Certolizumab pegol for the treatment of chronic plaque psoriasis: Results through 48 weeks of a phase 3, multicenter, randomized, double-blind, etanercept- and placebo-controlled study (CIMPACT)

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Conflicts of interest: Dr Lebwohl is an employee of Mount Sinai which receives research funds from AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Incyte, Janssen/Johnson & Johnson, Leo Pharmaceutucals, Medimmune/Astra Zeneca, Novartis, Pfizer, Sciderm, UCB, Valeant, and ViDac; and is a consultant for Allergan, Aqua, Boehringer-Ingelheim, LEO Pharma, Menlo, and Promius. Dr Blauvelt has received honoraria or fees for consulting, serving as a clinical investigator, and/or speaking for AbbVie, Aclaris, Allergan, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Dermira Inc, Eli Lilly and Company, Genentech/Roche, GSK, Janssen, LEO Pharma, Merck Sharp & Dohme, Novartis, Pfizer, Purdue Pharma, Regeneron, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB, Valeant, and Vidac. Dr Paul is a consultant and investigator for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Janssen/Johnson & Johnson, LEO Pharma, Novartis, Pierre Fabre, Pfizer, and Sanofi/Regeneron. Dr Sofen has received honoraria or fees for consulting, serving as a clinical investigator, and/or speaking for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Dermira Inc, Janssen, Eli Lilly, Merck, Novartis, Pfizer, Sun Pharma, UCB, and Valeant. Dr Węgłowska is an investigator and/or speaker for Amgen, Celgene, Coherus, Dermira Inc, Eli Lilly and Company, Galderma, Janssen, LEO Pharma, Merck, Pfizer, Regeneron, Sandoz, and UCB. Dr Piguet has received honoraria or fees for consulting and/or speaking for AbbVie, Almirall, Celgene, Janssen, Novartis, and Pfizer; and has received departmental support for Cardiff University from AbbVie, Almirall, Alliance, Beiersdorf UK Ltd, Biotest, Celgene, Dermal, Eli Lilly, Galderma, Genus Pharma, GlobeMicro, Janssen-Celag, LaRoche-Posay, L'Oreal, LEO Pharma, Meda, MSD, Novartis, Pfizer, Sinclair Pharma, Spirit, Stiefel, Samumed, Thornton Ross, TyPham, and UCB. Dr Augustin has received honoraria or fees for consulting and/or speaking for clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly and Company, GSK, Hexal, Janssen-Cilag, LEO Pharma, Medac, Merck, MSD, Mundipharma, Novartis, Pfizer, Sandoz, UCB BioSciences Inc, and Xenoport. Ms Drew and Dr Burge have received stock options from Dermira Inc. Mr Peterson owns stock in UCB Inc. Dr Rolleri has received stock options from UCB Inc.

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Background: Phase 2 psoriasis studies with the Fc-free, PEGylated, anti–tumor necrosis factor biologic certolizumab pegol demonstrated meaningful clinical activity.

Objective: Assess safety and efficacy of certolizumab in adults with moderate-to-severe chronic plaque psoriasis.

Methods: Patients were randomized 3:3:1:3 to certolizumab 400 mg, certolizumab 200 mg, or placebo every 2 weeks for 16 weeks or etanercept 50 mg twice weekly for 12 weeks. Certolizumab-treated patients achieving a ≥75% reduction in Psoriasis Area and Severity Index (PASI) at week 16 from baseline PASI were rerandomized to certolizumab or placebo for 32 weeks. The primary endpoint was responder rate (≥75% reduction in PASI from baseline PASI) versus placebo (primary analysis) and etanercept (secondary analysis) at week 12; secondary endpoints included responder rates on various measures versus placebo at weeks 12, 16, and 48. Safety was assessed by treatment-emergent adverse events.

Results: All endpoints were significantly greater for certolizumab versus placebo with the greatest response seen with 400 mg. Certolizumab 400 mg was superior to and 200 mg was noninferior to etanercept. Adverse events were consistent with the anti–tumor necrosis factor class of drugs.

Limitations: Etanercept was administered by unblinded study staff or self-administered, but efficacy assessments were performed by a blinded assessor.

Conclusion: Both certolizumab regimens improved psoriasis symptoms, with a greater response seen with the higher dose. No new safety signals were observed. (J Am Acad Dermatol 2018;79:266-76.)

Key words: anti-TNF; anti–tumor necrosis factor; certolizumab pegol; chronic plaque psoriasis; CIMPACT; etanercept; phase 3 trial.

Plaque psoriasis is a chronic, immune-mediated, inflammatory disease that affects ~3% of the adult US population[1,2] and ~2%-6% of adults in Europe.[3] Therapy for psoriasis varies by disease severity, with more severe disease treated with phototherapy, cyclosporine, methotrexate, apremilast, and biologic agents. Phase 3 clinical trials have demonstrated efficacy of biologic agents; however, nearly one-third of patients will discontinue treatment with their first biologic within 3 years due to loss of efficacy,[4] necessitating additional treatment options.[5,6]

Certolizumab pegol (CZP) is the only Fc-free, PEGylated, anti–tumor necrosis factor (TNF) biologic. Because the drug lacks an IgG Fc region, CZP does not bind the neonatal Fc receptor (FcRn) for IgG and is consequently not expected to undergo FcRn-mediated transfer across the placenta,[7] showing minimal placental transfer of CZP from mothers to infants.[8] PEGylation increases the half-life of CZP to 14 days.[9] CZP is approved for the treatment of adults with rheumatoid arthritis, psoriatic arthritis, Crohn disease (United States), ankylosing spondylitis, and nonradiographic axial spondyloarthritis (European Union). CZP is currently under investigation for the treatment of moderate-to-severe plaque psoriasis, with promising results in 2 phase 2 studies.[10] In this phase 3 trial (CIMPACT; NCT02346240), the efficacy of CZP compared with placebo and etanercept and the safety of CZP were assessed in adults with moderate-to-severe chronic plaque psoriasis.

CAPSULE SUMMARY

- Certolizumab pegol is an Fc-free, PEGylated anti–tumor necrosis factor biologic.
- In this phase 3 study, both certolizumab doses improved psoriasis symptoms at week 12. Improvement was maintained, after rerandomization, through week 48, with a safety profile consistent with its drug class.
- The higher dose of certolizumab might provide superior efficacy.

METHODS

Study design

CIMPACT is an ongoing phase 3, multinational (conducted at outpatient clinic sites in North America and Europe), randomized, double-blind, parallel-group, placebo-controlled and single-blind active-controlled trial beginning February 11, 2015 (Fig 1). The data cut-off for the week-48 analysis was December 5, 2016. During the initial period, patients

Abbreviations used:

CZP:	certolizumab pegol
FcRn:	neonatal Fc receptor
PASI:	Psoriasis Area and Severity Index
PASI 50:	≥50% reduction in PASI from baseline PASI
PASI 75:	≥75% reduction in PASI from baseline PASI
PASI 90:	≥90% reduction in PASI from baseline PASI
PGA:	Physician's Global Assessment
PGA 0/1:	PGA clear/almost clear, with ≥2-category improvement from baseline PGA
TEAE:	treatment-emergent adverse event
TNF:	tumor necrosis factor

were randomized 3:3:1:3 (stratified by site) to CZP 400 mg every 2 weeks or CZP 200 mg every 2 weeks (after 400-mg loading doses at weeks 0, 2, and 4) for 16 weeks, placebo every 2 weeks for 16 weeks, or etanercept 50 mg twice weekly for 12 weeks (the CZP loading dose and etanercept starting dose are consistent with the drugs' approved labeling). Double-blind CZP and placebo treatments were administered subcutaneously at the study site by study personnel not involved in any other study procedures; etanercept treatment was administered subcutaneously on-site by unblinded study staff or self-administered off-site by the patient after sufficient training. To maintain the single-blind for etanercept, efficacy assessments were performed by a designated blinded assessor not involved in any other study procedures during blinded study periods. Study drug kits were distributed based on the subject's interactive voice web response system—assigned randomization number; the randomization schedule was produced by an independent biostatistician.

At week 16, patients in the CZP-treatment groups achieving a PASI 75 (≥75% reduction in the Psoriasis Area and Severity Index [PASI] from baseline PASI) were rerandomized (2:2:1): from CZP 400 mg every 2 weeks to CZP 400 mg every 2 weeks, CZP 200 mg every 2 weeks, or placebo; and from CZP 200 mg every 2 weeks to CZP 400 mg every 4 weeks, CZP 200 mg every 2 weeks, or placebo for the 32-week maintenance period. Placebo-treated PASI 75 responders continued placebo for the maintenance period, and etanercept-treated PASI 75 responders, after a 4-week washout, were rerandomized (2:1) to CZP 200 mg every 2 weeks (after 400 mg loading doses at weeks 16, 18, and 20) or placebo. PASI 75 nonresponders at week 16 entered an escape arm and received treatment with CZP 400 mg every 2 weeks. Patients who were rerandomized and were PASI 50 nonresponders (had a <50% reduction in PASI from baseline PASI) at any visit during the maintenance period and patients who completed the double-blind maintenance period entered the open-label safety extension, which was ongoing at the time of publication, and received CZP 400 mg every 2 weeks. Outcomes at weeks 12, 16, and 48 are presented here.

The protocol was amended during the study to add PASI 90 (≥90% reduction in PASI from baseline PASI) as a secondary endpoint. This study was approved by local institutional review boards or independent ethics committees (for non-US sites) and carried out according to the Declaration of Helsinki.[11] Written informed consent was obtained from all patients, and the protocol received institutional review board approval (quorum review file no. 30064; December 12, 2014). This study is registered at ClinicalTrials.gov (NCT02346240) and EudraCT (2014-003492-36).

Study participants

Eligible patients were adults with moderate-to-severe plaque psoriasis for ≥6 months having a baseline PASI ≥12, body surface area affected ≥10%, and Physician's Global Assessment (PGA) ≥3 on a 5-point scale and were candidates for systemic psoriasis therapy, phototherapy, or photochemotherapy.

Patients were excluded if they had a history of treatment with CZP, etanercept, or >2 biologic agents; had a history of primary failure to any biologic (ie, no response within the first 12 weeks of treatment) or secondary failure to >1 biologic (ie, initially responded and then stopped treatment due to loss of response after week 12); had erythrodermic, guttate, or generalized pustular psoriasis; had a history of chronic or recurrent infections, including active or latent tuberculosis (assessed using an interferon-γ release assay) or were at high risk for infection; had a history of a lymphoproliferative disorder, including lymphoma; had a history of malignancy or demyelinating disease of the central nervous system; had congestive heart failure; or were breastfeeding, pregnant, planned to become pregnant, or had a partner who planned to become pregnant during the study or within 3-5 months after the last dose of study drug.

Efficacy and safety assessments

The primary efficacy endpoint was PASI 75 responder rate for both CZP doses versus placebo at week 12. Secondary efficacy endpoints were PASI 75 responder rate versus placebo at week 16; PGA 0/1 responder rate (clear/almost clear with ≥2-point improvement from baseline PGA score) versus placebo at weeks 12 and 16; PASI 90 responder rate

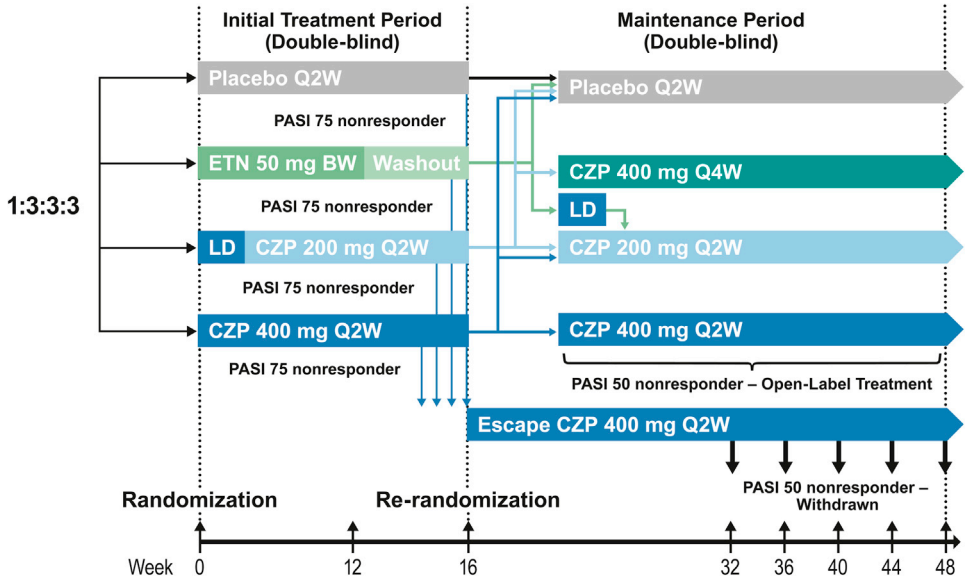

Fig 1. Study design. *BW*, Biweekly; *CZP*, certolizumab pegol; *ETN*, etanercept; *LD*, loading dose of CZP 400 mg at weeks 0, 2, and 4 or weeks 16, 18, and 20; *PASI*, Psoriasis Area and Severity Index; *PASI 50*, ≥50% reduction in PASI from baseline PASI; *PASI 75*, ≥75% reduction in PASI from baseline PASI; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks.

versus placebo at weeks 12 and 16; PASI 75 responder rate versus etanercept at week 12; and PASI 75 responder rates at week 48 for patients achieving PASI 75 at week 16. Safety was assessed by treatment-emergent adverse events (TEAEs).

Statistical analysis

On the basis of previous phase 2 results,[10] week-12 PASI 75 responder rates were assumed to be 80%, 75%, 5%, and 57% for CZP 400 mg, CZP 200 mg, placebo, and etanercept,[12] respectively. Using these values and a 3:3:1:3 randomization ratio, an overall sample size of 540 provided >90% power to detect a significant difference between CZP 200 mg and etanercept for week 12 PASI 75 responder rate with a 2-sided alpha-level of 0.05. The power for the primary endpoint evaluation was >99%.

Efficacy results are reported for patients in randomized and rerandomized treatment groups. Safety results are reported for all patients, including those in the escape arm. Analyses were based on the randomized set (all randomized patients), maintenance set (all patients who completed week 16 and had ≥1 efficacy assessment during the maintenance period), and safety set (all patients who received ≥1 dose of study medication). PASI 75, PGA 0/1, and PASI 90 responder rates were analyzed using a logistic regression model with fixed effects for treatment, region, and prior biologic exposure (yes/no). Imputation of missing data was performed using the Markov chain Monte Carlo method for multiple imputation during the initial period and nonresponder imputation during the maintenance period. In a post-hoc analysis, week-48 PASI 75 responder rates were compared between CZP doses using Fisher's exact test. The details of the fixed-sequence testing procedure used to account for multiplicity can be found in the Supplementary Methods (available at http://www.jaad.org).

RESULTS

Patient disposition, demographics, and baseline characteristics

In total, 559 patients were randomized. Completion rates were similar among treatment groups; >90% of randomized patients completed week 16 and >90% of week-16 PASI 75 responders who entered the maintenance phase completed week 48 (Fig 2). The CZP and etanercept treatment groups were well balanced with respect to baseline disease characteristics (Table I). The placebo group had a slightly lower disease activity (measured by body surface area affected and PASI) and less prior biologic use but also fewer patients compared with the other treatment groups (Table I).

Efficacy to week 16

By week 12, PASI 75 responder rate was significantly greater for CZP-treated patients versus placebo-treated patients (Table II). Differences were evident between the drug groups and the placebo group as early as week 4 and increased through

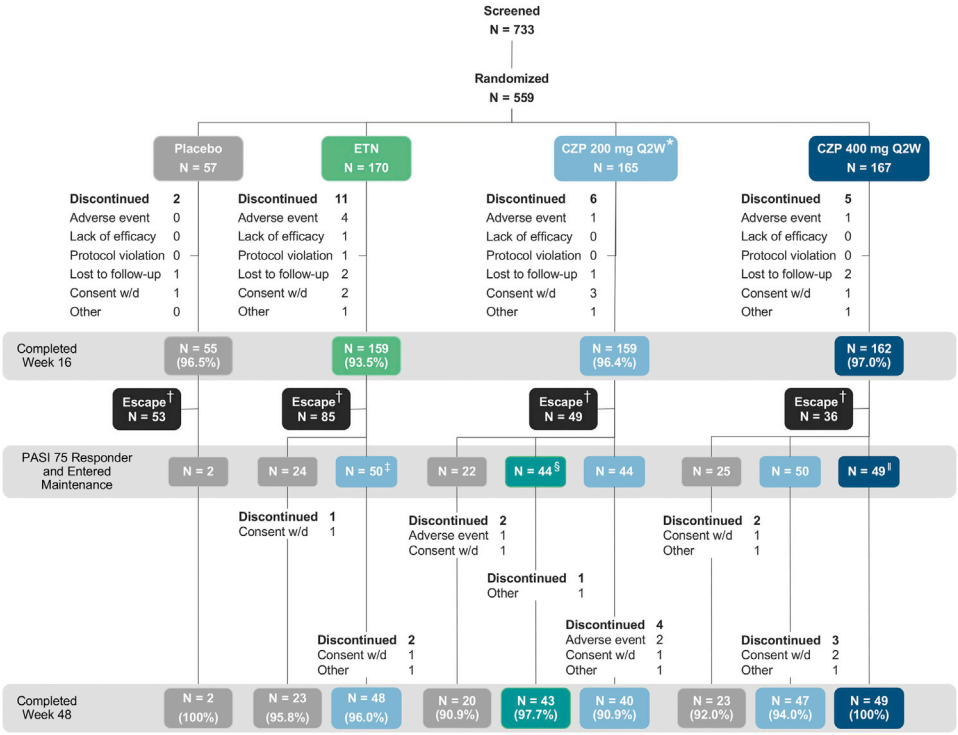

Fig 2. Patient disposition. *Patients received a loading dose of 400 mg at weeks 0, 2, and 4. †PASI 75 nonresponders at week 16 entered the escape arm for treatment with CZP 400 mg every 2 weeks. ‡ETN-treated PASI 75 responders rerandomized to CZP 200 mg every 2 weeks received an initial loading dose of 400 mg at weeks 16, 18, and 20. §Represents the CZP 400 mg every 4 weeks treatment group. ‖Two patients completed week 16 but did not enter the maintenance period (1 lost to follow-up; 1 consent withdrawn). *CZP*, Certolizumab pegol; *ETN*, etanercept; *PASI*, Psoriasis Area and Severity Index; *PASI 75*, ≥75% reduction in PASI from baseline PASI; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks, *w/d*, withdrawn.

week 16 (Fig 3). At week 12, CZP 400 mg was superior and CZP 200 mg was noninferior to etanercept for PASI 75 responder rate (Table II; Fig 3). Similar trends occurred for PGA 0/1 and PASI 90 responder rates for both doses of CZP versus placebo (Figs 4 and 5).

Efficacy from week 16 to week 48

Through week 48, PASI 75 responder rates were greater for patients rerandomized from CZP to either the same or a different dose of CZP than those rerandomized from CZP to placebo (Fig 6); greater responses were observed for patients continuing on CZP 400 mg every 2 weeks. In a post-hoc analysis, the week-48 PASI 75 responder rate was higher for patients rerandomized from CZP 400 mg every 2 weeks to CZP 400 mg every 2 weeks (98.0%) than for patients rerandomized from CZP 400 mg every 2 weeks to CZP 200 mg every 2 weeks (80.0%) ($P < .05$; Fisher's exact test); the response maintenance was similar for patients rerandomized from CZP 200 mg every 2 weeks to 400 mg every 4 weeks or to 200 mg every 2 weeks.

Similar trends occurred for week-48 PGA 0/1 and PASI 90 responder rates (Supplemental Figs 1 and 2; available at http://www.jaad.org); however, since participants were rerandomized on the basis of their PASI 75 response rather than their PGA 0/1 or PASI 90 response, the proportion of PGA 0/1 or PASI 90 responders varied at rerandomization across the groups.

For PASI 75 responders treated with etanercept in the initial period, week-48 PASI 75, PGA 0/1, and PASI 90 responder rates were 8.3%, 4.2%, and 4.2%, respectively, for patients who were rerandomized to placebo (N = 24); and 82.0%, 72.0%, and 78.0% for patients who were rerandomized to CZP 200 mg every 2 weeks (N = 50) in the maintenance period (data not graphed). Only 2 placebo-treated patients achieved PASI 75 at week 16 and continued to receive placebo during the maintenance period.

Safety assessments

By week 12, TEAEs were reported for similar proportions of patients across treatment groups, with the greatest proportion reported for patients

Table I. Demographics and baseline disease characteristics of randomized patients

Characteristic	Placebo, N = 57	Etanercept, N = 170	CZP 200 mg Q2W, N = 165	CZP 400 mg Q2W, N = 167
Demographics				
Age, y, mean ± SD	46.5 ± 12.5	44.6 ± 14.1	46.7 ± 13.5	45.4 ± 12.4
Male, n (%)	34 (59.6)	127 (74.7)	113 (68.5)	107 (64.1)
White, n (%)	57 (100)	163 (95.9)	158 (95.8)	162 (97.0)
Geographic region, n (%)				
North America	10 (17.5)	29 (17.1)	26 (15.8)	27 (16.2)
Central and Eastern Europe	36 (63.2)	111 (65.3)	107 (64.8)	109 (65.3)
Western Europe	11 (19.3)	30 (17.6)	32 (19.4)	31 (18.6)
Weight, kg, mean ± SD	93.7 ± 29.7	88.6 ± 20.7	89.7 ± 20.6	86.3 ± 20.0
BMI, kg/m^2, mean ± SD	31.2 ± 8.5	29.5 ± 6.3	29.8 ± 6.1	28.9 ± 5.9
Baseline disease characteristics				
Duration of psoriasis at screening, y, mean ± SD	18.9 ± 12.9	17.4 ± 12.0	19.5 ± 13.2	17.8 ± 11.5
Concurrent psoriatic arthritis, n (%)*	12 (21.1)	27 (15.9)	27 (16.4)	24 (14.4)
PASI, mean ± SD	19.1 ± 7.1	21.0 ± 8.2	21.4 ± 8.8	20.8 ± 7.7
DLQI, mean ± SD	13.2 ± 7.6	14.1 ± 7.4	12.8 ± 7.0	15.3 ± 7.3
BSA, %, mean ± SD	24.3 ± 13.8	27.5 ± 15.5	28.1 ± 16.7	27.6 ± 15.3
PGA score, n (%)				
3: moderate	40 (70.2)	115 (67.6)	114 (69.1)	113 (67.7)
4: severe	17 (29.8)	55 (32.4)	51 (30.9)	54 (32.3)
Prior biologic use, n (%)†	11 (19.3)	51 (30.0)	44 (26.7)	48 (28.7)
anti–TNF-α	5 (8.8)	8 (4.7)	4 (2.4)	4 (2.4)
anti–IL-17A	8 (14.0)	39 (22.9)	38 (23.0)	35 (21.0)
anti–IL-12/23	1 (1.8)	9 (5.3)	5 (3.0)	16 (9.6)

BMI, Body mass index; *BSA*, body surface area; *CZP*, certolizumab pegol; *DLQI*, Dermatology Life Quality Index; *IL*, interleukin; *PASI*, Psoriasis Area and Severity Index; *PGA*, Physician's Global Assessment; *Q2W*, every 2 weeks; *SD*, standard deviation; *TNF*, tumor necrosis factor.
*Presence of concurrent psoriatic arthritis was self-reported with medical history.
†Patients may have had exposure to >1 prior biologic therapy but ≤2 per exclusion criteria.

receiving placebo (Table III). The most frequently reported TEAEs (occurring in ≥5% of any CZP group) were nasopharyngitis and upper respiratory tract infection. Similar trends were observed for the overall summary of TEAEs to week 16 (not shown).

From baseline to week 48, the TEAE incidence rates per 100 patient-years were 201.3 for those treated with CZP 400 mg every 2 weeks and 214.0 for those treated with 200 mg every 2 weeks or 400 mg every 4 weeks (Supplemental Table I; available at http://www.jaad.org). One patient in the escape arm, after 22 weeks of CZP 400 mg every 2 weeks (combined initial and maintenance periods), had an incidental diagnosis of primary progressive multiple sclerosis. The patient reported a 2-year history of gait disturbances and recurrent falls predating entry into the clinical study (but none occurred during the study period) and was referred to a neurologist due to lower back pain. The neurologist diagnosed primary progressive multiple sclerosis after magnetic resonance imaging revealed lesions consistent with multiple sclerosis, and the event was considered by the investigator to be unrelated to the study treatment. A list of serious TEAEs reported through week 48 can be found in Supplemental Table II (available at http://www.jaad.org).

DISCUSSION

The efficacy and safety of CZP, an Fc-free, PEGylated anti-TNF biologic, in adult patients with moderate-to-severe chronic plaque psoriasis have been previously studied in phase 2 trials.[10] In this phase 3 trial of adult patients with moderate-to-severe chronic plaque psoriasis, treatment with CZP 400 mg or 200 mg resulted in statistically significant and clinically meaningful improvements in signs and symptoms of psoriasis at weeks 12 and 16 in comparison with treatment with placebo, with clinically meaningful differences in PASI 75 responses observed as early as week 4. At week 12, CZP 400 mg was superior and CZP 200 mg was noninferior to etanercept for PASI 75 responder rate.

During the maintenance period, efficacy and safety data were collected to assess the durability of treatment effects beyond the initial period; rerandomization also allowed for assessment of alternative dosing regimens. Considering the high

Table II. Primary and secondary efficacy endpoints to weeks 12 and 16*

Comparison	Placebo, N = 57	CZP 200 mg Q2W, N = 165	CZP 400 mg Q2W, N = 167
Primary endpoint vs placebo			
Week 12			
PASI 75 responder rate, %	5.0	61.3	66.7
OR vs placebo (95% CI)		30.0 (9.0 to 100.5)	38.0 (11.3 to 127.6)
P value		<.0001	<.0001
Secondary endpoints vs placebo			
Week 12			
PGA 0/1 responder rate, %	1.9	39.8	50.3
OR (95% CI)		36.6 (5.1 to 264.2)	56.1 (7.8 to 404.6)
P value		.0004	<.0001
PASI 90 responder rate, %	0.2	31.2	34.0
OR (95% CI)		35.1 (7.4 to 167.2)	39.9 (8.4 to 189.8)
P value		<.0001	<.0001
Week 16			
PASI 75 responder rate, %	3.8	68.2	74.7
OR (95% CI)		55.4 (13.1 to 233.8)	76.3 (18.0 to 324.1)
P value		<.0001	<.0001
PGA 0/1 responder rate, %	3.4	48.3	58.4
OR (95% CI)		27.2 (6.5 to 113.5)	40.7 (9.7 to 170.2)
P value		<.0001	<.0001
PASI 90 responder rate, %	0.3	39.8	49.1
OR (95% CI)		49.5 (10.0 to 245.3)	72.3 (14.7 to 356.6)
P value		<.0001	<.0001
Secondary endpoint vs etanercept	**Etanercept, N = 170**	**CZP 200 mg Q2W, N = 165**	**CZP 400 mg Q2W, N = 167**
Week 12			
PASI 75 responder rate, %	53.3	61.3	66.7
Difference in responder rate, estimate (95% CI)		8.0 (−2.9 to 18.9)	13.4 (2.7 to 24.1)
OR (95% CI)		1.4 (0.9 to 2.2)	1.8 (1.1 to 2.8)
P value		.1523	.0152

CI, Confidence interval; *CZP*, certolizumab pegol; *OR*, odds ratio; *PASI*, Psoriasis Area and Severity Index; *PASI 75*, ≥75% reduction in PASI from baseline PASI; *PASI 90*, ≥90% reduction in PASI from baseline PASI; *PGA 0/1*, Physician's Global Assessment clear/almost clear, with ≥2-category improvement from baseline PGA score; *Q2W*, every 2 weeks.
*Responder rate analysis was based on logistic regression model.

number of patients unsatisfied with their current psoriasis treatment,[13] the favorable every 2 week dosing frequency offers advantages over etanercept, which requires twice weekly dosing.[14,15] Notably, responder rates among patients receiving CZP 400 mg every 4 weeks were similar to those of patients receiving CZP 200 mg every 2 weeks (ie, same cumulative monthly dose). While both dosing regimens were efficacious, higher response rates occurred with CZP 400-mg every 2 weeks dosing. However, the CZP 200-mg every 2 weeks regimen could offer prescribing flexibility for physicians, depending on individual patient considerations.

An important secondary study objective included assessing the optimal maintenance dose of CZP. CZP-treated patients who were PASI 75 responders at week 16 continued to respond through week 48, with the greatest response achieved in patients receiving CZP 400 mg every 2 weeks in both the initial and maintenance periods. PGA 0/1 and PASI 90 responder rates continued to increase for patients randomized to CZP 400 mg every 2 weeks in both study periods. The maintenance of the CZP response, particularly for CZP 400 mg every 2 weeks at 48 weeks, appears to be greater than that reported in other short- and long-term clinical trials of biologic agents in psoriasis.[16,17] In addition, some PASI 75 responders rerandomized from CZP to placebo demonstrated a sustained response to treatment, suggesting the duration of CZP effect might extend well beyond withdrawal of treatment for some patients.

Adverse events reported in this study were consistent with the safety profile of the anti-TNF class of drugs in patients with moderate-to-severe chronic plaque psoriasis and with the profile previously reported for CZP treatment in other indications.[10,16,18] In addition, CZP-treated and

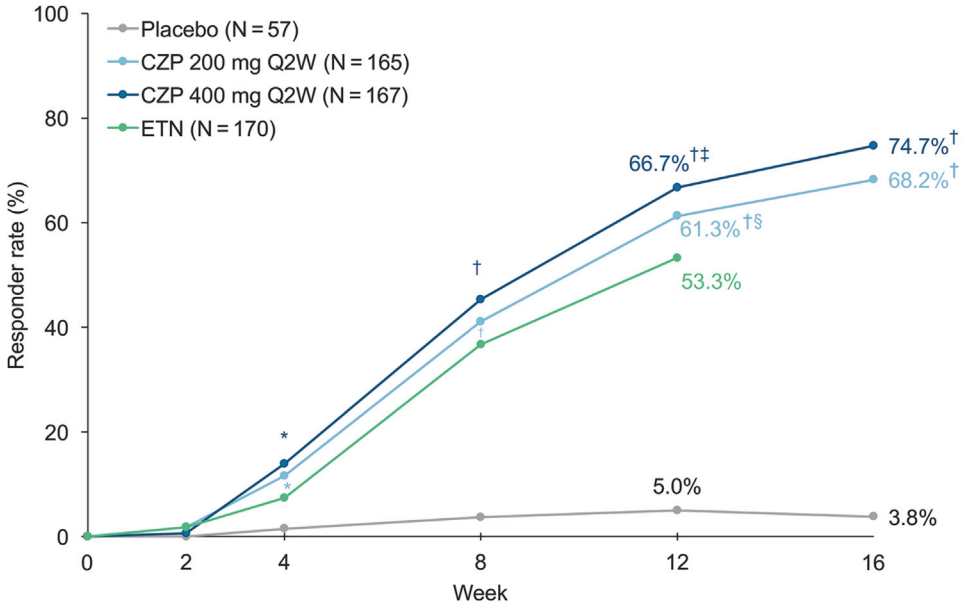

Fig 3. PASI 75 responder rate of randomized patients through week 12 (primary endpoint) and week 16, by visit. Analysis of the responder rate was based on the logistic regression model. Patients receiving CZP 200 mg every 2 weeks also received loading doses of CZP 400 mg at weeks 0, 2, and 4. *$P < .05$ versus placebo (controlled for multiplicity at weeks 12 and 16). †$P < .0001$ versus placebo (controlled for multiplicity at weeks 12 and 16). ‡Superior to ETN ($P = .0152$). §Noninferior to ETN (95% confidence interval −2.9 to 18.9). *CZP*, Certolizumab pegol; *ETN*, etanercept; *PASI*, Psoriasis Area and Severity Index; *PASI 75*, ≥75% reduction in PASI from baseline PASI; *Q2W*, every 2 weeks.

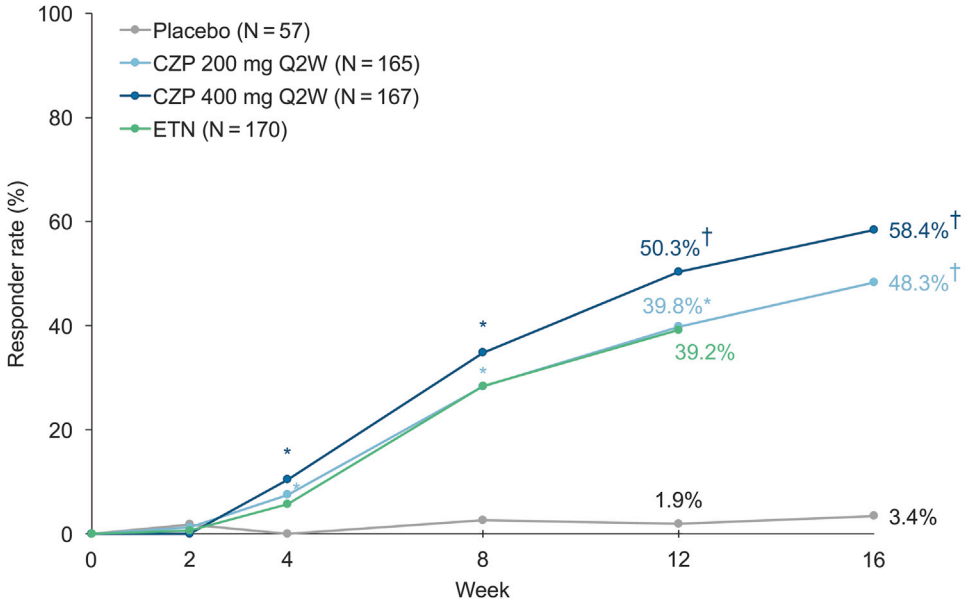

Fig 4. PGA 0/1 responder rate of randomized patients through week 12 and week 16, by visit. Analysis of the responder rate was based on the logistic regression model. Inferential statistical comparisons of CZP and ETN were not performed. Patients who received CZP 200 mg every 2 weeks also received loading doses of CZP 400 mg at weeks 0, 2, and 4. *$P < .05$ versus placebo (controlled for multiplicity at weeks 12 and 16). †$P < .0001$ versus placebo (controlled for multiplicity at weeks 12 and 16). *CZP*, Certolizumab pegol; *ETN*, etanercept; *PGA 0/1*, Physician's Global Assessment clear/almost clear, with ≥2-category improvement from baseline Physician's Global Assessment; *Q2W*, every 2 weeks.

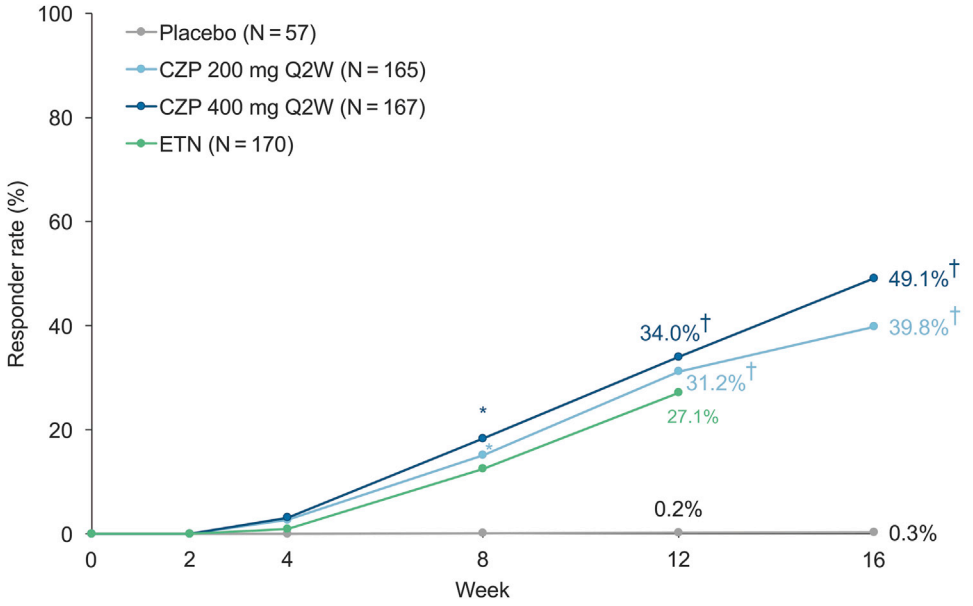

Fig 5. PASI 90 responder rate of randomized patients through week 12 and week 16, by visit. Analysis of the responder rate was based on the logistic regression model. Inferential statistical comparisons of CZP and ETN were not performed. Patients who received CZP 200 mg every 2 weeks also received loading doses of CZP 400 mg at weeks 0, 2, and 4. *$P < .05$ versus placebo (controlled for multiplicity at weeks 12 and 16). †$P < .0001$ versus placebo (controlled for multiplicity at weeks 12 and 16). *CZP*, Certolizumab pegol; *ETN*, etanercept; *PASI*, Psoriasis Area and Severity Index; *PASI 90*, ≥90% reduction in PASI from baseline PASI; *Q2W*, every 2 weeks.

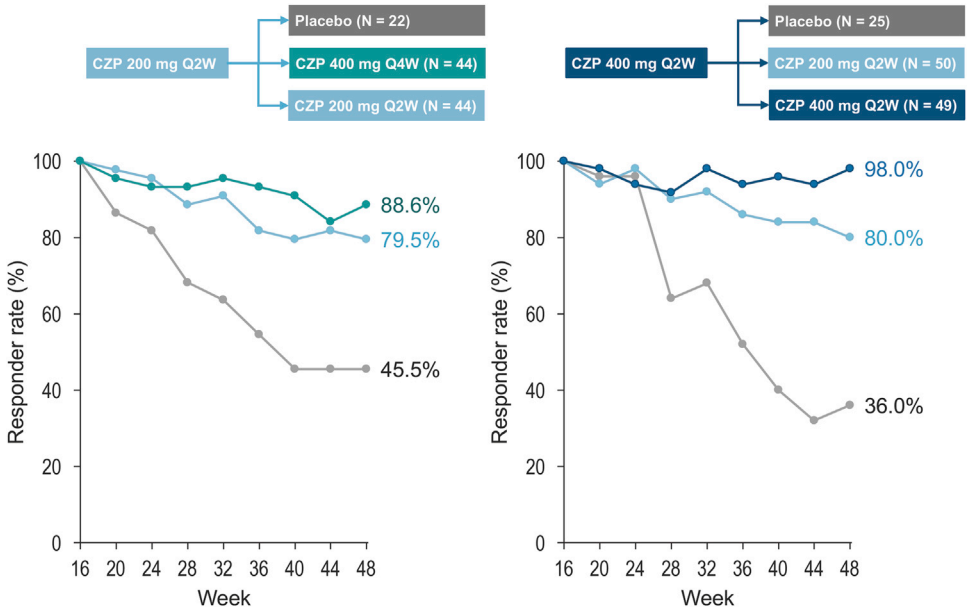

Fig 6. PASI 75 responder rate of maintenance set from week 16 through week 48, by visit. Analysis involved the imputation of data from nonresponders. *CZP*, Certolizumab pegol; *PASI*, Psoriasis Area and Severity Index; *PASI 75*, ≥75% reduction in PASI from baseline PASI; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks.

etanercept-treated groups had comparable safety profiles through week 12, and fewer CZP-treated patients than etanercept-treated patients discontinued due to adverse events. No new safety signals were observed with either CZP dose over 48 weeks of treatment, and incidence rates of TEAEs

Table III. Summary of TEAEs from baseline to week 12 (safety set)

Category	Placebo, N = 57	Etanercept, N = 168	CZP 200 mg Q2W, N = 165	CZP 400 mg Q2W, N = 167
TEAEs, n (%) [incidence rate, new cases/100 patient-years]				
Any	32 (56.1) [393.3]	78 (46.4) [295.6]	78 (47.3) [299.5]	82 (49.1) [309.2]
Drug-related*	7 (12.3)	20 (11.9)	16 (9.7)	22 (13.2)
Serious	5 (8.8) [41.0]	1 (0.6) [2.7]	1 (0.6) [2.7]	4 (2.4) [10.6]
Discontinuations due to TEAE, n (%)	0	4 (2.4)	1 (0.6)	1 (0.6)
Deaths, n (%)	0	0	0	0
Most frequently reported TEAEs,† n (%) [incidence rate, new cases/100 patient-years]				
Nasopharyngitis	5 (8.8) [40.8]	11 (6.5) [31.0]	14 (8.5) [38.8]	12 (7.2) [32.9]
Upper respiratory tract infection	6 (10.5) [47.7]	11 (6.5) [30.2]	6 (3.6) [16.2]	8 (4.8) [21.5]
Other TEAEs of interest, n (%) [incidence rate, new cases/100 patient-years]				
Infections and infestations	16 (28.1) [140.7]	39 (23.2) [120.0]	44 (26.7) [134.9]	38 (22.8) [113.1]
Latent tuberculosis	0	1 (0.6) [2.7]	0	0
Candida infections	0	1 (0.6) [2.7]‡	0	0
Oral fungal infection	0	0	0	0
Fungal skin infection	0	0	0	1 (0.6) [2.6]§
Herpes zoster	1 (1.8) [7.8]	0	0	0
Serious infections and infestations	0	0	0	1 (0.6) [2.6]‖
Malignancy	0	0	0	0
Depression	0	0	1 (0.6) [2.7]	0

Total exposure for all CZP patients from baseline to week 12 was 75.72 patient-years.
CZP, Certolizumab pegol; *Q2W*, every 2 weeks; *TEAE*, treatment-emergent adverse event.
*Incidence rate not calculated.
†Totaling ≥5% in any CZP group.
‡Skin *Candida*.
§Reported as fungal infection, preferred term in the database.
‖Pneumonia.

did not increase with longer-term CZP therapy. Adding to the total phase 3 exposure through week 48 of 727 patient-years, 2 additional phase 3 trials (CIMPASI-1 and CIMPASI-2) also evaluated CZP 200 mg every 2 weeks and 400 mg every 2 weeks treatment, in adult patients with moderate-to-severe chronic plaque psoriasis. In those trials, the rates of TEAEs through week 48 were comparable between both CZP doses and were in-line with other anti-TNF agents.[19-21]

As with any clinical study, patients in good general health were selected, perhaps leading to better efficacy outcomes and improved safety than what might be expected in clinical practice.[22] Etanercept treatment was limited to the initial 12-week period and single-blinded (versus double-blinded with CZP and placebo), but this difference was not expected to affect treatment comparisons; in addition, considerable efforts were taken to minimize risk for bias (ie, designated blinded efficacy assessors). Because CZP is approved for several indications and has clinical and post-marketing data, the total number of patients treated with CZP in this study was lower than other phase 3 psoriasis trials, especially for rerandomized patients within the maintenance set. Despite these limitations, the data are applicable to the general psoriasis population given that the demographics of the study participants were similar to that of other phase 3 psoriasis programs, efficacy was similar to that reported in previous phase 2 studies of CZP in psoriasis, and safety data were consistent with real-world experience in patients receiving CZP for other conditions.

Overall, treatment with either dose of CZP was associated with significant, clinically meaningful and sustained improvements in signs and symptoms of moderate-to-severe chronic plaque psoriasis. Generally, greater improvements in efficacy outcome measures were recorded with the higher dose. No new safety signals occurred at either dose over 48 weeks of treatment. These results support

that CZP, a unique anti-TNF biologic, affords a novel treatment option for psoriasis patients.

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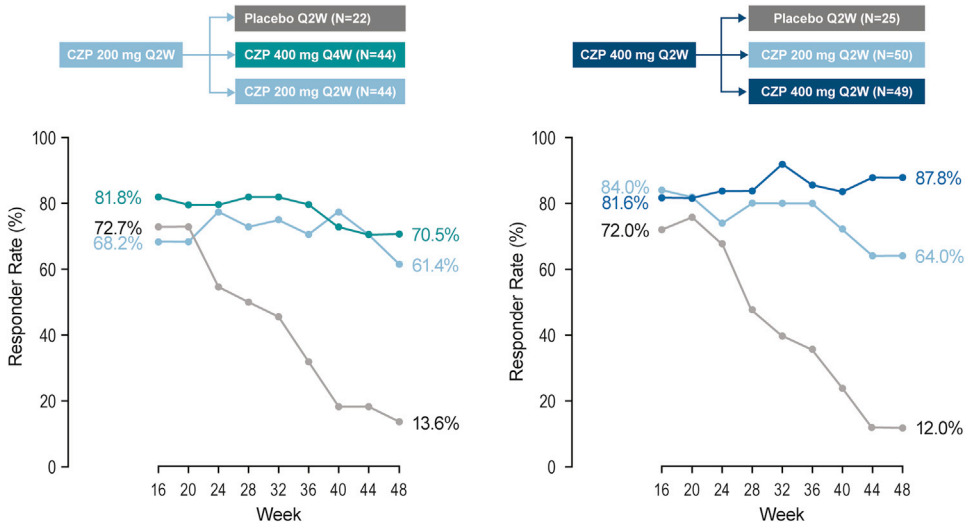
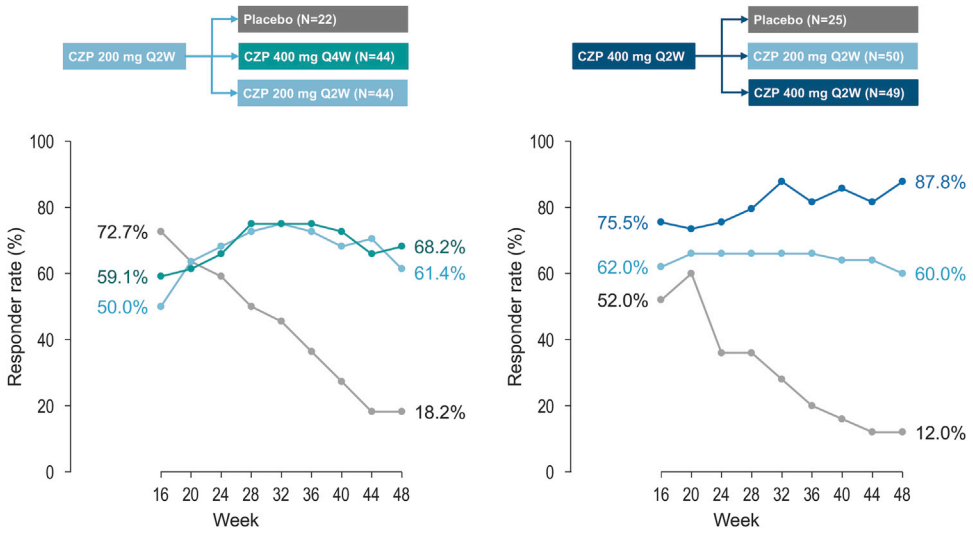
SUPPLEMENTARY METHODS.

To account for multiplicity, a fixed-sequence testing procedure was used: superiority to placebo for PASI 75 (≥75% reduction in Psoriasis Area and Severity Index [PASI] from baseline PASI), PGA 0/1 (Physician's Global Assessment [PGA] clear/almost clear, with ≥2-category improvement from baseline PGA), and then PASI 90 (≥90% reduction in PASI from baseline PASI) was evaluated by using a 2-sided alpha level of 0.05 at week 12 and then week 16. At each step, certolizumab pegol (CZP) 400 mg every 2 weeks was assessed first, followed by CZP 200 mg every 2 weeks. After comparisons with placebo, CZP 400 mg every 2 weeks was assessed for noninferiority to etanercept at week 12 based on a prespecified 10% noninferiority margin. Subsequently, CZP 400 mg every 2 weeks was assessed for superiority to etanercept at week 12, and CZP 200 mg every 2 weeks was assessed for noninferiority to etanercept at week 12 using the prespecified 10% noninferiority margin. These 2 assessments were performed simultaneously, and multiplicity was controlled for on the basis of the Hochberg method. Finally, CZP 200 mg every 2 weeks was assessed for superiority to etanercept at week 12. This procedure controlled the overall type 1 error rate at 5%.



Supplemental Fig 1. PGA 0/1 responder rate of maintenance set from week 16 through week 48, by visit. Analysis involved the imputation of data from nonresponders. *CZP*, Certolizumab pegol; *PGA 0/1*, Physician's Global Assessment of clear or almost clear with ≥2-category improvement from PGA baseline; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks.



Supplemental Fig 2. PASI 90 responder rate of maintenance set from week 16 through week 48, by visit. Analysis involved the imputation of data from nonresponders. *CZP*, Certolizumab pegol; *PASI*, Psoriasis Area and Severity Index; *PASI 90*, ≥90% reduction in PASI from baseline PASI; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks.

Supplemental Table I. Summary of TEAEs from baseline to week 48 (safety set)

Category	CZP 200 mg Q2W, N = 265	CZP 400 mg Q2W, N = 354
TEAEs, n (%) [incidence rate, new cases/100 patient-years]		
Any	175 (66.0) [214.0]	230 (65.0) [201.3]
Drug-related*	40 (15.1)	58 (16.4)
Serious	12 (4.5) [7.7]	23 (6.5) [11.3]
Discontinuations due to TEAE, n (%)	4 (1.5)	11 (3.1)
Deaths, n (%)	0	0
Most frequently reported TEAEs, † n (%) [incidence rate, new cases/100 patient-years]		
Nasopharyngitis	35 (13.2) [23.6]	44 (12.4) [22.6]
Upper respiratory tract infection	16 (6.0) [10.5]	29 (8.2) [14.4]
Hypertension	10 (3.8) [6.5]	17 (4.8) [8.3]
Viral upper respiratory tract infection	14 (5.3) [9.1]	8 (2.3) [3.8]
Other TEAEs of interest, n (%) [incidence rate, new cases/100 patient-years]		
Infections and infestations	108 (40.8) [93.8]	132 (37.3) [79.7]
Tuberculosis	0	1 (0.3) [0.5]
Candida infections	0	2 (0.6) [1.0]‡
Oral fungal infection	0	0
Fungal skin infection	0	1 (0.3) [0.5]§
Herpes zoster	3 (1.1) [1.9]	2 (0.6) [1.0]
Serious infections and infestations	3 (1.1) [1.9]‖	6 (1.7) [2.9]¶
Malignancy	0	2 (0.6) [1.0]
Multiple sclerosis	0	1 (0.3) [0.5]#
Microscopic colitis	0	1 (0.3) [0.5]
Depression	4 (1.5) [2.5]	1 (0.3) [0.5]

Patients who switched doses could have been counted in both CZP doses. Patients receiving CZP 400 mg Q4W were included in the CZP 200 mg Q2W group (same cumulative monthly dose). Total exposure for all CZP patients from baseline to week 48 was 370.81 patient-years. *CZP*, Certolizumab pegol; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *TEAE*, treatment-emergent adverse event.

*Incidence rate not calculated.

†Most frequent TEAEs occurred in ≥5% of the population of any group.

‡*Candida* infection, oral candidiasis, skin *Candida*, and vulvovaginal candidiasis in the same patient; genital candidiasis in a different patient.

§Reported as fungal infection, preferred term in the database.

‖Gastroenteritis, pancreas infection, and pneumonia.

¶*Escherichia coli* sepsis and pyelonephritis in the same patient; endophthalmitis, pneumonia, sepsis, erysipelas, and tuberculosis each in 1 patient.

#Primary progressive multiple sclerosis; incidental finding during evaluation for lower back pain (no TEAEs during study) and considered unrelated to treatment by the investigator.

Supplemental Table II. Summary of Serious TEAEs to week 48

Category	Placebo, N = 57	Etanercept,* N = 168	CZP 200 mg Q2W, N = 165	CZP 400 mg Q2W, N = 167
Any serious TEAE, n (%) [incidence, new cases/100 patient-years]	6 (10.5) [37.5]	1 (0.6) [2.7]	1 (0.6) [2.0]	7 (4.2) [14.0]
Baseline to week 16	Inguinal hernia; hepatic enzyme increase; back pain; metrorrhagia; rectocele; ulna fracture	Hepatic enzyme increased	Polymyalgia rheumatica	Pneumonia; lower limb fracture; migraine; bipolar I disorder; osteoarthritis; abdominal pain; acute coronary syndrome

	CZP 200 mg Q2W, N = 144	CZP 400 mg Q4W, N = 44	CZP 400 mg Q2W,† N = 273
Any serious TEAE, n (%) [incidence, new cases/100 patient-years]	7 (4.9) [8.6]	4 (9.1) [16.0]	16 (5.9) [10.3]
Week 16-48	Peptic ulcer; hepatitis; gastroenteritis; foot fracture, facial bones fracture, rib fracture‡; osteoarthritis; pregnancy with contraceptive device; uterine cyst	Pancreas infection; pneumonia; forearm fracture; psoriatic arthropathy	Cardiac failure; cataract, hemorrhoids, cholecystitis; *Escherichia coli* sepsis and pyelonephritis‡; endophthalmitis; sepsis; erysipelas; tuberculosis; ulna fracture; wrist fracture, rib fracture, laceration, and compartment syndrome‡; anaplastic oligodendroglioma and concussion‡; migraine; primary progressive multiple sclerosis;§ nephrolithiasis; guttate psoriasis

CZP, Certolizumab pegol; *MS*, multiple sclerosis; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *TEAE*, treatment-emergent adverse event.
*Data to week 12 are presented for etanercept.
†Includes patients who entered the escape arm for treatment with CZP 400 mg Q2W.
‡Group of TEAEs within semicolon occurred in same patient.
§Primary progressive multiple sclerosis; incidental finding during evaluation for lower back pain (no TEAEs during study) and considered unrelated to treatment by the investigator.