



Efficacy and Safety of Certolizumab Pegol in Japanese Patients with Generalized Pustular Psoriasis and Erythrodermic Psoriasis: 52-Week Results

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ABSTRACT

Introduction: We report an exploratory analysis of the efficacy and safety of certolizumab pegol (CZP) in Japanese patients with generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP) (NCT03051217).

Methods: Patients ≥ 20 years with GPP or EP were randomized 1:1 to open-label CZP 400 mg every 2 weeks (Q2W) or 200 mg Q2W (400 mg weeks 0/2/4) for 16 weeks; patients who achieved “much improved” or “very much improved” on the Global Improvement Score (GIS; for GPP) or a PASI 50 response ($\geq 50\%$ reduction from baseline Psoriasis Area and Severity Index; for EP) continued to week 52. Efficacy outcomes assessed included Clinical Global Impression of Improvement (CGI-I), Dermatology Life Quality Index (DLQI 0/1), and

Itch Numeric Rating Scale (INRS 0). GIS and Japanese Dermatological Association (JDA) severity index were assessed in patients with GPP, and PASI and Physician’s Global Assessment (PGA) in patients with EP. Treatment-emergent adverse events (TEAEs) were evaluated through weeks 0–52.

Results: Of 22 patients randomized, 19 completed week 52. At week 16, all reported outcomes improved with both CZP doses and were generally maintained through week 52. At week 52, 6/7 GPP and 12/12 EP patients achieved CGI-I response (“improved” or “remission”). Also, 4/7 GPP and 7/12 EP patients achieved DLQI 0/1; 2/7 GPP and 2/12 EP patients achieved INRS 0. Meanwhile, 6/7 patients with GPP achieved GIS response, and JDA severity index was reduced from baseline. We found that 9/12 and 5/12 patients with EP achieved PASI 90 and PGA 0/1, respectively. Overall, three serious TEAEs were reported in three CZP 400 mg Q2W-treated patients.

Conclusion: CZP treatment over 16 weeks improved the signs and symptoms of GPP and EP, and improvements were maintained through week 52. No new safety signals were identified.

Trial Registration: ClinicalTrials.gov identifier, NCT03051217.

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Key Summary Points

Why carry out this study?

Certolizumab pegol (CZP), an Fc-free PEGylated anti-tumor necrosis factor (TNF) biologic, dosed at 400 mg every 2 weeks (Q2W) and 200 mg Q2W over 52 weeks in Japanese patients, showed clinically meaningful improvements in moderate to severe plaque psoriasis (PSO), with no new safety signals identified.

Due to the similarity between the pathogenesis of generalized pustular psoriasis (GPP), erythrodermic psoriasis (EP), and PSO, biologic therapies such as anti-TNF and anti-interleukin (IL-12/23, IL-23, and IL-17) treatments, which have demonstrated short- and long-term efficacy and favorable safety profiles in PSO, have also been evaluated in GPP and EP.

Here, we present the efficacy and safety of 52-week CZP as an add-on treatment in Japanese patients with GPP and EP.

What was learned from the study?

Treatment with both doses of CZP resulted in consistent improvements at week 16 across all efficacy endpoints assessed, and these improvements were maintained through week 52. At week 52, 6/7 GPP and 12/12 EP patients achieved Clinical Global Impression of Improvement response, while 4/7 GPP and 7/12 EP patients achieved Dermatology Life Quality Index 0/1. No new safety signals were identified with 52 weeks of CZP treatment.

This study provides preliminary evidence to support use of CZP as a feasible treatment option for Japanese patients with GPP and EP.

INTRODUCTION

Generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP) are severe and potentially life-threatening forms of psoriasis [1]. Patients with GPP experience recurrent flare-ups of sudden widespread sterile pustulosis [2], while patients with EP typically present with generalized cutaneous symptoms such as erythema, edema, pruritus, and occasionally, exudative lesions and palmoplantar or diffuse desquamation [3]. EP may develop slowly from chronic psoriasis, or may appear abruptly in patients with mild psoriasis [4]. Both GPP and EP are characterized by systemic inflammation and extracutaneous organ involvement, which can result in significant morbidity and, in severe cases, mortality [2, 3].

In Japan, the estimated prevalence of psoriasis is 0.3% [5]. Among patients with psoriasis in Japan, the prevalence of GPP and EP is estimated to be 1.1% and 0.4%, respectively [5]. The prevalence of GPP and EP varies depending on ethnicity, with Asians reporting a higher prevalence compared with Caucasians (GPP: 9% versus 3% and EP: 4% versus 2% of patients with psoriasis) [6].

The clinical management of GPP and EP is challenging due to various factors including the complexity of the disease and the limited clinical evidence available to support treatment strategies [7, 8]. Current conventional treatment for GPP and EP includes retinoids, cyclosporine, methotrexate, and ultraviolet (UV) phototherapy. However, many patients do not respond to these therapies [2]. Additionally, treatments can be associated with agent-specific safety concerns, such as teratogenicity with retinoids and nephrotoxicity with cyclosporine [2, 3, 7, 8]. Due to the similarity between the pathogenesis of GPP/EP and plaque psoriasis (PSO), biologic therapies such as anti-tumor necrosis factor (TNF) and anti-interleukin (IL-12/23, IL-23, and IL-17) treatments, which have demonstrated short- and long-term efficacy and favorable safety profiles in PSO, have also been evaluated in GPP and EP [2, 3, 7, 8]. In Japan, the Japanese Dermatological Association (JDA) recommends the use of anti-TNF and other

biologics (such as anti-IL-17 and anti-IL-12/23) for the treatment of skin symptoms of GPP [9].

Certolizumab pegol (CZP) is a unique Fc-free PEGylated anti-TNF biologic. PEGylation increases the half-life of CZP to 14 days [10]. Unlike other anti-TNF agents, CZP lacks the IgG Fc region that binds the neonatal Fc receptor for IgG (FcRn), and therefore results in no to minimal placental transfer from mothers to infants [11]. In Japan, CZP is currently approved for the treatment of GPP, EP, PSO, psoriatic arthritis, and rheumatoid arthritis [12].

CZP dosed at 400 mg every 2 weeks (Q2W) and 200 mg Q2W over 52 weeks in Japanese patients showed clinically meaningful improvements in moderate to severe PSO, with no new safety signals identified compared with previously reported data in PSO [13, 14]. CZP efficacy and safety has also been demonstrated through 144 weeks, in three global phase 3 trials (CIMPASI-1, CIMPASI-2, and CIMPACT) in North America and Europe [15, 16]. Here, we present the efficacy and safety of 52-week CZP treatment in Japanese patients with GPP and EP.

METHODS

Study Design

This study was an exploratory analysis of a 52-week, phase 2/3, double-blind, placebo-controlled, multicenter, randomized trial conducted in Japan (NCT03051217) [13, 14]. Patients were enrolled across 18 sites in Japan and were randomized 1:1 to open-label CZP 400 mg Q2W and CZP 200 mg Q2W (with a loading dose of CZP 400 mg Q2W at weeks 0, 2, and 4), for 16 weeks of treatment during the initial treatment period (Fig. 1). Patients who achieved a “much improved” or “very much improved” response on the Global Improvement Score (GIS; for patients with GPP) or a PASI 50 response (defined as at least 50% reduction from baseline Psoriasis Area and Severity Index; for patients with EP) continued their randomized treatment to week 52. During the maintenance period, patients in the CZP 200 mg Q2W group who failed to achieve a response could have their dose increased to

CZP 400 mg Q2W, at the discretion of the investigator. In the opinion of the investigator, if the patient failed to achieve a response with the CZP 400 mg Q2W dose, the patient could be withdrawn from the study. Patients were withdrawn if they developed, in the opinion of the investigator, an aggravation of the primary disease or concomitant disease with hospitalization. All CZP treatments were administered subcutaneously at the study site by trained site personnel not involved in any other study procedures.

This study protocol was reviewed by the institutional review board (IRB) of each institution prior to implementation. Written informed consent was obtained from all patients. 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.

Study Participants

Eligible patients were ≥ 20 years of age with a diagnosis of GPP (based on the JDA criteria for GPP diagnosis) [9] or EP at screening. Patients with a diagnosis of EP had a history of plaque-type PSO and $\geq 80\%$ of baseline body surface area (BSA) affected by PSO. All patients were of Japanese ethnicity.

Patients were excluded if they had a history of primary failure to any prior biologic therapy (no response within the first 12 weeks of treatment); had a total score of ≥ 14 at baseline on the JDA Severity Index (for patients with GPP); had a differential diagnosis of the erythroderma (e.g., erythroderma caused by lymphoma or drug eruption) other than EP (for patients with EP); 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) [17]; had a history of, or suspected to have, demyelinating disease of the central nervous system; were breastfeeding, pregnant, or planned to become

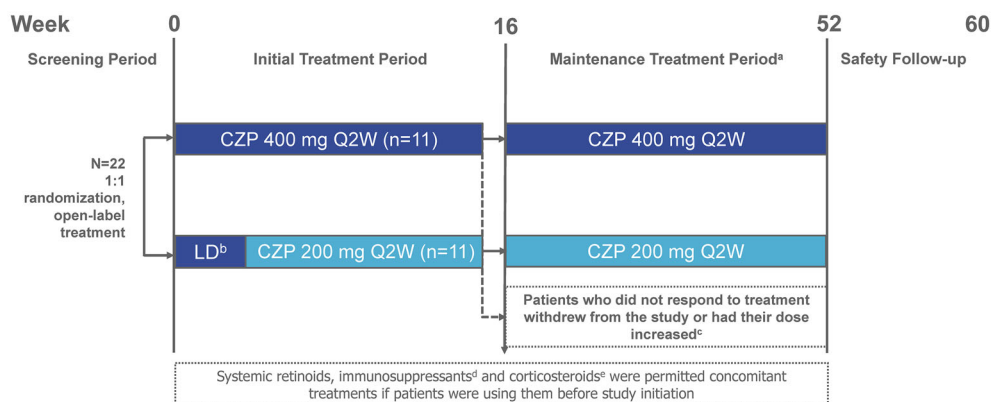


Fig. 1 Study design. ^aPatients who achieved “much improved” or “very much improved” in GIS (GPP) or a PASI 50 response (EP) continued therapy to week 52; ^bPatients received a CZP 400 mg loading dose at weeks 0, 2, and 4; ^cPatients in the CZP 200 mg Q2W group who failed to achieve a response could have their dose increased to CZP 400 mg Q2W, at the discretion of the investigator. In the opinion of the investigator, if the patient failed to achieve a response with the CZP 400 mg Q2W dose, the

patient could be withdrawn from the study; ^de.g., methotrexate, cyclosporine, azathioprine; ^eAt a daily dose of ≤ 10 mg/day of prednisone or its equivalent. CZP certolizumab pegol, EP erythrodermic psoriasis, GIS Global Improvement Score, GPP generalized pustular psoriasis, LD loading dose, PASI 50 $\geq 50\%$ reduction from baseline in Psoriasis Area and Severity Index, Q2W every 2 weeks

pregnant/had a partner who planned to become pregnant during the study or within 5 months of the last dose of study drug.

Efficacy Evaluations

The following clinical assessments were made through weeks 0–52: Clinical Global Impression of Improvement response (CGI-I, defined as “remission” or “improved”), Dermatology Life Quality Index 0/1 (defined as absolute DLQI score of ≤ 1), Itch Numeric Rating Scale (INRS 0; defined as absolute INRS score of 0), and absolute INRS scores. Additionally, GIS response (defined as “very much improved,” “much improved,” or “minimally improved”) and JDA Severity Index were assessed in patients with GPP. PASI 75/90 response (defined as $\geq 75/90\%$ reduction from baseline PASI) and Physician’s Global Assessment (PGA) response (defined as absolute score of 0 or 1 with ≥ 2 -point improvement from baseline on a five-point scale) were assessed in patients with EP.

Safety Evaluations

Safety data were reported for all patients who received ≥ 1 dose of CZP through weeks 0–52. Adverse events (AEs) were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. Treatment-emergent AEs (TEAEs) were defined as events with onset at the time on or after the first dose of study medication and up to 70 days after the final dose of study medication. 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. The predefined AEs of interest (AEOI) were: serious infections, including opportunistic infections; malignancies, including lymphoma; congestive heart failure; demyelinating-like disorders; 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 $\geq 3 \times$ the upper limit of normal (ULN) in alanine transaminase (ALT) or aspartate transaminase (AST) with coexisting $\geq 2 \times$ ULN in total bilirubin, in the absence of $\geq 2 \times$ ULN in alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality.

Statistical Analyses

The full analysis set (FAS) consisted of randomized patients who received at least one dose of CZP and who had valid efficacy assessment (JDA score or PASI for patients with GPP and EP, respectively) for baseline and for at least one post-baseline visit. The GPP and EP set consisted of patients in the FAS with GPP and EP, respectively, at baseline. The safety set (SS) consisted of randomized patients with GPP or EP who received at least one dose of study medication.

Data are summarized descriptively according to patients' originally randomized treatment group at week 0. Data during the maintenance treatment period were summarized according to the treatments that patients received. Observed case data are presented. No statistical tests were performed.

RESULTS

Patient Disposition and Baseline Characteristics

Of the 24 patients screened, 22 patients were randomized to CZP 400 mg Q2W (GPP: $n = 3$; EP: $n = 8$) and CZP 200 mg Q2W (GPP: $n = 4$, EP: $n = 7$; Fig. 2). Demographics and baseline disease characteristics were generally balanced across the CZP treatment groups (Table 1). In patients with GPP, the mean (standard deviation [SD]) baseline JDA total score was 6.3 (4.0) for the CZP 400 mg Q2W group and 5.5 (2.4) for the CZP 200 mg Q2W group. In patients with EP, the mean (SD) baseline PASI was 43.7 (17.9)

for the CZP 400 mg Q2W group and 34.3 (9.2) for the CZP 200 mg group. Four patients with GPP and 10 patients with EP were receiving concomitant systemic medications for PSO (Supplementary Table 1).

In total, 19 patients completed week 52 (CZP 400 mg Q2W, GPP: $n = 3$, EP: $n = 7$; CZP 200 mg Q2W, GPP: $n = 4$, EP: $n = 5$). Three patients (two with EP and one with GPP) on CZP 200 mg Q2W had their dose increased to CZP 400 mg Q2W in the maintenance treatment period (Fig. 2).

Efficacy Outcomes from Weeks 0 to 52 in Patients with GPP

CGI-I Response

At week 2, 6/7 patients achieved a CGI-I response. The number of patients who achieved a CGI-I response increased over time, and by week 16, all patients achieved a CGI-I response (Fig. 3a; Supplementary Fig. 1). The response was generally maintained at week 52, with CGI-I response observed in 6/7 patients.

DLQI 0/1

At week 2, none of the patients achieved DLQI 0/1. The number of patients who achieved DLQI 0/1 increased over time through to week 16. At week 16, 2/7 patients achieved DLQI 0/1. At week 52, the response improved with 4/7 patients achieving DLQI 0/1 (Fig. 4a). Absolute DLQI scores for each patient over 52 weeks are shown in Supplementary Fig. 2a.

INRS 0 and Score

At week 2, none of the patients achieved INRS 0. At week 16, 1/7 patients with GPP achieved INRS 0. At week 52, INRS 0 was achieved by 2/7 patients (Table 2). Reductions from baseline were generally observed in INRS scores at weeks 16 and 52 (Fig. 5a). Absolute INRS scores for each patient over 52 weeks are shown in Supplementary Fig. 3a.

GIS Response

At week 2, all patients with GPP achieved a GIS response, and this was maintained through to week 16. At week 52, 6/7 patients achieved a GIS

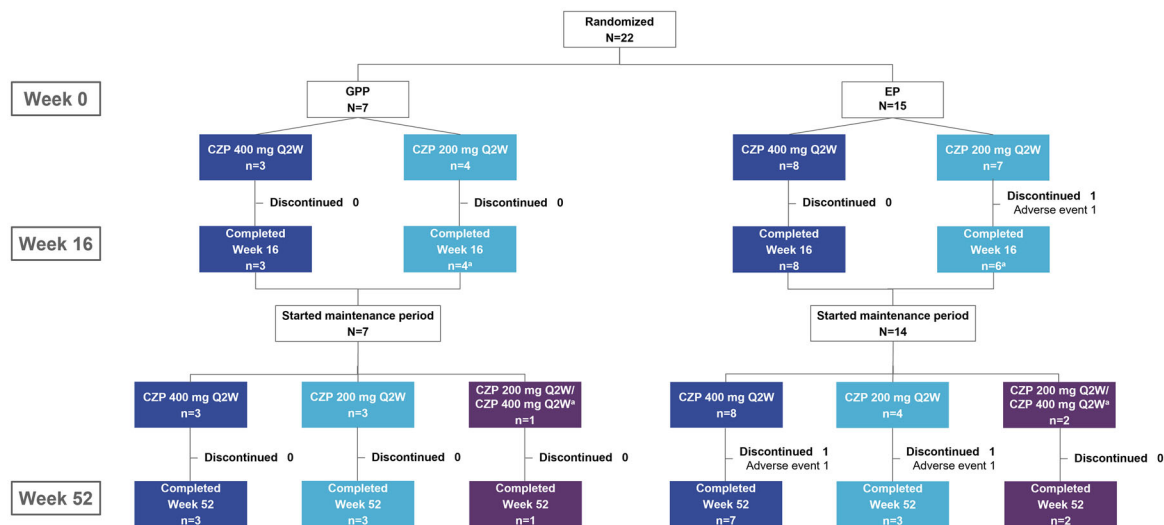


Fig. 2 Patient disposition to week 52. ^aThree patients (one with GPP and two with EP) who had received CZP 200 mg Q2W during the initial treatment period were not in response during the maintenance treatment period, and

response (Table 2). GIS responses for each patient over 52 weeks are shown in Supplementary Fig. 4.

JDA Severity Index Total Score

In patients with GPP, improvements from baseline were observed in the mean JDA total scores (2.0–2.5) at week 16; further improvements were observed through week 52 (1.7–2.0) (Fig. 6). Generally, improvements from baseline were also observed in the subtotal for skin symptoms and for systemic symptoms and laboratory findings (Table 3). JDA severity scores for each patient over 52 weeks are shown in Supplementary Fig. 5.

Efficacy Outcomes in Patients Who Underwent Dose Titration

One patient with GPP on CZP 200 mg Q2W had their dose increased to CZP 400 mg Q2W in the maintenance treatment period. At week 52, CGI-I response was achieved (Fig. 3a). The GPP patient who underwent dose titration also achieved a GIS response at week 52 (Table 2).

their dose was increased to CZP 400 mg Q2W. CZP certolizumab pegol, EP erythrodermic psoriasis, GPP generalized pustular psoriasis, Q2W every 2 weeks

Efficacy Outcomes from Weeks 0 to 52 in Patients with EP

CGI-I Response

At week 2, 9/15 patients achieved a CGI-I response. The number of patients who achieved a CGI-I response increased over time, and by week 16, all patients (14/14) achieved a CGI-I response (Fig. 3b; Supplementary Fig. 1). The response was generally maintained at week 52, with all patients (12/12) achieving a CGI-I response at week 52.

DLQI 0/1

At week 2, 2/15 patients achieved DLQI 0/1. The number of patients who achieved DLQI 0/1 increased over time through to week 16. At week 16, 6/14 patients achieved DLQI 0/1. At week 52, the response improved with 7/12 patients achieving DLQI 0/1 (Fig. 4b). Absolute DLQI scores for each patient over 52 weeks are shown in Supplementary Fig. 2b.

INRS 0 and Score

At week 2, 2/15 patients achieved INRS 0. At week 16, 3/14 EP patients achieved INRS 0. At week 52, INRS 0 was achieved by 2/12 patients

Table 1 Demographics and baseline disease characteristics

Mean (SD) unless stated	GPP (<i>N</i> = 7)		EP (<i>N</i> = 15)	
	CZP 400 mg Q2W (<i>n</i> = 3)	CZP 200 mg Q2W (<i>n</i> = 4)	CZP 400 mg Q2W (<i>n</i> = 8)	CZP 200 mg Q2W (<i>n</i> = 7)
Demographics				
Age, years	44.7 (8.3)	51.0 (14.6)	47.8 (11.3)	56.0 (8.5)
Male, <i>n</i> (%)	1 (33.3)	2 (50.0)	6 (75.0)	7 (100.0)
Weight (kg)	57.2 (14.9)	65.3 (13.6)	69.7 (13.0)	73.5 (15.2)
BMI (kg/m ²)	21.8 (5.7)	25.9 (6.8)	25.6 (4.1)	26.3 (5.1)
Baseline disease characteristics				
PASI	Not available	Not available	43.7 (17.9)	34.3 (9.2)
BSA affected (%)	N/A	N/A	87.1 (6.8)	86.6 (3.6)
PGA score, <i>n</i> (%)				
3	Not available	Not available	1 (12.5)	4 (57.1)
4	Not available	Not available	5 (62.5)	3 (42.9)
DLQI	5.7 (1.2)	11.0 (8.0)	9.6 (10.4)	8.3 (6.4)
INRS	6.3 (2.9)	4.3 (3.0)	4.5 (3.3)	4.1 (3.1)
JDA severity index	6.3 (4.0)	5.5 (2.4)	N/A	N/A
Skin symptoms	4.7 (3.2)	3.8 (1.7)	N/A	N/A
Systemic symptoms and laboratory findings	1.7 (1.2)	1.8 (1.3)	N/A	N/A
Duration of disease, years	6.2 (10.3)	3.1 (3.4)	4.7 (5.3)	9.0 (10.7)
Concurrent PsA, <i>n</i> (%)	1 (33.3)	2 (50.0)	2 (25.0)	2 (28.6)
Any systemic PSO treatment, <i>n</i> (%)	2 (66.7)	4 (100.0)	7 (87.5)	5 (71.4)
Previous systemic nonbiologic therapy, <i>n</i> (%)	2 (66.7)	4 (100.0)	6 (75.0)	5 (71.4)
1 therapy	2 (66.7)	3 (75.0)	2 (25.0)	4 (57.1)
2 therapies	0 (0.0)	0 (0.0)	3 (37.5)	0 (0.0)
≥ 3 therapies	0 (0.0)	1 (25.0)	1 (12.5)	1 (14.3)
Previous biologic therapy used, <i>n</i> (%)	1 (33.3)	2 (50.0)	5 (62.5)	1 (14.3)
1 therapy	1 (33.3)	2 (50.0)	4 (50.0)	0 (0.0)
2 therapies	0 (0.0)	0 (0.0)	1 (12.5)	1 (14.3)
≥ 3 therapies	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prior chemophototherapy or phototherapy, <i>n</i> (%)	1 (33.3)	1 (25.0)	7 (87.5)	3 (42.9)

Table 1 continued

Mean (SD) unless stated	GPP (N = 7)		EP (N = 15)	
	CZP 400 mg Q2W (n = 3)	CZP 200 mg Q2W (n = 4)	CZP 400 mg Q2W (n = 8)	CZP 200 mg Q2W (n = 7)
Previous anti-TNF therapy used, n (%)	0 (0.0)	1 (25.0)	1 (12.5)	0 (0.0)

Full analysis set

BMI body mass index, BSA body surface area, CZP certolizumab pegol, DLQI Dermatology Life Quality Index, EP erythrodermic psoriasis, GPP generalized pustular psoriasis, JDA Japanese Dermatological Association, INRS Itch Numeric Rating Scale, N/A not applicable, PASI Psoriasis Area and Severity Index score, PGA Physician's Global Assessment, PsA psoriatic arthritis, PSO psoriasis, Q2W every 2 weeks, SD standard deviation, TNF tumor necrosis factor

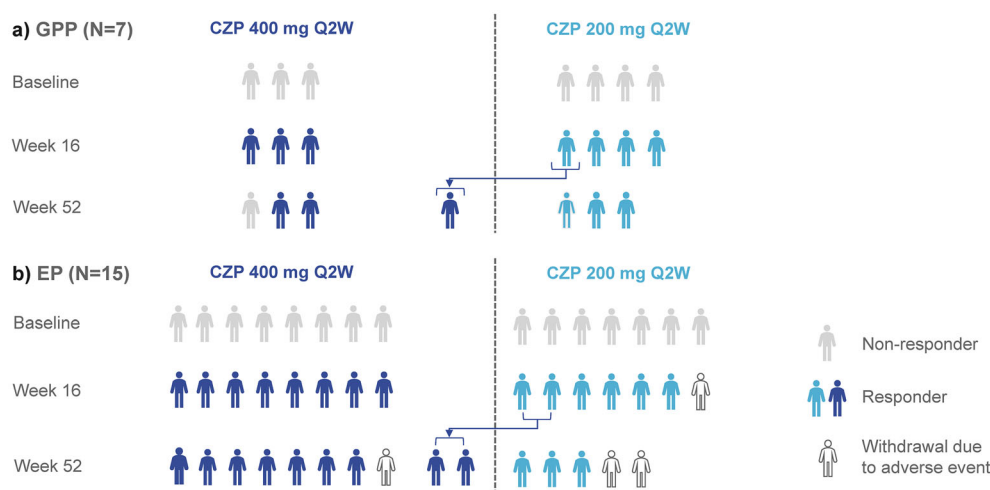


Fig. 3 CGI-I response in patients with GPP and EP at weeks 16 and 52 of CZP treatment. Full analysis set. Observed case. Data summarized according to patients' originally randomized treatment group at week 0. Total *n* at each timepoint may vary, being the summation of the number of patients who were responders and

nonresponders. CGI-I responders defined as patients who achieved "remission" or "improved." CGI-I Clinical Global Impression of Improvement, CZP certolizumab pegol, EP erythrodermic psoriasis, GPP generalized pustular psoriasis, Q2W every 2 weeks

(Table 2). Reductions from baseline were generally observed in INRS scores at weeks 16 and 52 (Fig. 5b). Absolute INRS scores for each patient over 52 weeks are shown in Supplementary Fig. 3b.

PASI Response

At week 4, 4/15 patients achieved PASI 75 or PASI 90 response, and the response improved over time, with 9/14 patients achieving response at week 16. At week 52, 10/12 patients

achieved PASI 75 response and 9/12 achieved PASI 90 response (Table 2). At week 16, a reduction from baseline in absolute PASI was observed in both CZP groups (mean [SD]: 8.2 [9.2] for the CZP 400 mg Q2W group and 6.9 [10.2] for the CZP 200 mg Q2W group). Further reduction was observed during weeks 16–52 with week 52 mean (SD) score of 3.2 (3.2) for the CZP 400 mg Q2W/CZP 400 mg Q2W group, 4.5 (4.5) for the CZP 200 mg Q2W/CZP 200 mg Q2W group, and 1.2 (0.6) for the

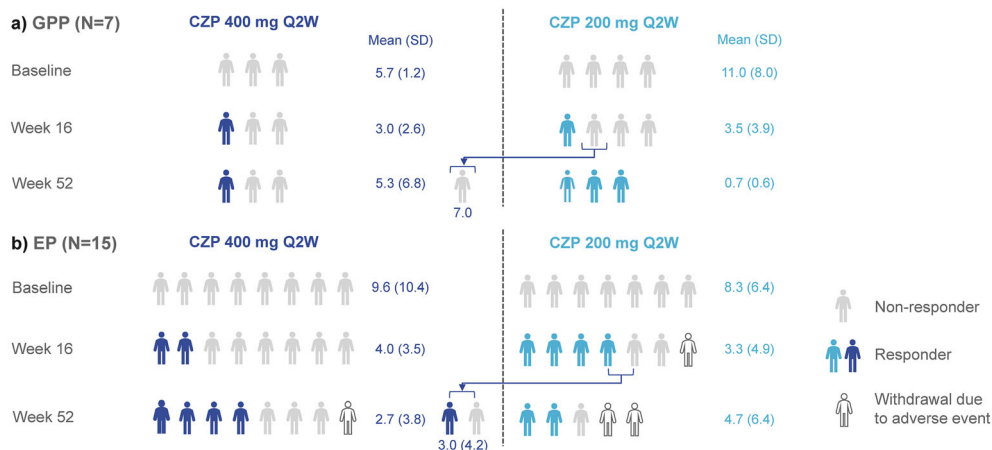


Fig. 4 DLQI 0/1 in patients with GPP and EP at weeks 16 and 52 of CZP treatment. Full analysis set. Observed case. Data summarized according to patients’ originally randomized treatment group at week 0. Total *n* at each time point may vary, being the summation of the number of patients who were responders and nonresponders.

DLQI 0/1 defined as patients who had absolute DLQI score of ≤ 1 . CZP certolizumab pegol, DLQI Dermatology Life Quality Index, EP erythrodermic psoriasis, GPP generalized pustular psoriasis, Q2W every 2 weeks, SD standard deviation

CZP 200 mg Q2W/CZP 400 mg Q2W group (Fig. 7). Absolute PASI scores for each patient over 52 weeks are shown in Supplementary Fig. 6.

PGA 0/1

At week 8, 2/14 patients achieved PGA 0/1 response, and the response improved over time with 4/14 patients achieving response at week 16; the response was maintained through week 52 (Table 2). Absolute PGA scores for each patient over 52 weeks are shown in Supplementary Fig. 7.

Efficacy Outcomes in Patients Who Underwent Dose Titration

Two patients with EP on CZP 200 mg Q2W had their dose increased to CZP 400 mg Q2W in the maintenance treatment period. At week 52, CGI-I response was achieved by both patients (Fig. 3b). At week 52, among both patients with EP who underwent dose titration, one patient achieved DLQI 0/1, one patient achieved INRS 0, both achieved PASI 75 and PASI 90, and one patient achieved PGA 0/1 (Table 2).

Safety

After 52 weeks of CZP treatment, the patient exposures were 4.2 patient-years (PY) and 3.8 PY for patients with GPP receiving CZP 400 mg Q2W and CZP 200 mg Q2W, respectively. For patients with EP, patient exposures were 9.6 PY and 5.7 PY for the CZP 400 mg Q2W and CZP 200 mg Q2W group, respectively (Table 4). TEAEs were reported in 7/7 GPP and 14/15 EP patients. The most common TEAE was nasopharyngitis, which was reported in 2/7 GPP and 7/15 EP patients. In total, three serious TEAEs were reported in three CZP 400 mg Q2W-treated patients: one case of neutropenia reported in a patient with GPP, one case of erythema multiforme reported in a patient with EP (both considered drug-related by the investigator), and one case of pustular psoriasis reported in a patient with GPP (Table 4). No other AEOIs were reported from weeks 0–52; there were no opportunistic infections (including active tuberculosis), malignancies (including lymphoma), TEAEs related to congestive heart failure, serious cardiovascular events, serious skin disorders (such as Stevens–Johnson), lupus, or deaths. In total,

Table 2 Efficacy outcomes in patients with GPP and EP at weeks 16 and 52 of CZP treatment

GPP (<i>N</i> = 7)	Week 16		Week 52		
	CZP 400 mg Q2W (<i>n</i> = 3)	CZP 200 mg Q2W (<i>n</i> = 4)	CZP 400 mg Q2W/ CZP 400 mg Q2W (<i>n</i> = 3)	CZP 200 mg Q2W/ CZP 200 mg Q2W (<i>n</i> = 3)	CZP 200 mg Q2W/ CZP 400 mg Q2W (<i>n</i> = 1)
INRS 0 ^a	0/3	1/4	1/3	1/3	0/1
GIS response ^b	3/3	4/4	2/3	3/3	1/1
EP (<i>N</i> = 15)	CZP 400 mg Q2W (<i>n</i> = 8)	CZP 200 mg Q2W (<i>n</i> = 7)	CZP 400 mg Q2W/ CZP 400 mg Q2W (<i>n</i> = 8)	CZP 200 mg Q2W/ CZP 200 mg Q2W (<i>n</i> = 4)	CZP 200 mg Q2W/ CZP 400 mg Q2W (<i>n</i> = 2)
	INRS 0 ^a	1/8	2/6	1/7	0/3
PASI 75 ^c	5/8	4/6	6/7	2/3	2/2
PASI 90 ^c	5/8	4/6	6/7	1/3	2/2
PGA 0/1 ^c	2/8	2/6	3/7	1/3	1/2

Observed cases

CZP certolizumab pegol, EP erythrodermic psoriasis, GIS Global Improvement Score, GPP generalized pustular psoriasis, INRS Itch Numeric Rating Scale, PASI Psoriasis Area and Severity Index, PGA Physician's Global Assessment, Q2W every 2 weeks

^aFull analysis set; INRS 0 defined as patients who had absolute INRS score of 0

^bGPP set; GIS responders defined as patients who achieved "very much improved," "much improved," or "minimally improved"

^cEP set; PASI 75/90 responders defined as patients who achieved $\geq 75/90\%$ reduction from baseline PASI and PGA 0/1 responders defined as patients who had absolute score of 0 or 1 (with ≥ 2 -point improvement from baseline)

three patients with EP discontinued CZP due to TEAEs: one patient receiving CZP 400 mg Q2W discontinued due to erythema multiforme, and two patients receiving CZP 200 mg Q2W discontinued, one due to latent tuberculosis and one due to psoriasis.

DISCUSSION

This is the first study to report the safety and efficacy of CZP treatment in patients with GPP and EP. Treatment with CZP 400 mg Q2W and 200 mg Q2W doses resulted in consistent improvements at week 16 across all efficacy

endpoints assessed, and these improvements were maintained through week 52. No new safety signals were identified with 52 weeks of CZP treatment.

Current recommended first-line treatment in the management of GPP and EP are retinoids (such as etretinate and acitretin) and cyclosporine [3, 9]. However, these treatments are associated with safety concerns (including teratogenicity and renal toxicity, and long-term AEs) [2, 3, 8]. In severe cases of GPP and EP, where rapid and effective treatments are essential to prevent complications and mortality, the response observed with conventional agents is often inadequate [2, 3, 7, 8]. As such, there is a

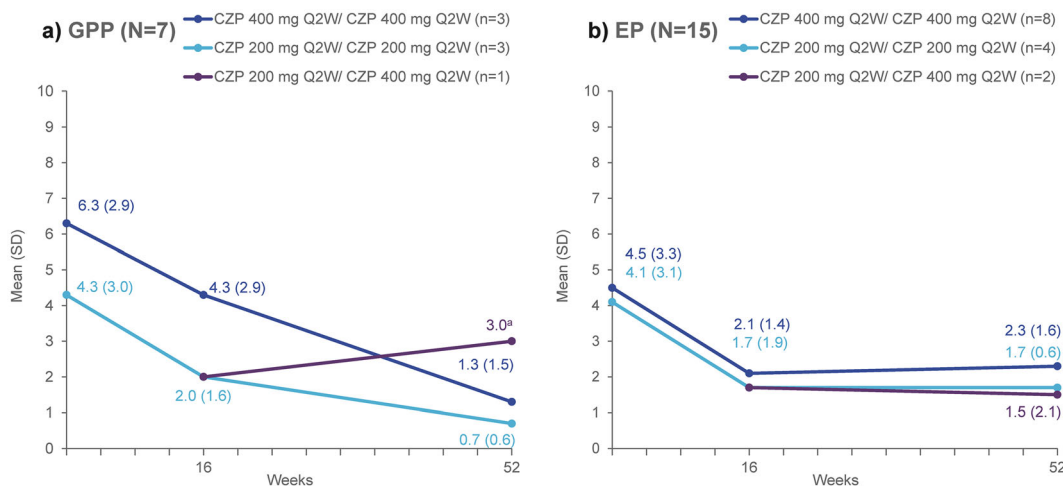


Fig. 5 INRS absolute score in patients with GPP and EP over weeks 0–52. Full analysis set. Observed case. Data summarized according to the treatments that patients received. ^aNo SD available as $n = 1$. CZP certolizumab

pegol, EP erythrodermic psoriasis, GPP generalized pustular psoriasis, INRS Itch Numeric Rating Scale, Q2W every 2 weeks, SD standard deviation

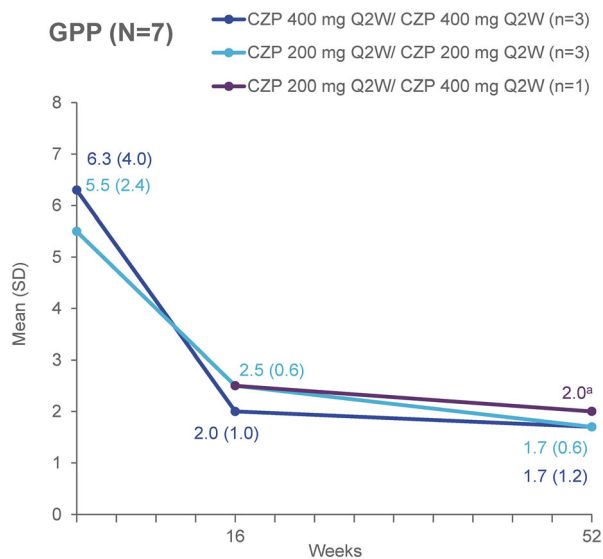


Fig. 6 JDA total score in patients with GPP over weeks 0–52. GPP set. Observed case. Data summarized according to the treatments that patients received. ^aNo SD available as $n = 1$. CZP certolizumab pegol, GPP generalized pustular psoriasis, JDA Japanese Dermatological Association, Q2W every 2 weeks, SD standard deviation

similarities in pathophysiology, recent evidence has identified the role of IL-36 as a key contributor in the pathophysiology of GPP, compared with PSO, which is predominantly driven by the TNF- α /IL-23/IL-17 axis [8, 18, 19]. As such, anti-IL-36 therapies are currently being studied for the treatment of GPP. Clinical trials for these anti-IL-36 therapies are still ongoing, although phase 1 results have been promising [20]. However, given that these anti-IL-36 therapies are still in very early stages of development and clinical trials, it is still uncertain if they will demonstrate efficacy with a good safety profile. On the other hand, anti-TNFs are available now and are well established in other chronic inflammatory diseases. For patients with GPP and EP, anti-TNFs will provide more immediate and certain treatment options.

With CZP treatment, more than half of the patients achieved CGI-I response at week 2, and by week 16, all patients were CGI-I responders. Improvements in patient health-related quality of life and severity of itch (as measured by DLQI 0/1 and INRS 0, respectively) were also observed for both CZP-treated groups at week 16. In patients with GPP, improvements were observed as early as week 2 and through week 16, based on the GIS response and JDA

need for new treatment options for patients with these severe forms of psoriasis. Although current treatment options for GPP are based on therapies indicated for PSO due to the

Table 3 JDA severity index in patients with GPP at weeks 16 and 52 of CZP treatment

	CZP 400 mg Q2W/ CZP 400 mg Q2W (<i>n</i> = 3)			CZP 200 mg Q2W/ CZP 200 mg Q2W (<i>n</i> = 3)			CZP 200 mg Q2W/ CZP 400 mg Q2W (<i>n</i> = 1)		
	BL	Week 16	Week 52	BL	Week 16	Week 52	BL	Week 16	Week 52
Skin symptoms subtotal, ^a mean (SD)	4.7 (3.2)	1.7 (1.2)	1.3 (0.6)	4.0 (2.0)	2.0 (0.0)	0.7 (0.6)	3.0 ^d	1.0 ^d	2.0 ^d
Erythematous area (BSA %), <i>n</i>									
≥ 75	1	0	0	1	0	0	0	0	0
≥ 25 to < 75	1	0	1	1	2	0	1	0	0
< 25	1	3	2	1	1	2	0	1	1
0	0	0	0	0	0	1	0	0	0
Erythematous area with pustule (BSA %), <i>n</i>									
≥ 50	0	0	0	0	0	0	0	0	0
≥ 10 to < 50	2	0	0	1	0	0	0	0	0
< 10	0	1	0	1	1	0	1	0	1
0	1	2	3	1	2	3	0	1	0
Edematous area (BSA %), <i>n</i>									
≥ 50	0	0	0	0	0	0	0	0	0
≥ 10 to < 50	2	0	0	1	0	0	0	0	0
< 10	0	1	0	1	0	0	0	0	0
0	1	2	3	1	3	3	1	1	1
Systemic symptoms and laboratory findings, ^b mean (SD)	1.7 (1.2)	0.3 (0.6)	0.3 (0.6)	2.3 (0.6)	0.3 (0.6)	1.0 (1.0)	0.0 ^d	2.0 ^d	0.0 ^d
Fever (°C), <i>n</i>									
≥ 38.5	0	0	0	0	0	0	0	0	0
≥ 37.0 to < 38.5	2	1	1	2	1	1	0	1	0
< 37.0	1	2	2	1	2	2	1	0	1
WBC count/μL, <i>n</i>									
≥ 15,000	0	0	0	0	0	0	0	0	0
≥ 10,000 to < 15,000	1	0	0	2	0	0	0	0	0
< 10,000	2	3	3	1	3	3	1	1	1
CRP (mg/dL), <i>n</i>									
≥ 7.0	0	0	0	0	0	0	0	0	0

Table 3 continued

	CZP 400 mg Q2W/ CZP 400 mg Q2W (<i>n</i> = 3)			CZP 200 mg Q2W/ CZP 200 mg Q2W (<i>n</i> = 3)			CZP 200 mg Q2W/ CZP 400 mg Q2W (<i>n</i> = 1)		
	BL	Week 16	Week 52	BL	Week 16	Week 52	BL	Week 16	Week 52
≥ 0.3 to < 7.0	2	0	0	3	0	2	0	1	0
< 0.3	1	3	3	0	3	1	1	0	1
Serum albumin (g/dL), <i>n</i>									
< 3.0	0	0	0	0	0	0	0	0	0
≥ 3.0 to < 3.8	0	0	0	0	0	0	0	0	0
≥ 3.8	3	3	3	3	3	3	1	1	1
Severity classification of GPP, ^c <i>n</i>									
Mild (total score 0–6)	1	3	3	1	3	3	1	1	1
Moderate (total score 7–10)	2	0	0	2	0	0	0	0	0
Severe (total score 11–17)	0	0	0	0	0	0	0	0	0

GPP set. Observed case. Data summarized according to the treatments that patients received
BL baseline, *BSA* body surface area, *CRP* C-reactive protein, *CZP* certolizumab pegol, *GPP* generalized pustular psoriasis, *JDA* Japanese Dermatological Association, *Q2W* every 2 weeks, *SD* standard deviation, *WBC* white blood cell

^aIn the JDA severity index of GPP, skin symptoms were evaluated based on erythematous area, erythematous area with pustules, and edematous area

^bIn the JDA severity index of GPP, systemic symptoms and laboratory findings were evaluated based on fever, WBC count, CRP, and serum albumin

^cThe sum of the two subtotals gives the total JDA severity score, which is classified into mild, moderate, and severe

^dNo SD available as *n* = 1

severity index. In patients with EP, improvements in PASI 75, PASI 90, and PGA 0/1 response were observed at week 16 in both CZP-treated groups. These results suggest that CZP may be a feasible treatment option for patients with GPP and EP due to the rapid onset of response observed across efficacy outcomes. Furthermore, as CZP has previously demonstrated minimal levels of placental transfer from mothers to infants [11], and no to minimal transfer from plasma into breast milk, it may be a viable option for female patients of child-bearing age with GPP or EP [21], at various stages of their family planning journey. As both GPP and EP are potentially life-threatening and may result in adverse pregnancy outcomes

[22, 23], CZP may provide additional benefits to these patients.

Generally, the improvements observed at week 16 across the collection of efficacy endpoints were maintained through week 52. At week 52, PASI 75 response achieved by patients with EP was comparable to the PASI 75 response achieved by Japanese patients with PSO treated with CZP (CZP 400 mg Q2W: 44/53 [83.0%]; CZP 200 mg Q2W: 35/48 [72.9%]) [14]. During the maintenance treatment period, three patients (two with EP and one with GPP) in the CZP 200 mg Q2W group did not achieve response and underwent a dose escalation to receive CZP 400 mg Q2W, at the discretion of the investigator. At week 52, these patients

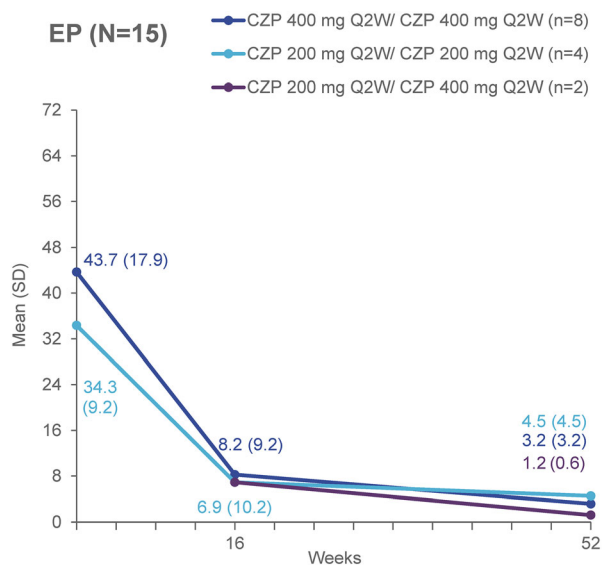


Fig. 7 Absolute PASI in patients with EP over weeks 0–52. EP set. Observed case. Data summarized according to the treatments that patients received. *CZP* certolizumab pegol, *EP* erythrodermic psoriasis, *PASI* Psoriasis Area and Severity Index, *Q2W* every 2 weeks

achieved improvements across most efficacy endpoints. These data suggest that dose escalation may be a useful strategy in patients with EP and GPP who do not achieve adequate response with CZP 200 mg Q2W.

The results of this study are comparable to those of other studies evaluating the efficacy of biologics in Japanese patients with GPP and EP. In a phase 3 trial evaluating the efficacy of the anti-TNF adalimumab, in Japanese patients with GPP ($n = 10$), the mean change from baseline (CfB) in the total JDA score at week 52 was approximately -6.0 [24]. This was similar to the reduction observed in this study (mean CfB: -4.7). In phase 3 trials of Japanese patients with EP, mean (SD) CfB in absolute PASI at week 52 was -39.9 (9.9) for ixekizumab (anti-IL-17, $n = 8$) [25, 26] and -36.9 (13.4) for guselkumab (anti-IL-23, $n = 10$) [27]. This was

also comparable to the results observed in this study (CZP 400 mg Q2W/CZP 400 mg Q2W: -41.7 [18.9], CZP 200 mg Q2W/CZP 200 mg Q2W: -22.1 [6.6], and CZP 200 mg Q2W/CZP 400 mg Q2W: -41.8 [1.6]). In Japanese patients with EP, improvements from baseline PASI were observed to be faster with ixekizumab (week 1 CfB, -21.7) [28], than with CZP in this study (week 2 CfB, CZP 400 mg Q2W: -15.7 and CZP 200 mg Q2W: -18.7). By week 12, 100% achieved PASI 75 with ixekizumab [28], compared with 62.5–66.7% with CZP. It is important to note that, owing to the small patient population and difference in study design and population of these trials, comparisons of data between these studies should be interpreted with caution.

Over 52 weeks of treatment, although the incidence of TEAEs and serious TEAEs were slightly higher in this group of patients compared with Japanese patients with PSO, no new safety signals were identified when compared with previously reported data for CZP in other indications, and other anti-TNF medications approved for PSO [16, 29–32].

Limitations of this trial include a lack of active comparator and the exclusion of patients with history of primary failure to biologic therapy. As this was a clinical trial, the strict inclusion and exclusion criteria may affect the generalizability of these results to clinical practice, and therefore there is a need to use real-world data to monitor the long-term efficacy and safety of CZP in patients with GPP and EP. Lastly, due to the low prevalence of GPP and EP, this study had a small sample size. As such, the results should be interpreted with caution. Sample sizes were also small in clinical trials that evaluated the efficacy of other biologics for the treatment of GPP and EP in Japanese patients, with patient numbers ranging from 10 to 21 [24–27, 33, 34].

Table 4 Safety over 52 weeks of CZP treatment (safety set)

	All CZP (N = 22)	GPP		EP	
		CZP 400 mg Q2W (n = 4) ^a	CZP 200 mg Q2W (n = 4)	CZP 400 mg Q2W (n = 10) ^a	CZP 200 mg Q2W (n = 7)
Total patient exposure, patient-years at risk	23.3	4.2	3.8	9.6	5.7
Any TEAE, ^{b,c} n [#]	21 [100]	4 [20]	3 [17]	9 [37]	5 [26]
Nasopharyngitis	9 [17]	1 [2]	1 [5]	6 [9]	1 [1]
Cough	3 [3]	0	0	1 [1]	2 [2]
Pruritus	3 [3]	0	1 [1]	2 [2]	0
Psoriasis	5 [5]	1 [1]	0	3 [3]	1 [1]
Serious TEAEs, ^b n [#]	3 [3]	2 [2]	0	1 [1]	0
Neutropenia	1 [1]	1 [1]	0	0	0
Erythema multiforme	1 [1]	0	0	1 [1]	0
Pustular psoriasis	1 [1]	1 [1]	0	0	0
Discontinuation due to TEAEs, n [#]	3 [3]	0	0	1 [1]	2 [2]
Drug-related TEAEs, ^d n [#]	9 [14]	2 [2]	1 [1]	3 [6]	3 [5]
Severe TEAEs, ^e n [#]	2 [3]	1 [1]	0	1 [2]	0
Erythema multiforme	1 [1]	0	0	1 [1]	0
Psoriasis	1 [1]	0	0	1 [1]	0
Pustular psoriasis	1 [1]	1 [1]	0	0	0
Deaths, n [#]	0	0	0	0	0
Deaths due to TEAEs, n [#]	0	0	0	0	0

Note: n = number of patients reporting ≥ 1 TEAE within the category being summarized; [#] is the number of events
 CZP certolizumab pegol, EP erythrodermic psoriasis, GPP generalized pustular psoriasis, ICH International Council for
 Harmonization, Q2W every 2 weeks, TEAE treatment-emergent adverse event

^aPatients who were receiving CZP 200 mg Q2W and had their dose up-titrated to CZP 400 mg Q2W in the maintenance
 period were counted in both CZP 200 mg Q2W and CZP 400 mg Q2W groups, but only once in the “All CZP” group

^bDefined as per ICH Harmonized Tripartite Guideline. Clinical Safety Data Management: Definitions and Standards for
 Expedited Reporting. [https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/
 E2A_Guideline.pdf](https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf)

^cPreferred terms with incidence of $\geq 10\%$ in the “All CZP” group were reported

^dDrug-related TEAEs are those TEAEs considered related to study medication

^eSevere TEAEs are TEAEs with an intensity grading of severe (as compared with mild or moderate)

CONCLUSION

Overall, these data show CZP efficacy in Japanese patients with GPP and EP over 52 weeks of treatment, with no new safety signals identified. This study provides preliminary evidence to support use of CZP as a feasible treatment option for patients with GPP and EP.

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Compliance with Ethics Guidelines. This study protocol was reviewed by the institutional review board (IRB) of each institution prior to implementation. Written informed consent was obtained from all patients. 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.

Data Availability. Underlying data from this manuscript may be requested by qualified researchers six months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after trial

completion. Investigators may request access to anonymized 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 <http://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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