Week 16 responder rates for CZP 400 mg/200 mg Q2W versus placebo were 87.1%/73.0% versus 7.9% for PASI 75; 75.7%/53.8% versus 0.2% for PASI 90; 66.7%/52.7% versus 0.0% for PGA 0/1 (all $p < 0.0001$ for both CZP doses versus placebo). Significant improvements in DLQI and INRS were reported at week 16 by patients receiving both CZP doses compared with placebo ($p < 0.0001$). Incidence of treatment-emergent adverse events within the CZP 400 mg Q2W, CZP 200 mg Q2W, and placebo groups were 326.1, 404.9, and 682.4 per 100 patient-years. No new safety signals were identified compared to previously reported data.

Conclusion: CZP dosed at 400 mg or 200 mg Q2W was associated with improved PSO signs and symptoms.

Trial Registration: ClinicalTrials.gov identifier, NCT03051217.

Keywords: Certolizumab pegol; Japan; Plaque psoriasis; Tumor necrosis factor-alpha

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Key Summary Points

Why carry out this study?

Plaque psoriasis (PSO) is an immune-mediated inflammatory disease, associated with multiple comorbidities and reduced health-related quality of life.

Certolizumab pegol (CZP) is an Fc-free, PEGylated anti-tumor necrosis factor (TNF) which has demonstrated favorable efficacy and safety in moderate to severe PSO over three global phase 3 trials.

As the epidemiology of PSO may be different in the Japanese population as compared with the Western population, this study was conducted to evaluate the effectiveness of CZP in a Japanese population of patients with moderate to severe PSO.

What was learned from the study?

CZP dosed at 400 mg or 200 mg every 2 weeks (Q2W) was associated with improved PSO signs and symptoms over 16 weeks, with numerically higher responses in the CZP 400 mg Q2W group.

These interim data provide evidence that CZP may be a suitable treatment option for moderate to severe PSO in Japanese patients.

Results over the full 52-week trial period are needed to further define the efficacy and safety of CZP for the treatment of PSO in this population.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13625888.

INTRODUCTION

Plaque psoriasis (PSO) is an immune-mediated inflammatory disease that affects around 0.3% of the population in Japan [1]. PSO manifests as red, raised, sharply demarcated, dry plaques which are usually covered by white or silvery scales [2, 3]. These plaques most often affect the scalp, elbows, knees and lower back, and cause itching and stinging [2, 3]. In addition to skin involvement, PSO can also affect the nails, and some patients develop psoriatic arthritis (PsA), affecting the joints [2]. The pathogenic effects of PSO have a systemic impact, and patients have an increased risk of metabolic syndrome and cardiovascular disease, with the latter reported to reduce the life expectancy of patients with moderate to severe PSO by approximately 5 years [4–8]. In addition, conditions associated with chronic systemic inflammation, such as obesity, are known aggravating factors for PSO [9–12].

Alongside the physical manifestations, PSO is associated with reduced health-related quality of life (QoL), with some patients experiencing a psychological burden that affects their relationships, social activities, and emotional well-being [13, 14]. Factors that contribute towards decreased QoL include the negative effect on body image caused by skin lesions, and the itching and interference with sleep that can accompany PSO flares [14].

Therapies for PSO vary according to disease severity. Treatment options for patients with a mild form of the disease include topical therapies such as corticosteroids or vitamin D analogues, whilst more severe disease can be treated with phototherapy, methotrexate, retinoids, cyclosporine A, apremilast, or biologics, including agents that interfere with the function of tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-23, or IL-12/23 [15–19].

Certolizumab pegol (CZP) is an Fc-free, PEGylated, anti-TNF biologic. CZP lacks the immunoglobulin G (IgG) Fc region that binds the neonatal Fc receptor for IgG (FcRn), retained on other anti-TNFs [20], and the conjugation to polyethylene glycol (PEG) increases the half-life of the agent [21]. CZP was first approved in the

USA and European Union in 2008 and 2009, respectively, for the treatment of rheumatoid arthritis (RA). Currently, it is additionally approved for the treatment of moderate to severe plaque psoriasis (PSO), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) (comprising both ankylosing spondylitis [AS] and non-radiographic axial spondyloarthritis [nr axSpA]) [22, 23]. In the USA and Switzerland, it is also approved for the treatment of Crohn's disease [22, 24]. In Japan, CZP is currently approved for the treatment of RA, PSO, PsA, generalized pustular psoriasis (GPP), and erythrodermic psoriasis (EP) [25]. Three phase 3 trials, conducted in North America and Europe, have evaluated CZP in moderate to severe PSO over the long-term (CIMPASI-1 [NCT02326298], CIMPASI-2 [NCT02326272], and CIMPACT [NCT02346240]). In these 3-year trials, with a combined total of 1020 randomized patients, CZP has demonstrated favorable efficacy, and a safety profile consistent with the anti-TNF class, with data currently reported through 48 weeks [26–28]. Here, we report efficacy and safety results from the initial 16 weeks of a 52-week phase 2/3 trial of CZP in Japanese patients with moderate to severe PSO (NCT03051217); this study is the first to evaluate CZP for the treatment of psoriasis in this patient population.

METHODS

Study Design

This was a phase 2/3, randomized, double-blind, placebo-controlled trial conducted at 33 sites in Japan, beginning February 21, 2017 (NCT03051217). Following a 2–5 week screening period to confirm eligibility, an interactive response technology (IRT) was used to randomize patients 2:2:1 to CZP 400 mg every 2 weeks (Q2W), CZP 200 mg Q2W (with a loading dose of CZP 400 mg Q2W at weeks 0, 2, and 4), and placebo, according to the randomization schedule produced by the IRT vendor (stratified by prior biologic exposure [yes/no] and concurrent PsA [yes/no]). All CZP and placebo treatments were administered subcutaneously at the study site by unblinded, trained site personnel not involved in any other study procedures. At week 16, patients either continued for a further 36 weeks of double-blind maintenance treatment or entered an open-label escape arm (Fig. 1). Here, outcomes from the first 16 weeks of the study are presented.

The study was carried out in accordance with the applicable regulatory and International Council for Harmonization-Good Clinical Practice requirements, and the Helsinki Declaration of 1964, and its later amendments. The study protocol was reviewed and approved by an institutional review board prior to implementation. Written informed consent was obtained from all patients.

Study Participants

Eligible patients were at least 20 years of age with moderate to severe PSO for at least 6 months with baseline Psoriasis Area and Severity Index (PASI) $\geq$ 12, body surface area (BSA) affected $\geq$ 10% and Physician's Global Assessment (PGA) $\geq$ 3 on a 5-point scale, and were candidates for systemic PSO therapy, phototherapy, or chemophototherapy. All patients were of Japanese ethnicity.

Patients were excluded if they had a history of treatment with CZP or more than two biologic agents; had a history of primary failure to any biologic (no response within the first 12 weeks of treatment) or secondary failure to more than two biologics (patients who initially responded then discontinued treatment due to loss of response after 12 weeks of treatment); had a diagnosis of any inflammatory arthritis other than psoriatic arthritis; had guttate, drug-induced, erythrodermic or pustular psoriasis; had a history of chronic or recurrent infection, including active or untreated latent tuberculosis (assessed using an interferon-γ release assay), or were at high risk of infection; had a history of a lymphoproliferative disorder; had class III or IV congestive heart failure (New York Heart Association 1964 criteria) [29]; had a history of, or suspected to have, demyelinating disease of the central nervous system; were breastfeeding, pregnant, planned to become pregnant/had a partner who planned to become pregnant

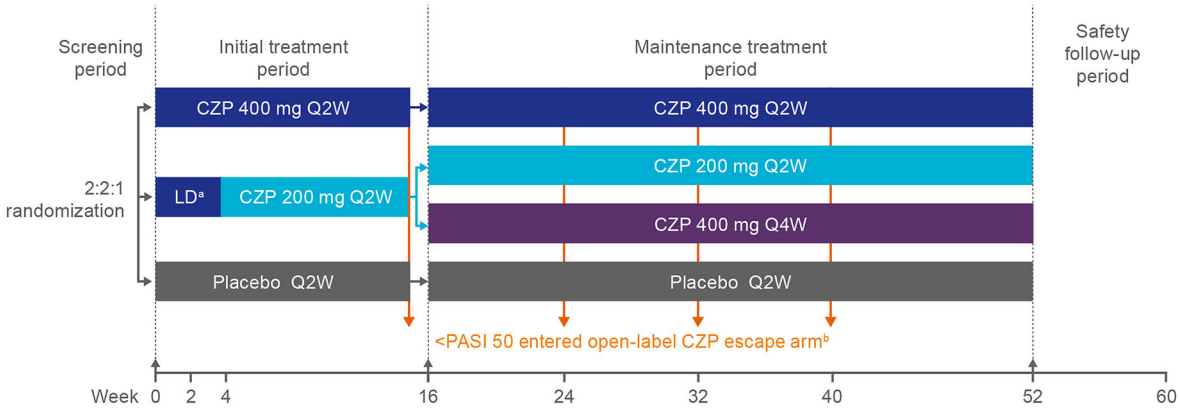


Fig. 1 Study design. [a]Patients received a CZP 400 mg loading dose at weeks 0, 2 and 4; [b]Patients who did not achieve PASI 50 at week 16, 24, 32, or 40 entered an open-label escape arm and received CZP 200 mg Q2W (CZP 400 mg Q2W loading dose for the first three visits). Patients receiving open-label CZP 200 mg Q2W in the escape arm and not achieving a PASI 50 response were permitted to have their dose increased to CZP 400 mg Q2W, at the discretion of the investigator. CZP certolizumab pegol, LD loading dose, PASI 50 $\geq$ 50% improvement in from baseline in Psoriasis Area and Severity Index, Q2W every 2 weeks, Q4W every 4 weeks

during the study or within 5 months of the last dose of study drug.

Efficacy Evaluations and Patient-Reported Outcomes

The primary endpoint was the proportion of patients achieving at least 75% improvement from baseline in PASI (PASI 75) for each CZP dose versus placebo at week 16. Secondary endpoints at week 16 were at least 90% improvement from baseline in PASI (PASI 90), "clear" or "almost clear" PGA with at least a 2-point improvement from baseline (PGA 0/1), change from baseline in Dermatology Life Quality Index (DLQI), and change from baseline in Itch Numeric Rating Scale (INRS). The INRS is a simple questionnaire that asks the patient to describe the worst level of itching due to PSO in the 24 h prior to the clinic visit on a scale from 0 (no itching) to 10 (worst itch imaginable) [30].

The rate of DLQI 0/1 (remission), defined as the achievement of a DLQI score of 1 or less, and the rate of INRS 0 (remission), defined as the achievement of an INRS score of 0, were also evaluated.

Safety Evaluations

Week 16 safety data are presented for all patients who received at least one dose of study medication through weeks 0–16 (the safety set). Adverse events (AEs) were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

Serious AEs were defined as AEs that met one or more of the following criteria: death; life-threatening; significant or persistent disability or incapacity; congenital anomaly or birth defect (including that occurring in a fetus); an important medical event that may jeopardize the patient and may require surgical intervention; initial inpatient hospitalization or prolongation of hospitalization. In this analysis, an AE was defined as treatment-emergent (a TEAE) if it occurred within the first 16 weeks of treatment. For patients who discontinued during this period, AEs were also considered treatment-emergent if they occurred within 70 days of the last dose of study medication. Incidence rates (IR) were calculated as incidence of new cases per 100 patient-years (PY).

The pre-defined AEs of interest were serious infections, including opportunistic infections; malignancies, including lymphoma; congestive heart failure; demyelinating-like disorders;

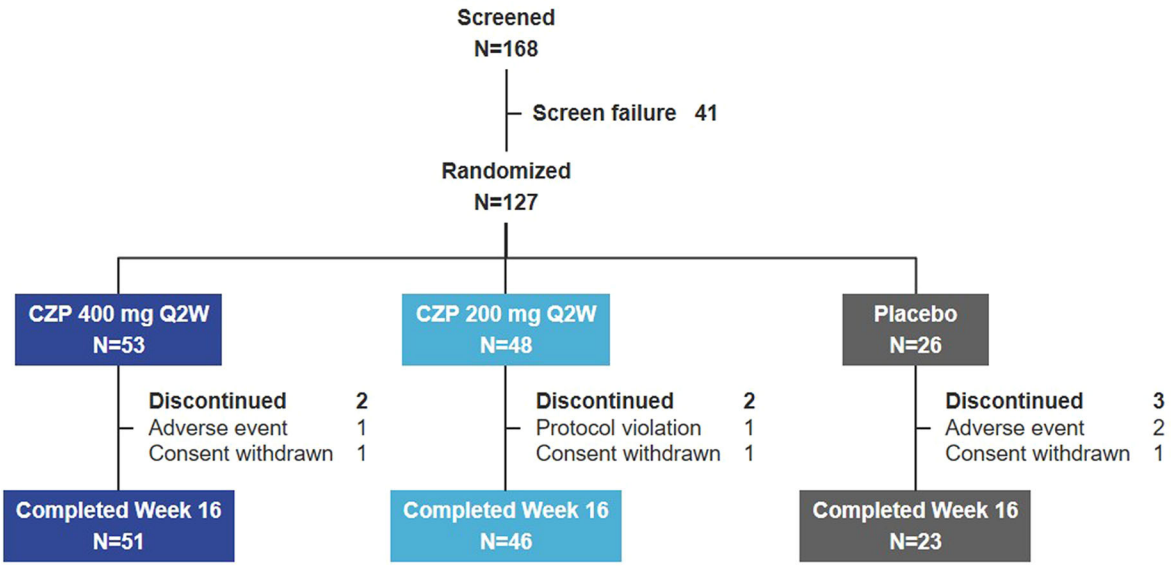


Fig. 2 Patient disposition. CZP certolizumab pegol, Q2W every 2 weeks. Screen failure are reported for patients with PSO, erythrodermic psoriasis, and generalized pustular psoriasis, the reasons being ineligibility (n = 39/43; 20.3%), adverse event (n = 3/43; 1.6%) and consent withdrawn (n = 1/43; 0.5%)

aplastic anemia, pancytopenia, thrombocytopenia, neutropenia, and leukopenia; serious bleeding events; lupus and lupus-like illness; serous skin reactions such as Stevens–Johnson syndrome, toxic epidermal necrosis, and erythema multiforme; potential Hy's law case, defined as at least three times the upper limit of normal (ULN) in alanine transaminase (ALT) or aspartate transaminase (AST) with coexisting at least two times the ULN total bilirubin, in the absence of at least two times the ULN in alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality.

Calculation of Sample Size

Week 16 PASI 75 responses were assumed to be 75%, 70%, and 15% for CZP 400 mg Q2W, CZP 200 mg Q2W, and placebo, respectively. Under these assumptions, a sample size of 125 (allocated 2:2:1 to CZP 400 mg Q2W, CZP 200 mg Q2W, and placebo) was calculated to provide more than 99% power to detect a difference between either dose of CZP and placebo, with a two-sided test significance level of 0.025.

Statistical Analyses

For PASI and PGA outcomes, missing data were imputed using Markov chain Monte Carlo (MCMC) multiple imputation methodology. Responder rates and treatment group comparisons were based on a logistic regression model with factors for treatment group and prior biologic exposure. If there were no responders in one or more treatment groups, the logistic regression model may have been unable to converge. In such instances, prior biologic exposure was removed from the model. If the model was still unable to converge, exact logistic regression was applied and odds ratios, associated exact confidence intervals, and exact p values were determined. For PASI and PGA outcomes, sensitivity analyses were performed wherein missing data was imputed using non-responder imputation (NRI).

For DLQI and INRS change from baseline values, missing data were imputed using the last observation carried forward (LOCF) approach, and treatment group comparisons were performed using an analysis of covariance (ANCOVA) model with treatment group and prior biologic exposure as factors and baseline

Table 1 Demographics and baseline disease characteristics

Characteristic	CZP 400 mg Q2W (*N* = 53)	CZP 200 mg Q2W (*N* = 48)	Placebo (*N* = 26)
Demographics			
Age, years, mean ± SD	52.4 ± 11.6	48.4 ± 13.5	47.9 ± 11.4
Male, *n* (%)	42 (79.2)	36 (75.0)	21 (80.8)
Weight, kg, mean ± SD	71.6 ± 14.3	72.6 ± 14.3	75.1 ± 15.8
Height, cm, mean ± SD	165.6 ± 7.5	167.5 ± 7.5	165.7 ± 7.1
BMI, kg/m^2, mean ± SD	26.0 ± 4.3	26.0 ± 5.5	27.3 ± 5.1
Baseline disease characteristics			
Duration of disease, years, mean ± SD	13.2 ± 9.3	12.7 ± 10.1	12.7 ± 8.6
Concurrent PsA, *n* (%)	10 (18.9)	6 (12.5)	5 (19.2)
PASI, mean ± SD	26.5 ± 11.0	24.5 ± 12.6	24.5 ± 10.4
DLQI, mean ± SD	9.2 ± 7.4	10.5 ± 6.6	10.5 ± 7.2
INRS, mean ± SD	5.7 ± 2.6	5.6 ± 2.4	6.1 ± 2.5
BSA affected, %, mean ± SD	39.7 ± 21.4	38.7 ± 21.9	38.3 ± 17.2
PGA score, *n* (%)			
3: moderate	31 (58.5)	31 (64.6)	17 (65.4)
4: severe	22 (41.5)	17 (35.4)	9 (34.6)
Any systemic PSO treatment, *n* (%)	37 (69.8)	39 (81.3)	20 (76.9)
Prior biologic use, *n* (%)			
1 therapy	16 (30.2)	14 (29.2)	8 (30.8)
2 therapies	3 (5.7)	0 (0.0)	0 (0.0)
Anti-TNF	3 (5.7)	3 (6.3)	1 (3.8)

BMI body mass index, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *INRS* Itch Numeric Rating Scale, *PASI* Psoriasis Area and Severity Index, *PGA* Physician's Global Assessment, *PsA* psoriatic arthritis, *PSO* psoriasis, *Q2W* every 2 weeks, *SD* standard deviation, *TNF* tumor necrosis factor

scores as covariates. For DLQI 0/1 and INRS 0 responder rates, missing data were imputed using NRI. Treatment group comparisons were made using logistic regression models based on these imputed data.

Multiplicity was controlled via a fixed sequence testing procedure split by dose (the overall alphas of 0.05 were allocated as 0.025 to each dose).

RESULTS

Patient Disposition and Baseline Characteristics

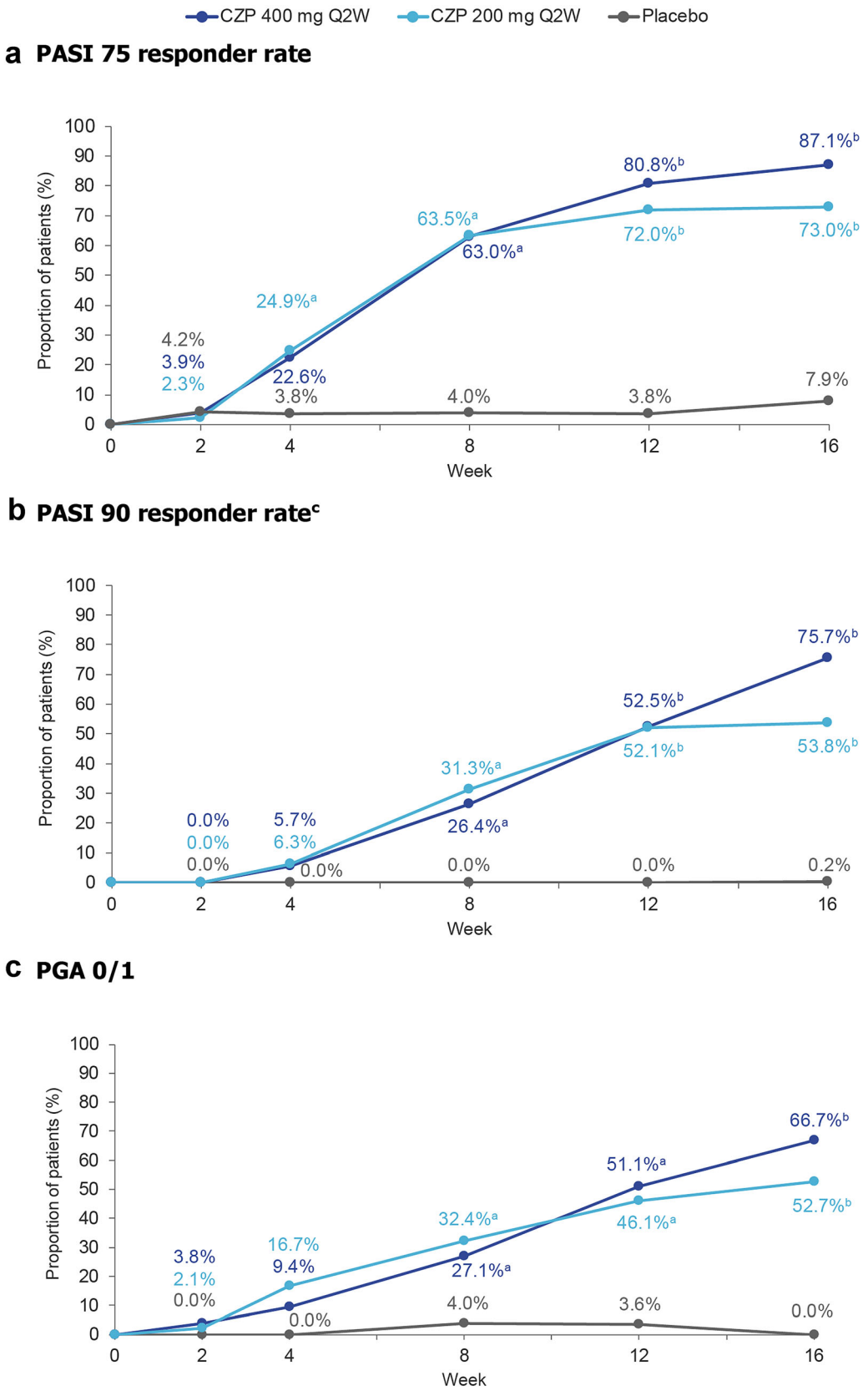
Of the 168 patients screened, 127 were randomized to CZP 400 mg Q2W (*N* = 53), CZP 200 mg Q2W (*N* = 48), or placebo (*N* = 26) (Fig. 2). Demographics and baseline characteristics were balanced across treatment groups

Table 2 Efficacy outcomes at week 16

	CZP 400 mg Q2W (*N* = 53)	CZP 200 mg Q2W (*N* = 48)	Placebo (*N* = 26)
Primary endpoint			
PASI 75 responder rate, %	87.1	73.0	7.9
OR vs placebo (97.5% CI)	79.1 (11.7 to 533.2)	31.7 (5.1 to 195.9)	–
p value	< 0.0001	< 0.0001	–
Secondary endpoints			
PASI 90 responder rate,[a] %	75.7	53.8	0.2
OR vs placebo (97.5% CI)	100.5 (15.5 to 649.4)	38.7 (6.0 to 247.6)	–
p value	< 0.0001	< 0.0001	–
PGA 0/1 responder rate, %	66.7	52.7	0.0
OR vs placebo (97.5% CI)	69.6 (11.1 to 434.7)	38.2 (6.1 to 238.6)	–
p value	< 0.0001	< 0.0001	–
DLQI change from baseline, mean ± SD	− 6.4 ± 7.1	− 7.2 ± 5.8	− 0.7 ± 4.9
AMD vs placebo (97.5% CI)	− 6.5 (− 9.1 to − 3.9)	− 6.5 (− 9.1 to − 3.8)	–
p value	< 0.0001	< 0.0001	–
INRS change from baseline, mean ± SD	− 4.0 ± 2.9	− 2.9 ± 3.1	0.0 ± 1.4
AMD vs placebo (95% CI)	− 4.2 (− 5.3 to − 3.1)	− 3.1 (− 4.3 to − 2.0)	–
p value	< 0.0001	< 0.0001	–
Other outcomes			
DLQI 0/1, %	62.3	56.3	7.7
OR vs placebo (97.5% CI)	19.7 (4.2 to 92.5)	15.5 (3.3 to 73.1)	–
p value	0.0002	0.0005	–
INRS 0, %	37.7	22.9	0.0
OR vs placebo (97.5% CI)	20.8 (4.2 to 101.5)	10.4 (2.0 to 53.1)	–
p value	0.0002	0.0104	–

AMD adjusted mean treatment difference, *CI* confidence interval, *CZP* certolizumab pegol, *DLQI* Dermatology Life Quality Index, *DLQI 0/1* achievement of a DLQI score of ≤ 1 (remission), *INRS* Itch Numeric Rating Scale, *INRS 0* achievement of an INRS score of 0 (remission), *OR* odds ratio, *PASI 75/90* ≥ 75%/90% improvement from baseline in Psoriasis Area and Severity Index, *PGA 0/1* Physician's Global Assessment clear/almost clear with ≥ 2-category improvement from baseline, *Q2W* every 2 weeks

[a] Exact regression was used to estimate odds ratios, associated exact confidence intervals and exact *p* values, and simple proportions were calculated for PASI 90 responder rate


CZP 400 mg Q2W
CZP 200 mg Q2W
Placebo
a PASI 75 responder rate
Proportion of patients (%)
Week
4.2%
3.9%
2.3%
24.9%a
22.6%
3.8%
63.5%a
63.0%a
4.0%
80.8%b
72.0%b
3.8%
87.1%b
73.0%b
7.9%
b PASI 90 responder ratec
0.0%
0.0%
0.0%
5.7%
6.3%
0.0%
31.3%a
26.4%a
0.0%
52.5%b
52.1%b
0.0%
75.7%b
53.8%b
0.2%
c PGA 0/1
3.8%
2.1%
0.0%
16.7%
9.4%
0.0%
32.4%a
27.1%a
4.0%
51.1%a
46.1%a
3.6%
66.7%b
52.7%b
0.0%

◀**Fig. 3** Efficacy outcomes to week 16 (MCMC). [a]$p < 0.05$; [b]$p \leq 0.0001$ versus placebo; [c]At weeks 4, 8, 12, and 16 exact regression was used to estimate odds ratios and simple proportions were calculated for PASI 90 responder rate. CZP certolizumab pegol, MCMC Markov chain Monte Carlo, PASI 75/90 ≥ 75%/90% improvement from baseline in Psoriasis Area and Severity Index, PGA 0/1 Physician's Global Assessment clear/almost clear with ≥ 2-category improvement from baseline, Q2W every 2 weeks

(Table 1). Of the randomized patients, 120 completed the initial 16-week treatment period; completion rates were slightly higher in the two CZP groups (greater than 95%) compared with the placebo group (89%) (Fig. 2).

Primary Efficacy Outcome

PASI 75 responder rates at week 16 were 87.1% for the CZP 400 mg Q2W group, 73.0% for the CZP 200 mg Q2W group, and 7.9% for the placebo group (Table 2). The PASI 75 responder rate was significantly higher for both CZP dose groups compared with placebo from week 8 onwards (Fig. 3a). Similar results were observed at week 16 with NRI analysis (Table S1 in Supplementary Material).

Secondary Efficacy Outcomes

The PASI 90 and PGA 0/1 responder rates were also significantly greater for both groups of CZP-treated patients than for placebo-treated patients through weeks 8–16 (Fig. 3b, c). PASI 90 responder rates at week 16 were 75.7% for the CZP 400 mg Q2W group, 53.8% for the CZP 200 mg Q2W group, and 0.2% for the placebo group (Table 2). At weeks 4, 8, 12, and 16, the logistic regression model was unable to converge and PASI 90 responder rates were calculated as simple proportions, as per the statistical analysis plan, with exact regression used to calculate odds ratios and associated confidence intervals, and exact p values determined (Table 2). PGA 0/1 responder rates at week 16 were 66.7% for the CZP 400 mg Q2W group, 52.7% for the CZP 200 mg Q2W group, and 0.0% for the placebo group (Table 2). Similar results were observed at week 16 with NRI analysis (Table S1 in Supplementary Material).

Quality of Life: Patient-Reported Outcomes

CZP-treated patients reported significantly greater changes from baseline in DLQI at week 16 than patients treated with placebo, and more patients achieved DLQI 0/1 (Table 2; Fig. 4). Similarly, significantly greater changes from baseline in INRS were reported by patients treated with CZP than patients treated with placebo, with more patients achieving INRS 0 (Table 2; Fig. 5).

Safety Assessments

After 16 weeks, the total treatment exposure was 16.2 PY in the CZP 400 mg Q2W group, 14.8 PY in the CZP 200 mg Q2W group, and 7.6 PY in the placebo group. The greatest incidence of TEAEs was reported in the placebo group, and the IR of TEAEs was similar between the CZP 400 mg Q2W and CZP 200 mg Q2W treatment groups (Table 3).

Regarding AEs of interest, there was one serious infection, a case of herpes zoster reported by a patient receiving CZP 400 mg Q2W. No other AEs of interest were reported in this period. There were no malignancies (including lymphoma), TEAEs related to congestive heart failure, serious cardiovascular events, serious skin disorders (such as Stevens–Johnson or lupus), or deaths.

DISCUSSION

In this phase 2/3 trial, 16 weeks of treatment with CZP dosed at either 400 mg or 200 mg Q2W resulted in significant improvements in the symptoms of PSO in Japanese patients, compared with placebo. The response to treatment was rapid and significantly greater proportions of CZP-treated patients achieved PASI 75, PASI 90, and PGA 0/1 as early as week 8, compared with the placebo group, with

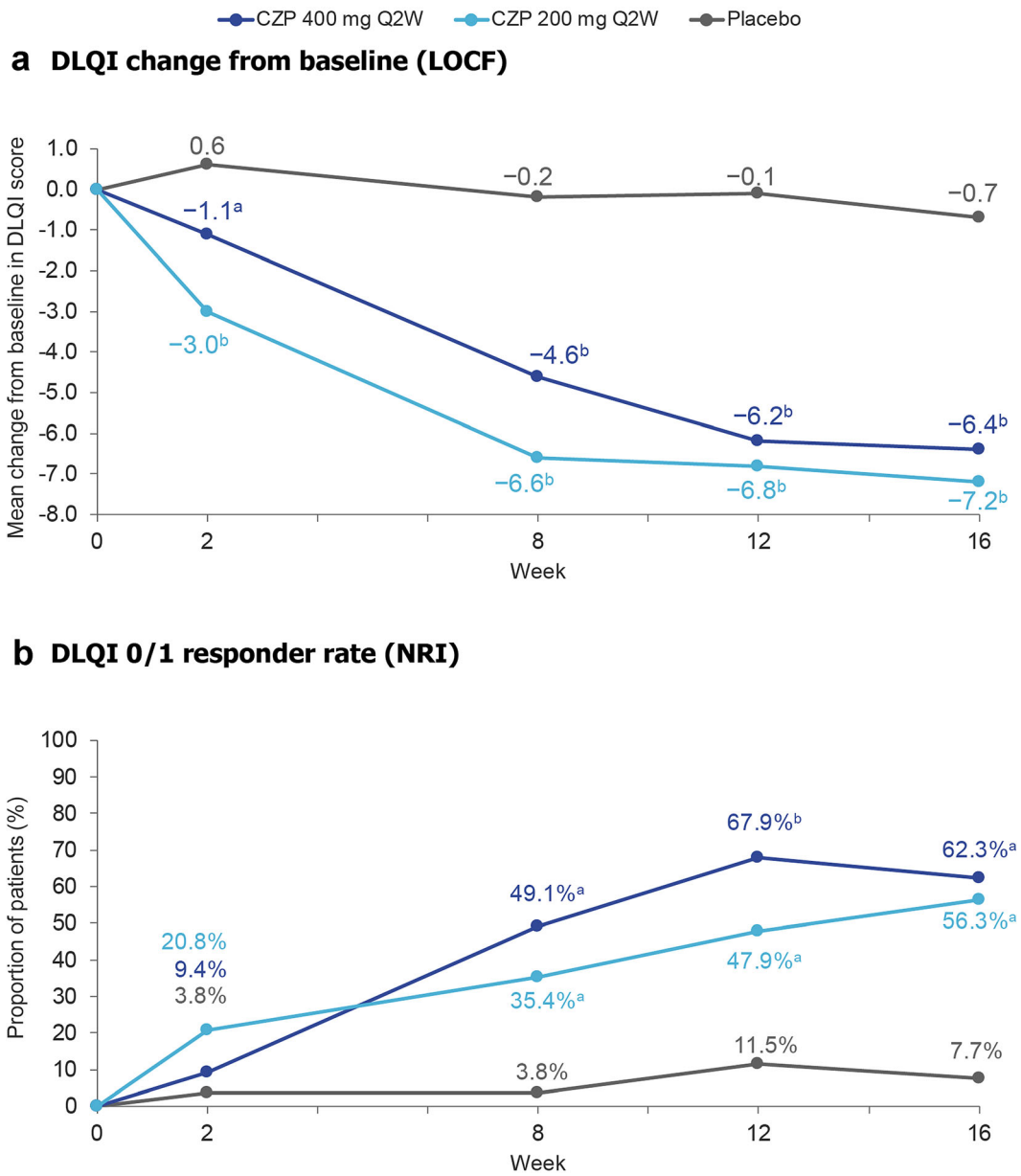


Fig. 4 DLQI outcomes to week 16. A reduced DLQI score represents an improvement. DLQI is measured on a scale of 0–30. [a] $p < 0.05$; [b] $p < 0.0001$ versus placebo. CZP certolizumab pegol, DLQI Dermatology Life Quality Index, DLQI 0/1 achievement of a DLQI score of ≤ 1 (remission), LOCF last observation carried forward, NRI non-responder imputation, Q2W every 2 weeks

further improvements to week 16. At week 16, PASI and PGA responses were numerically higher for patients receiving CZP 400 mg Q2W compared with those receiving CZP 200 mg Q2W, particularly for the more stringent outcome of PASI 90. No new safety signals were identified with 16 weeks of CZP treatment, compared to previously reported data in North America and Europe [26–28], and the overall incidence of TEAEs, serious TEAEs, and discontinuations due to TEAEs were low for all CZP-treated patients.

The results from this study in Japanese patients were comparable with the larger

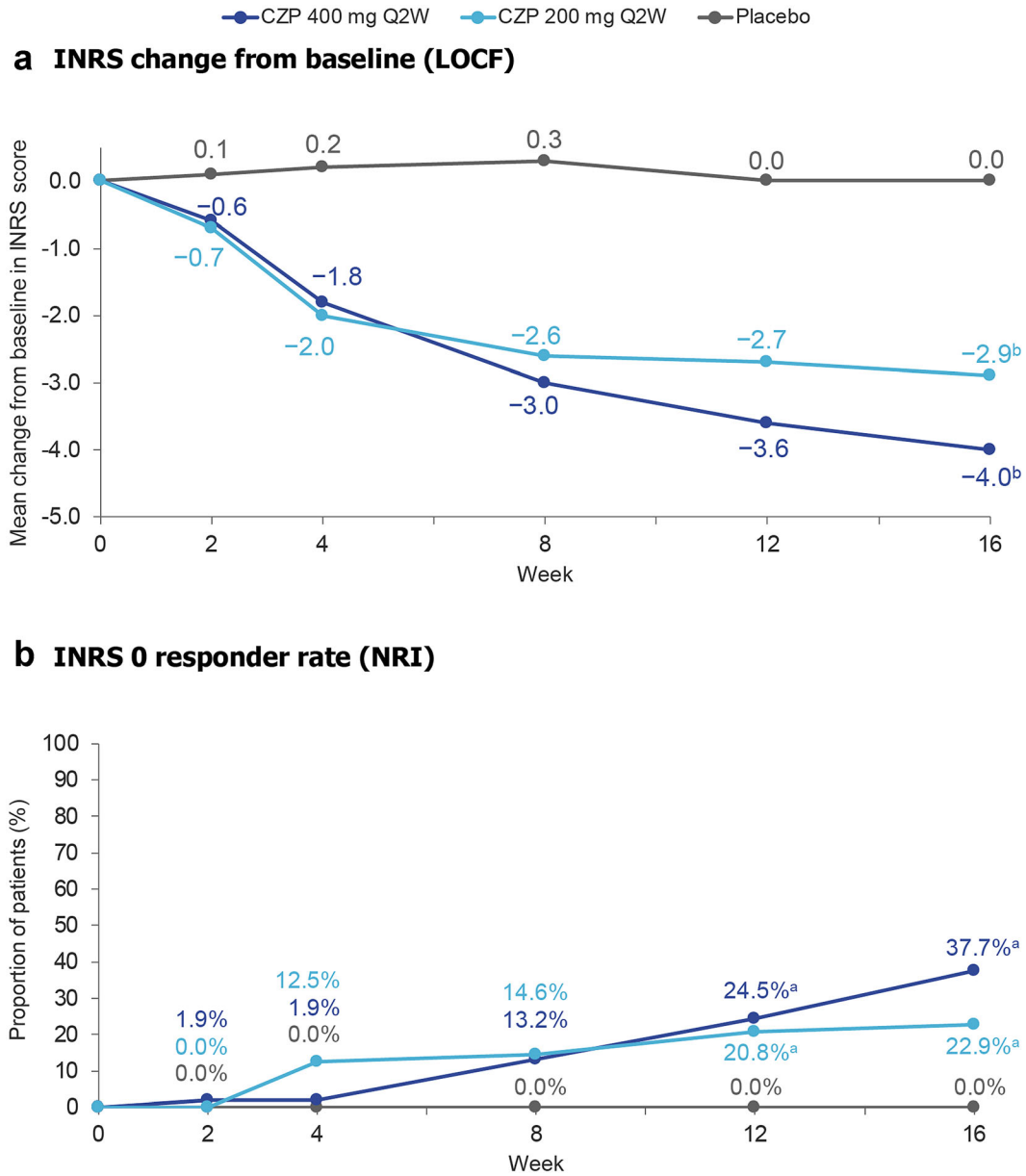


Fig. 5 INRS outcomes to week 16. A reduced INRS score represents an improvement. INRS is measured on a scale of 0–10. [a]$p < 0.05$; [b]$p \leq 0.0001$ versus placebo. CZP certolizumab pegol, INRS Itch Numeric Rating Scale, INRS 0 achievement of an INRS score of 0 (remission), LOCF last observation carried forward, NRI non-responder imputation, Q2W every 2 weeks

phase 3 trials conducted in North America and Europe [28]. For example, PASI 75 responder rates at week 16 in this trial were 87.1% and 73.0% for CZP 400 mg Q2W and CZP 200 mg Q2W, respectively, compared to 80.1% and 74.5% in the pooled analysis of the CIMPASI-1, CIMPASI-2, and CIMPACT trials; PASI 90 and PGA 0/1 responder rates also follow similar trends [28].

The PASI response after 16 weeks reported here was comparable with that of other biologic agents in Japanese patients in the initial periods

Table 3 Summary of TEAEs and serious TEAEs from baseline to week 16

	CZP 400 mg Q2W (*N* = 53)	CZP 200 mg Q2W (*N* = 48)	Placebo (*N* = 26)
Exposure, PY	16.2	14.8	7.6
All TEAEs, *n* (%), IR (95% CI)	33 (62.3), 326.1 (224.5, 458.0)	33 (68.8), 404.9 (278.7, 568.6)	21 (80.8), 682.4 (422.4, 1043.1)
Serious	2 (3.8), 12.6 (1.5, 45.5)	0	1 (3.8), 13.4 (0.3, 74.4)
Gastrointestinal disorders	1 (1.9), 6.2 (0.2, 34.6)	0	1 (3.8), 13.4 (0.3, 74.4)
Large intestine poly	1 (1.9), 6.2 (0.2, 34.6)	0	1 (3.8), 13.4 (0.3, 74.3)
Dental disorders NEC	0	0	1 (3.8), 13.4 (0.3, 74.4)
Dental cyst	0	0	1 (3.8), 13.4 (0.3, 74.4)
Infections and infestations	1 (1.9), 6.3 (0.2, 34.9)	0	0
Herpes zoster	1 (1.9), 6.3 (0.2, 34.9)	0	0
Drug-related TEAEs, *n* (%)	11 (20.8)	6 (12.5)	6 (23.1)
Discontinuations due to TEAE, *n* (%)	2 (3.8)	2 (4.2)	2 (7.7)
Deaths, *n* (%)	0	0	0

CI confidence interval, *CZP* certolizumab pegol, *IR* incidence rate of new cases per 100 patient-years, *NEC* not elsewhere classified, *PY* patient-years, *Q2W* every 2 weeks, *TEAE* treatment-emergent adverse event

of their respective trials [31–35]. For example, the PASI 75 responder rate for adalimumab, another anti-TNF agent, dosed at 80 mg every other week is reported as 81.0% after 16 weeks [31]. PASI 75 responder rates in Japanese patients for guselkumab (anti-IL-23) after 16 weeks, and secukinumab (anti-IL-17A), ustekinumab (anti-IL12/23), brodalumab (anti-IL-17 receptor), and ixekizumab (anti-IL-17A) after 12 weeks were also comparable to the CZP 400 mg Q2W results after the first 16 weeks of this trial [32–36].

A meaningful impact on QoL from CZP treatment was demonstrated in this study, with over half of CZP-treated patients achieving DLQI 0/1 at week 16. Patients receiving CZP also reported significant reductions in INRS score. In a survey on patient perspectives in the management of PSO, 43% of patients indicated itching to be among the most bothersome signs or symptoms of PSO [37]. Therefore, the results reported here are likely to represent an important improvement in QoL.

Limitations of this trial include the lack of active comparator and the exclusion of patients with a history of primary failure to biologic therapy. While this trial included a smaller sample size to those conducted in North America and Europe, the results from the 127 patients in this analysis were comparable with those from the 850 CZP- or placebo-treated patients included in a pooled week 16 analysis of the CIMPASI-1, CIMPASI-2, and CIMPACT trials. [28] Although the patient background was different, the effectiveness and safety of CZP was demonstrated in a real-world study conducted in Italy [38]. These results indicate that the results of this study may be generalizable to the wider patient population, including in the real-life setting in Japan.

CONCLUSIONS

These data show that CZP is an effective treatment in Japanese patients with moderate to severe PSO over 16 weeks of treatment and CZP may provide a suitable treatment option for patients with PSO in Japan. Data over the full 52 weeks of this trial will further define the efficacy and safety profiles of CZP for the treatment of PSO in this population.

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Compliance with Ethics Guidelines. The study was carried out in accordance with the applicable regulatory and International Council for Harmonization-Good Clinical Practice requirements, and the Helsinki Declaration of 1964, and its later amendments. The study protocol was reviewed and approved by an institutional review board prior to implementation. Written informed consent was obtained from all patients.

Data Availability. Underlying data from this manuscript may be requested by qualified researchers 6 months after product approval in the USA and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymised individual patient-level data and redacted trial documents which may include analysis-ready datasets, study protocol, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a pre-specified time, typically 12 months, on a password-protected portal.

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