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Long-term efficacy of certolizumab pegol for the treatment of plaque psoriasis: 3-year results from two randomized phase III trials (CIMPASI-1 and CIMPASI-2)

K.B. Gordon[1] R.B. Warren,[2] A.B. Gottlieb,[3] A. Blauvelt,[4] D. Thaçi,[5] C. Leonardi,[6] Y. Poulin,[7] M. Boehnlein,[8] F. Brock,[9] C. Ecoffet[10] and K. Reich[11]

[1]Department of Dermatology, Medical College of Wisconsin, Milwaukee, WI, USA
[2]Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester NIHR Biomedical Research Centre, The University of Manchester, Manchester, UK
[3]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[4]Oregon Medical Research Center, Portland, OR, USA
[5]Institute and Comprehensive Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany
[6]Central Dermatology and Saint Louis University School of Medicine, St Louis, MO, USA
[7]Centre de Recherche Dermatologique du Québec Métropolitain, Québec, QC, Canada
[8]UCB Pharma, Monheim, Germany
[9]UCB Pharma, Slough, UK
[10]UCB Pharma, Brussels, Belgium
[11]Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf and Skinflammation® Center, Hamburg, Germany

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Summary

Background Certolizumab pegol (CZP) is an Fc-free, PEGylated anti-tumour necrosis factor biologic.
Objectives To report the 3-year efficacy of CZP in plaque psoriasis, pooled from the CIMPASI-1 (NCT02326298) and CIMPASI-2 (NCT02326272) phase III trials.
Methods Adults with moderate-to-severe psoriasis for ≥ 6 months were randomized 2 : 2 : 1 to CZP 200 mg, CZP 400 mg or placebo, every 2 weeks (Q2W) for up to 48 weeks. Patients entering the open-label period (weeks 48–144) from double-blinded CZP initially received CZP 200 mg Q2W. Patients not achieving ≥ 50% improvement in Psoriasis Area and Severity Index (PASI 50) at week 16 entered an open-label CZP 400 mg Q2W escape arm (weeks 16–144). Dose adjustments based on PASI response were permitted during open-label treatment. Outcomes included PASI 75, PASI 90 and Physician's Global Assessment (PGA) 0/1 responder rates, based on a logistic regression model (missing data imputed using Markov Chain Monte Carlo methodology).
Results In total, 186 patients were randomized to CZP 200 mg Q2W and 175 to CZP 400 mg Q2W. At week 48, PASI 75/90 was achieved by 72·7%/51·3% of patients randomized to CZP 200 mg and 84·4%/62·7% randomized to CZP 400 mg. Patients entering the open-label period at week 48, from blinded treatment, received CZP 200 mg Q2W. At week 144, PASI 75/90 was achieved by 70·6%/48·7% patients randomized to CZP 200 mg and 72·9%/42·7% randomized to CZP 400 mg. At week 16, 72 placebo-randomized patients entered the CZP 400 mg Q2W escape arm; 75.7%/58.5% achieved PASI 75/90 at week 144.
Conclusions Both CZP 200 mg and 400 mg Q2W demonstrated sustained, durable efficacy, with numerically higher responses for some outcomes with 400 mg Q2W.

What is already known about this topic?

- Certolizumab pegol is an Fc-free, PEGylated, anti-tumour necrosis factor biologic approved for adults with moderate-to-severe plaque psoriasis.

Correspondence
Kenneth Gordon.
Email: Gordon.Kenneth@att.net

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Conflicts of interest statements can be found in Appendix 1.

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- Efficacy data from the first 48 weeks of phase III trials have shown significant improvements in the signs and symptoms of psoriasis with certolizumab pegol dosed at either 400 mg or 200 mg every 2 weeks.
- Numerically greater improvements were observed for patients treated with the higher dose.

What does this study add?

- Plaque psoriasis is a chronic, systemic disease that requires long-term management and sustained efficacy of therapies.
- Three-year efficacy data pooled from the CIMPASI-1 and CIMPASI-2 phase III trials demonstrate a sustained and durable response to certolizumab pegol dosed at either 400 mg or 200 mg every 2 weeks.
- Additional long-term clinical benefits may be obtained from the higher dose.

Biologic therapies, including agents that block tumour necrosis factor (TNF)-α, interleukin (IL)-12, IL-23 and IL-17,[1] have become central to the treatment of moderate-to-severe plaque psoriasis.[1,2] While alternative treatment options for plaque psoriasis are available, including phototherapy, topical therapies and traditional systemic agents,[3–5] a survey conducted in Canada in 2016 reported greater treatment satisfaction among patients treated with biologics compared with nonbiologic therapies.[6] However, despite the fact that psoriasis is a chronic disease that may affect patients over much of their lifetime,[7] loss of response over time has been observed with some biologics in this indication.[8] It is therefore important to understand whether the efficacy of new therapies is sustained over multiple years of treatment.[9]

Of the biologic agents currently available for the treatment of plaque psoriasis, anti-TNF agents have had the longest period of time to allow clinical experience to accumulate.[1] Certolizumab pegol (CZP) is an Fc-free, PEGylated, anti-TNF biologic that is currently approved for the treatment of adults with moderate-to-severe plaque psoriasis, alongside axial spondyloarthritis, Crohn's disease, psoriatic arthritis and rheumatoid arthritis.[10,11] Unlike other anti-TNF agents, CZP lacks the IgG Fc region that binds to the neonatal Fc receptor for IgG (FcRn),[12,13] and a prospective study has demonstrated no to minimal placental transfer of CZP from mothers to infants.[12] In addition, the incorporation of PEGylation into CZP increases the half-life to 14 days.[14]

Outcomes for CZP in moderate-to-severe plaque psoriasis over 48 weeks have previously been reported from three large, phase III trials conducted in North America and Europe: CIMPASI-1 (NCT02326298), CIMPASI-2 (NCT02326272) and CIMPACT (NCT02346240).[15–17] After 16 weeks of CZP treatment in these trials, significant improvements compared with placebo in the signs and symptoms of psoriasis were observed,[15] and these improvements were sustained to week 48.[16,17] In a pooled analysis of the safety data from all three trials over 3 years of treatment, no new safety signals were identified compared to previous studies of CZP.[16–18] There was no increased risk with longer exposure, and the safety profiles of the CZP 400 mg every 2 weeks (Q2W) and CZP 200 mg Q2W dose groups were similar.[18] Here we present the long-term efficacy outcomes of CZP in patients with moderate-to-severe plaque psoriasis over 3 years, pooled from the CIMPASI-1 and CIMPASI-2 trials.

The data from these studies are available for qualified researchers. Details of data sharing are provided in Appendix 2.

Patients and methods

Study designs

CIMPASI-1 (NCT02326298) and CIMPASI-2 (NCT02326272) were 3-year (144-week) phase III, randomized, multicentre trials with identical study designs conducted in North America and Europe, which were completed on 24 October 2018 and 12 September 2018, respectively. The trials were double-blinded and placebo-controlled to week 16, double-blinded to week 48, and open-label to week 144 (Figure 1).

Patients were randomized 2 : 2 : 1 to CZP 200 mg Q2W (loading dose of CZP 400 mg at weeks 0, 2 and 4), CZP 400 mg Q2W or placebo Q2W (allocation ratio selected to minimize patient exposure to placebo). Patients who did not achieve ≥ 50% reduction from baseline in Psoriasis Area and Severity Index (PASI 50) at week 16 entered the open-label CZP 400 mg Q2W escape arm. The full study designs and methods up to week 48 have been reported previously.[16]

Patients who achieved PASI 50 at week 48 entered the open-label period. It was mandatory for all patients entering the open-label period from blinded treatment to initially receive CZP 200 mg Q2W, in order to maintain the blinding of the initial and maintenance periods. Patients who completed treatment to week 48 in the open-label CZP 400

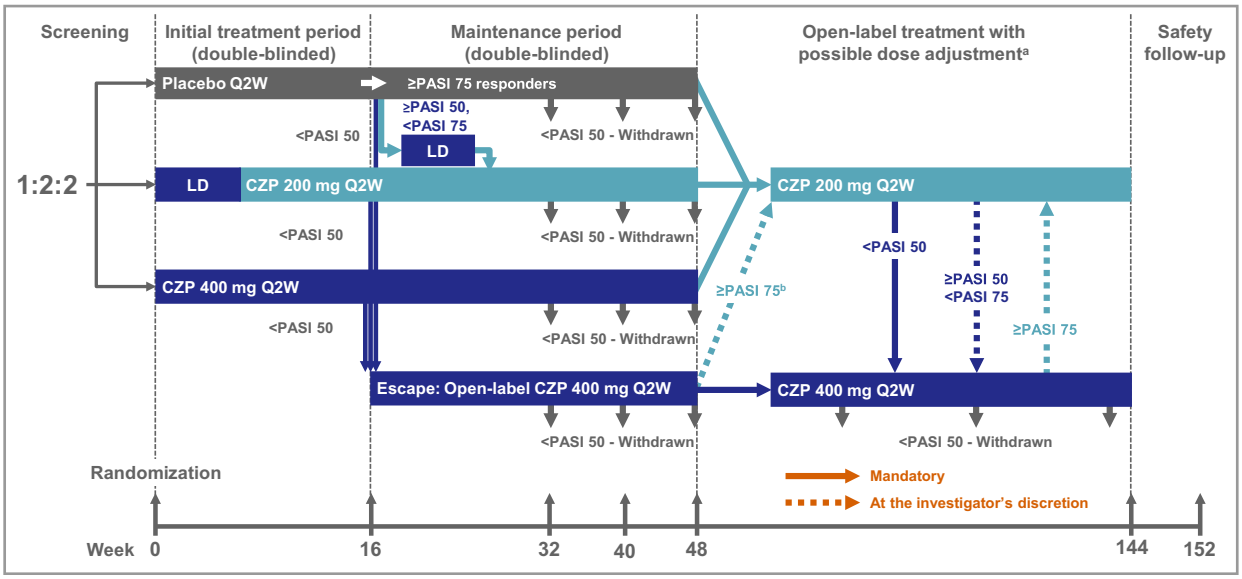

Figure 1 The initial, maintenance and open-label periods of the CIMPASI-1 and CIMPASI-2 phase III trials. CZP, certolizumab pegol; LD, loading dose [CZP 400 mg every 2 weeks (Q2W) at weeks 0, 2 and 4, or weeks 16, 18 and 20]; PASI, Psoriasis Area and Severity Index. [a]Dose adjustments were permitted through weeks 60–132; dose escalation was mandatory in patients not achieving ≥ 50% reduction from baseline in PASI (PASI 50), and at the investigator's discretion in patients achieving PASI 50 but not PASI 75; patients who had received CZP 400 mg Q2W for at least 12 weeks could have had their dose reduced, at the investigator's discretion, if they achieved PASI 75, and were withdrawn if they did not achieve PASI 50. [b]Patients entering the open-label period from the CZP 400 mg Q2W escape arm continued to receive CZP 400 mg Q2W but may have had their dose reduced to CZP 200 mg Q2W at week 48, at the discretion of the investigator, if they achieved PASI 75.

mg Q2W escape arm and entered the open-label period continued to receive CZP 400 mg Q2W unless they achieved PASI 75 at week 48, in which case they could have their dose reduced to CZP 200 mg Q2W, at the investigator's discretion.

For all patients enrolled in the open-label period, adjustments between the two doses of CZP were permitted at study visits (every 12 weeks) through weeks 60–132 of the study. Dose increase to CZP 400 mg Q2W was mandatory in patients not achieving PASI 50, and at the investigator's discretion in patients achieving PASI 50 but not PASI 75. Patients who had received CZP 400 mg Q2W for at least 12 weeks were withdrawn if they did not achieve PASI 50, or could have had their dose reduced to CZP 200 mg Q2W, at the investigator's discretion, if they achieved PASI 75.

During the initial and maintenance periods, study treatment was administered subcutaneously by dedicated, unblinded, trained site staff in the clinic. During the open-label period, CZP injections were self-administered by the patients, following training by study staff.

Study participants

The inclusion and exclusion criteria were identical for CIMPASI-1 and CIMPASI-2. Each trial enrolled adults (≥ 18 years of age) with moderate-to-severe plaque psoriasis of disease duration ≥ 6 months, with PASI ≥ 12, ≥ 10% body surface area (BSA) affected and Physician's Global Assessment (PGA) ≥ 3 on a 5-point scale. All participants were candidates for systemic psoriasis therapy, phototherapy and/or photochemotherapy.

Patients were excluded if they had previously been treated with CZP and/or more than two biologics; had a history of primary failure to any biologic (no response within the first 12 weeks of treatment) or secondary failure to more than one biologic (initial response then treatment stopped due to loss of response after week 12); had erythrodermic, guttate or generalized pustular psoriasis; or had current, or a history of, chronic or recurrent viral, bacterial or fungal infection. The full exclusion criteria have been published previously.[16]

Outcomes

We report outcomes through weeks 0–144 for patients initially randomized to CZP 200 mg Q2W or CZP 400 mg Q2W, with data presented according to randomization group. We also report outcomes for patients initially randomized to placebo who did not achieve PASI 50 at week 16, who then entered the open-label CZP 400 mg Q2W escape arm. In addition, for each patient population we report outcomes for the subset of patients who achieved PASI 75 or PASI 90 after 16 weeks of CZP treatment.

Clinical efficacy was assessed using the proportions of patients achieving PASI 75, PASI 90 and PGA 0/1 [PGA score of 0 or 1 ('clear' or 'almost clear') with ≥ 2-point improvement from baseline]. The proportions of patients achieving absolute PASI < 5, < 3 or < 2 are also reported. Patient-reported health-related quality of life was assessed as the

proportions achieving DLQI 0/1 (Dermatology Life Quality Index of 0 or 1; no effect of disease on quality of life).

Statistical analyses

Patients who met the criteria for mandatory withdrawal at week 32 or later were treated as nonresponders at subsequent timepoints, as were patients randomized to CZP if they did not achieve PASI 50 at week 16. All other missing data were imputed using Markov Chain Monte Carlo multiple imputation methodology, with 100 imputations.

Estimates of PASI 75, PASI 90, PGA 0/1, DLQI 0/1 and absolute PASI threshold responder rates were the adjusted predicted probabilities from a logistic regression model, using a logit link, with factors for treatment, region, study and prior biologic exposure, and interaction terms for study by prior biologic exposure and study by region. Model factors were weighted based on frequencies in the analysis population using the OBSMARGIN option within SAS. Supporting observed-case analyses are also provided in Tables S1, 2 and 3 (see Supporting Information), alongside data imputed with Markov Chain Monte Carlo methodology at weeks 16, 32, 48, 96 and 144, with associated 95% confidence intervals. Statistical analyses were specified within an integrated statistical analysis plan and were performed in SAS version 9·4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient disposition and baseline characteristics

At week 0, 186 patients were randomized to CZP 200 mg Q2W, 175 to CZP 400 mg Q2W and 100 to placebo (Figure 2). Of those randomized to placebo, 72 (72%) failed to achieve PASI 50 at week 16 and entered the open-label CZP 400 mg Q2W escape arm. Of the 461 patients randomized at week 0, 275 (60%) completed the trial to week 144. Demographics and baseline characteristics were balanced across treatment groups (Table 1).

Patients randomized to certolizumab pegol 200 mg every 2 weeks

At week 48, 73% of patients initially randomized to CZP 200 mg Q2W achieved PASI 75, and 51% achieved PASI 90 (Figure 3a). On entering the open-label period from blinded treatment at week 48, these patients continued to receive CZP 200 mg Q2W. Dose adjustments were permitted from week 60, but of the 132 patients who entered the open-label period from blinded CZP 200 mg Q2W, 73% remained on this dose without adjusting (Figure S1; see Supporting Information). Among the 35 patients who increased their dose, 94% remained on CZP 400 mg Q2W for the remainder of the trial.

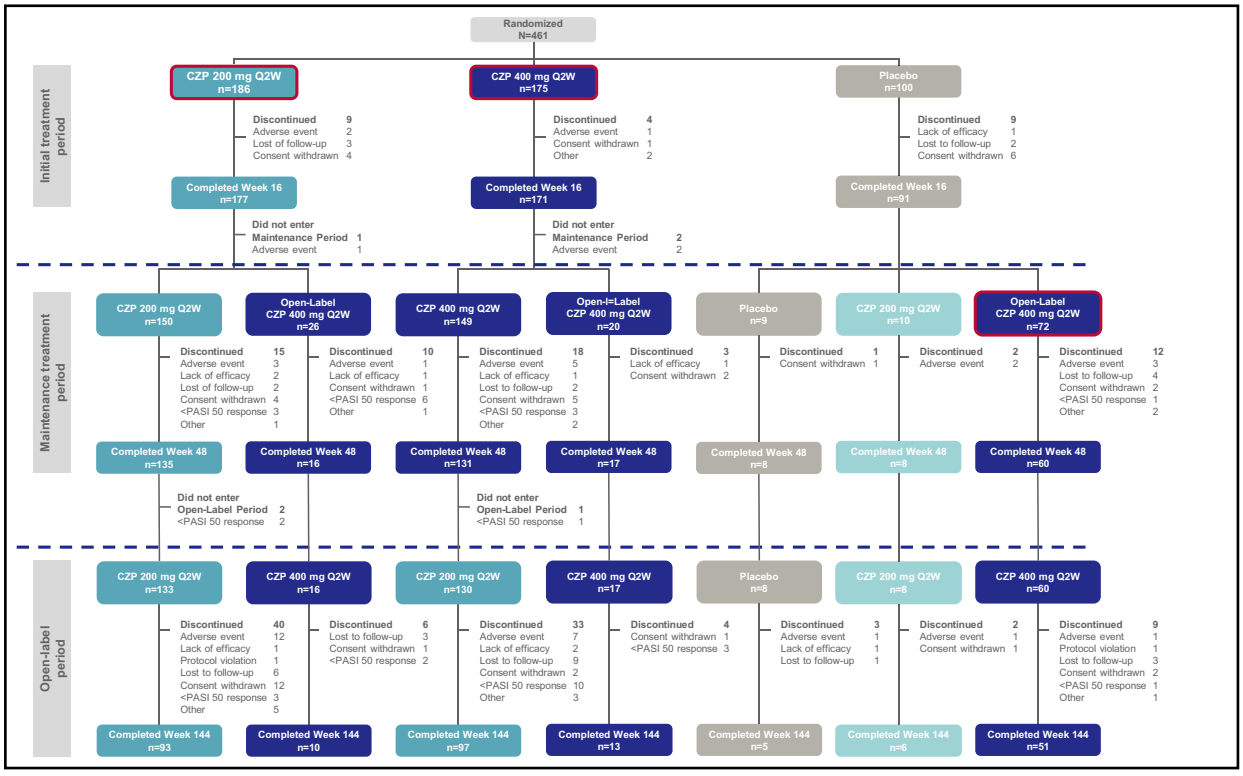

Figure 2 Patient disposition to week 144. The patient populations discussed in this manuscript are outlined in red. Dose adjustments during the open-label period are described in Figure S1 (see Supporting Information). CZP, certolizumab pegol; PASI 50, ≥ 50% reduction from baseline in Psoriasis Area and Severity Index; Q2W, every 2 weeks.

Table 1 Demographics and baseline characteristics

	CZP 200 mg Q2W (N = 186)	CZP 400 mg Q2W (N = 175)	All CZP[a] (N = 361)	Open-label CZP 400 mg Q2W from week 16[b] (N = 72)
Demographics				
Age (years), mean ± SD	45·6 ± 13·2	45·0 ± 12·9	45·3 ± 13·0	46·7 ± 13·1
Male, n (%)	125 (67·2)	103 (58·9)	228 (63·2)	48 (66.7)
White, n (%)	173 (93·0)	160 (91·4)	333 (92·2)	64 (88.9)
Geographical region, n (%)				
North America	110 (59·1)	106 (60·6)	216 (59·8)	44 (61.1)
Europe	76 (40·9)	69 (39·4)	145 (40·2)	28 (38.9)
Weight (kg), mean ± SD	95·1 ± 23·4	92·0 ± 24·8	93·6 ± 24·1	91·6 ± 21·6
BMI (kg m^{-2}), mean ± SD	32·0 ± 7·8	31·2 ± 7·9	31·6 ± 7·8	31·1 ± 7·2
Baseline disease characteristics				
Disease duration (years), mean ± SD	17·7 ± 12·9	18·5 ± 12·6	18·1 ± 12·7	16·9 ± 11·9
Concurrent PsA (self-reported), n (%)	32 (17·2)	41 (23·4)	73 (20·2)	8 (11.1)
PASI, mean ± SD	19·2 ± 7·2	19·6 ± 7·3	19·4 ± 7·3	18·3 ± 6·3
DLQI, mean ± SD	14·3 ± 7·4	13·7 ± 6·9	14·0 ± 7·1	12·9 ± 7·4
BSA affected (%), mean ± SD	23·5 ± 14·9	23·6 ± 14·3	23·5 ± 14·6	22·4 ± 13·8
PGA, n (%)				
3: moderate	128 (68·8)	126 (72·0)	254 (70·4)	53 (73.6)
4: severe	58 (31·2)	49 (28·0)	107 (29·6)	19 (26.4)
Any systemic psoriasis treatment, n (%)	131 (70·4)	124 (70·9)	255 (70·6)	52 (72.2)
Prior treatment, n (%)				
Biologic therapy	62 (33·3)	59 (33·7)	121 (33·5)	23 (31.9)
0	124 (66·7)	116 (66·3)	240 (66·5)	49 (68.1)
1	44 (23·7)	43 (24·6)	87 (24·1)	19 (26.4)
2	18 (9·7)	15 (8·6)	33 (9·1)	4 (5.6)
≥ 3	0 (0·0)	1 (0·6)	1 (0·3)	0 (0.0)
Anti-TNF-α	44 (23·7)	40 (22·9)	84 (23·3)	14 (19.4)
Anti-IL-17A	16 (8·6)	8 (4·6)	24 (6·6)	4 (5.6)
Anti-IL-12/IL-23	3 (1·6)	10 (5·7)	13 (3·6)	6 (8.3)

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; PsA, psoriatic arthritis; Q2W, every 2 weeks; TNF, tumour necrosis factor. [a]Includes all patients randomized to CZP 200 mg Q2W or CZP 400 mg Q2W at week 0. [b]These patients were randomized to placebo at week 0, failed to achieve ≥ 50% improvement reduction from baseline in PASI at week 16, and entered the open-label CZP 400 mg Q2W escape arm.

At week 144, the PASI 75 responder rate among patients randomized to CZP 200 mg Q2W was 71% and the PASI 90 responder rate was 49%, demonstrating sustained responses from week 48 to week 144 (Figure 3a). Similar trends were observed for PGA 0/1, DLQI 0/1 and absolute PASI thresholds (Figures 3a and 4a). Among those who achieved PASI 75 at week 16, the responder rate gradually declined to 88% at week 48, which was maintained through the open-label period, with a rate of 84% at week 144 (Figure 5a). Within this subset of patients who achieved PASI 75 at week 16, 59% also achieved PASI 90, and this proportion was maintained to 63% at week 144 (Figure 5a). A similar trend was observed for PASI 90 responder rates among patients who achieved PASI 90 at week 16 (Figure 6a).

Patients randomized to certolizumab pegol 400 mg every 2 weeks

At week 48, 84% of patients initially randomized to CZP 400 mg Q2W achieved PASI 75, and 63% achieved PASI 90 (Figure 3b). These responder rates were numerically greater than those for patients receiving CZP 200 mg Q2W to week 48 (Figure 3a). The same trends were observed for PGA 0/1, DLQI 0/1 and absolute PASI thresholds (Figures 3a, b and 4a, b).

As per the study design, all patients who were initially randomized to CZP 400 mg Q2W, then completed double-blinded maintenance treatment and entered the open-label period, were mandated to receive CZP 200 mg Q2W at week 48. Subsequent dose adjustments were permitted through weeks 60–144. Of the 130 patients who entered the open-label period from blinded CZP 400 mg Q2W treatment and underwent mandatory dose reduction, 62% remained on CZP 200 mg Q2W without adjusting (Figure S1; see Supporting Information). Among the 49 patients who returned to the higher dose, 94% remained on CZP 400 mg Q2W for the remainder of the trial.

From week 48, responder rates in patients randomized to CZP 400 mg Q2W gradually declined until week 84, following which the rates remained stable through to week 144

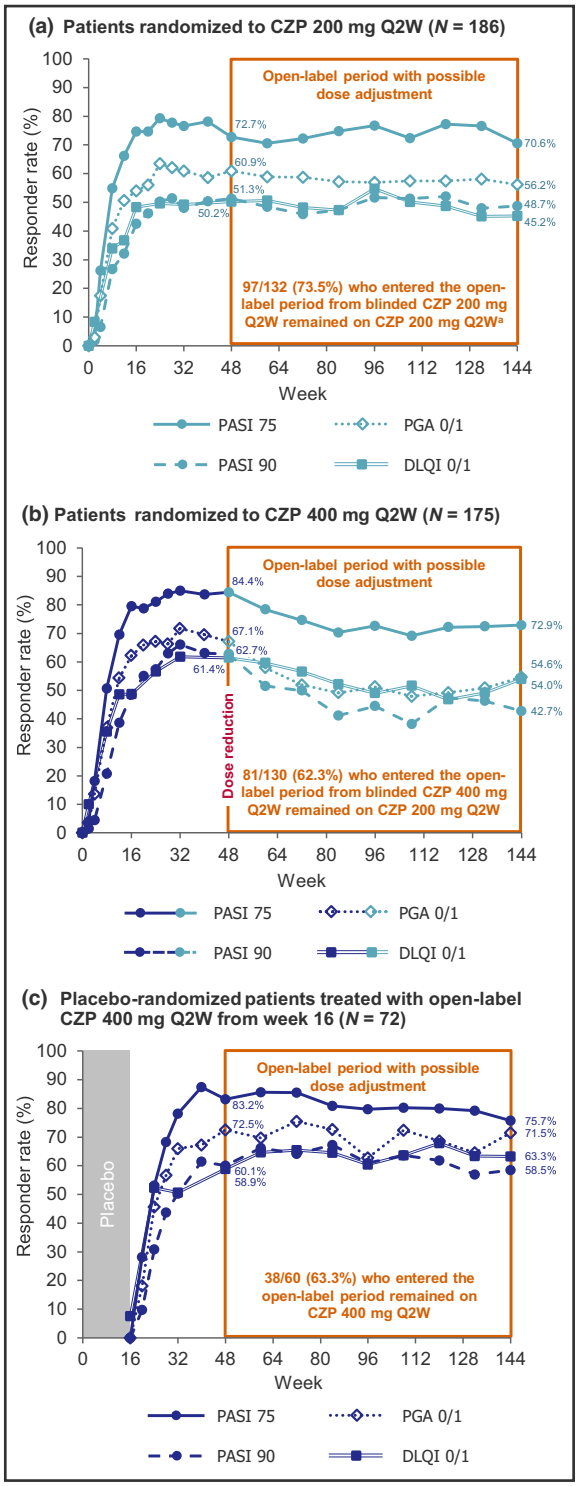

Figure 3 PASI 75, PASI 90, PGA 0/1 and DLQI 0/1 responses over time. DLQI 0/1, Dermatology Life Quality Index score 0 or 1; PASI 75/90, ≥ 75%/90% improvement in Psoriasis Area and Severity Index; PGA 0/1, Physician's Global Assessment score 0 or 1 (clear or almost clear, with ≥ 2-point improvement from baseline). Data are presented according to initial randomization for the certolizumab pegol (CZP) 200 mg every 2 weeks (Q2W) (a) and CZP 400 mg Q2W (b) groups, and for placebo-randomized patients who entered the open-label CZP 400 mg escape arm at week 16 (c). Estimates of responder rate were based on a logistic regression model, including patients who either did or did not have their dose adjusted during the open-label period. At week 48, patients entering the open-label period from blinded CZP 200 mg Q2W or CZP 400 mg Q2W initially received CZP 200 mg Q2W, and patients entering from the open-label escape arm initially received CZP 400 mg Q2W (or may have had their dose reduced to CZP 200 mg Q2W at the discretion of the investigator if they achieved PASI 75). Subsequent dose adjustments were permitted through weeks 60–144. [a]One patient considered to have entered the open-label period from blinded CZP 200 mg Q2W did not receive CZP treatment from week 42 onwards and is not counted in this calculation.

(Figures 3b and 4b). At week 144, PASI 75 was achieved by 73% of these patients, and PASI 90 by 43% (Figure 3b).

Within the subset of patients randomized to CZP 400 mg Q2W who achieved PASI 75 at week 16, 98% still achieved PASI 75 at week 48 (Figure 5b). Of these patients, 62% also achieved PASI 90 at week 16, and this response rate increased to 75% at week 48 (Figure 5b). Following mandatory dose reduction at week 48, responder rates gradually declined, stabilized by week 84 and were subsequently maintained. At week 144, 85% of week 16 PASI 75 responders still achieved PASI 75, and 50% also achieved PASI 90 (Figure 5b).

Among patients who achieved PASI 90 at week 16, PASI 90 response gradually declined through to week 84, and was subsequently maintained; at week 144 the PASI 90 rate was 56% (Figure 6b). DLQI 0/1 rates in week 16 PASI 75 and PASI 90 responders increased from week 16 to week 48, after which responses gradually declined, stabilized by week 96, and were subsequently maintained through week 144 (Figures 5b and 6b).

Placebo-randomized patients who entered the open-label certolizumab pegol 400 mg every 2 weeks escape arm

To assess the long-term efficacy of CZP 400 mg Q2W, data are presented for patients who were initially randomized to placebo, failed to achieve PASI 50 at week 16, and entered the open-label escape arm, receiving CZP 400 mg Q2W for up to 128 weeks of treatment. Patients who achieved PASI 75 at week 48 could have had their dose reduced to CZP 200 mg Q2W at the investigator's discretion. In addition, as with patients entering the open-label period at week 48 from blinded treatment, dose adjustments were permitted from week 60 onwards based on PASI response and were either mandatory or at the investigator's discretion. Of the 60 patients in this group who entered the open-label period at week 48, 37% had discretionary dose reduction to CZP 200 mg Q2W (Figure S1; see Supporting Information). Among the 22 patients who had their dose reduced, 68% remained on CZP 200 mg Q2W for the remainder of the trial.

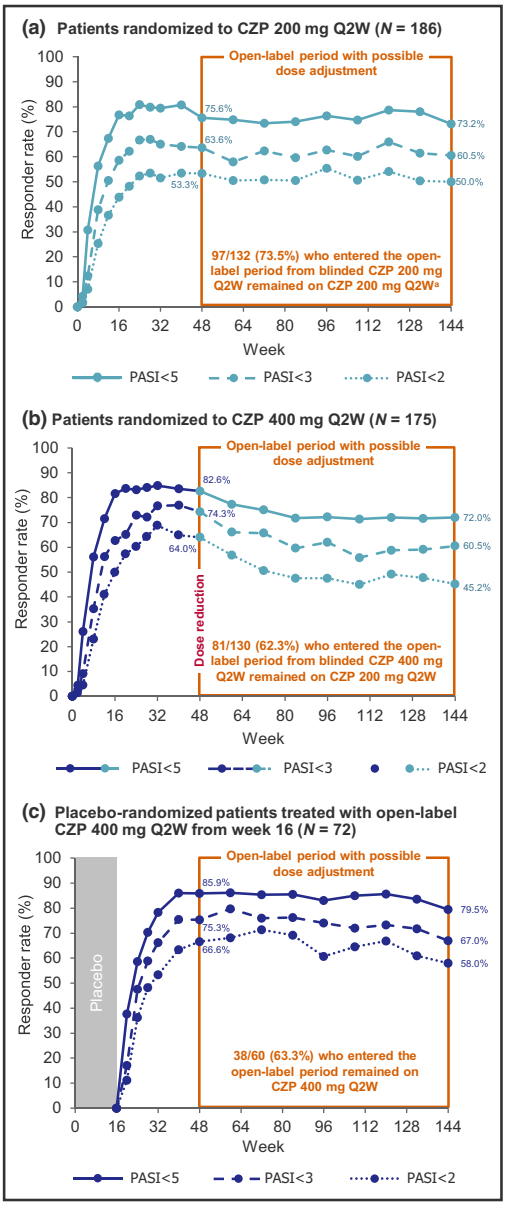

Figure 4 The proportion of patients achieving clinically relevant absolute Psoriasis Area and Severity Index (PASI) thresholds: PASI < 5, < 3 and < 2. Data are presented according to initial randomization for the certolizumab pegol (CZP) 200 mg every 2 weeks (Q2W) (a) and CZP 400 mg Q2W (b) groups, and for placebo-randomized patients who entered the open-label CZP 400 mg escape arm at week 16 (c). Estimates of responder rate were based on a logistic regression model, including patients who either did or did not have their dose adjusted during the open-label period. At week 48, patients entering the open-label period from blinded CZP 200 mg Q2W or CZP 400 mg Q2W initially received CZP 200 mg Q2W, and patients entering from the open-label escape arm initially received CZP 400 mg Q2W (or may have had their dose reduced to CZP 200 mg Q2W at the discretion of the investigator if they achieved ≥ 75% improvement in PASI). Subsequent dose adjustments were permitted through weeks 60–144. [a]One patient considered to have entered the open-label period from blinded CZP 200 mg Q2W did not receive CZP treatment from week 42 onwards and is not counted in this calculation.

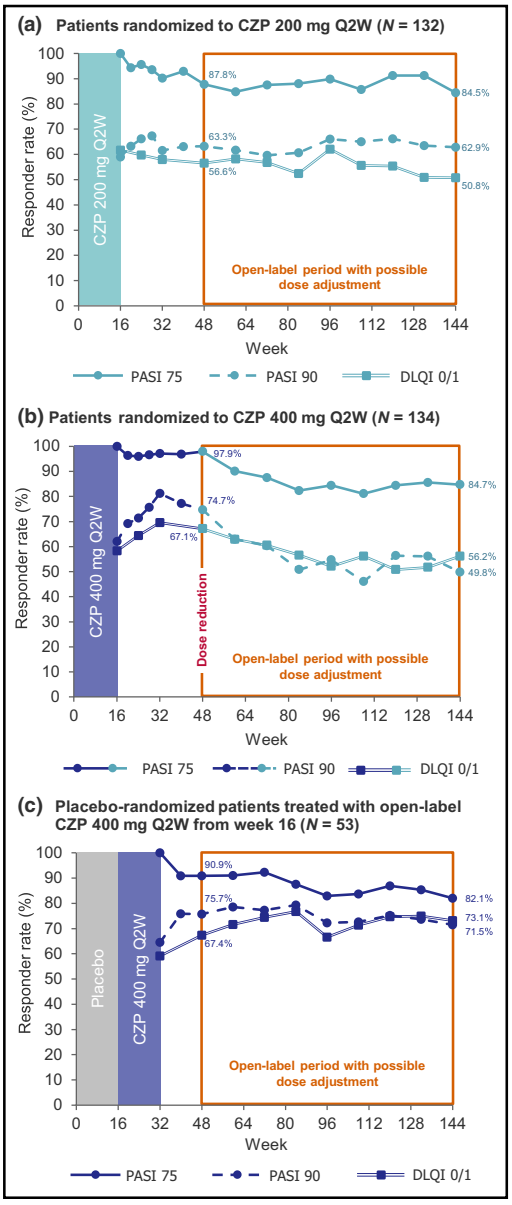

Figure 5 PASI 75, PASI 90 and DLQI 0/1 responses over time in patients who achieved PASI 75 after 16 weeks of certolizumab pegol (CZP) treatment. PASI 75/90, ≥ 75%/90% improvement in Psoriasis Area and Severity Index; DLQI 0/1, Dermatology Life Quality Index score 0 or 1. Data are presented for patients who achieved PASI 75 after 16 weeks of CZP treatment according to initial randomization for the CZP 200 mg every 2 weeks (Q2W) (a) and CZP 400 mg Q2W (b) groups, and for placebo-randomized patients who entered the open-label CZP 400 mg escape arm at week 16 (c). Estimates of responder rate were based on a logistic regression model, including patients who either did or did not have their dose adjusted during the open-label period. At week 48, patients entering the open-label period from blinded CZP 200 mg Q2W or CZP 400 mg Q2W initially received CZP 200 mg Q2W, and patients entering from the open-label escape arm initially received CZP 400 mg Q2W (or may have had their dose reduced to CZP 200 mg Q2W at the discretion of the investigator if they achieved PASI 75). Subsequent dose adjustments were permitted through weeks 60–144.

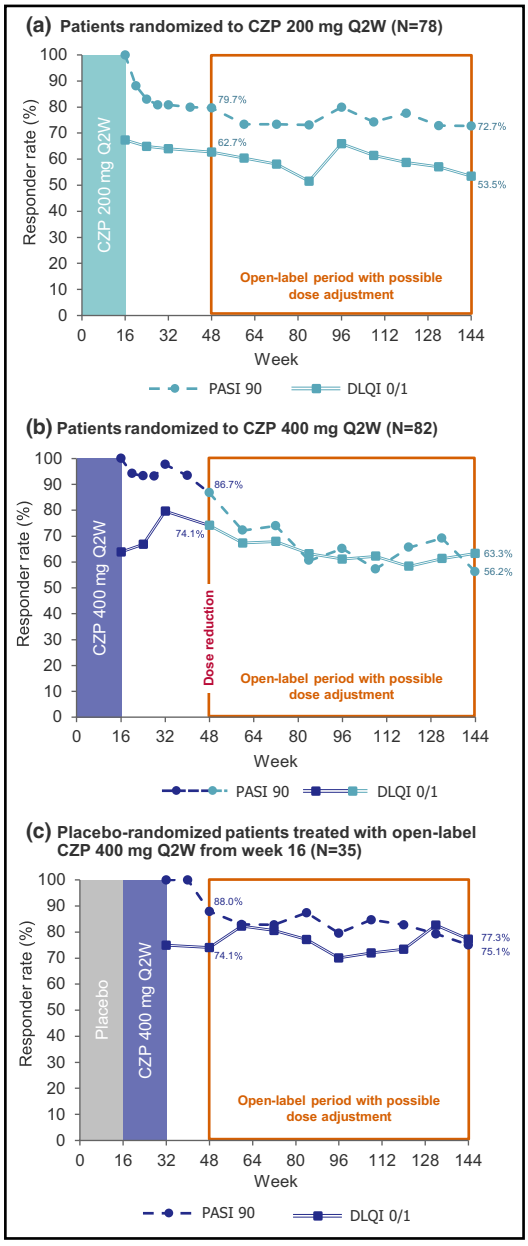

Figure 6 PASI 90 (≥ 90% improvement in Psoriasis Area and Severity Index) and DLQI 0/1 (Dermatology Life Quality Index score 0 or 1) responses over time in patients who achieved PASI 90 after 16 weeks of certolizumab pegol (CZP) treatment. Data are presented for patients who achieved PASI 90 after 16 weeks of CZP treatment according to initial randomization for the CZP 200 mg every 2 weeks (Q2W) (a) and CZP 400 mg Q2W (b) groups, and for placebo-randomized patients who entered the open-label CZP 400 mg escape arm at week 16 (c). Estimates of responder rate were based on a logistic regression model, including patients who either did or did not have their dose adjusted during the open-label period. At week 48, patients entering the open-label period from blinded CZP 200 mg Q2W or CZP 400 mg Q2W initially received CZP 200 mg Q2W, and patients entering from the open-label escape arm initially received CZP 400 mg Q2W (or may have had their dose reduced to CZP 200 mg Q2W at the discretion of the investigator if they achieved PASI 75). Subsequent dose adjustments were permitted through weeks 60–144.

After 32 weeks of CZP 400 mg Q2W treatment (week 48 of the study), 83% of these placebo-randomized patients achieved PASI 75, and 60% achieved PASI 90 (Figure 3c). These responder rates were sustained over the long term, with 76% achieving PASI 75 and 59% achieving PASI 90 after 128 weeks of treatment (week 144 of the study) (Figure 3c). Similar trends were observed for PGA 0/1, DLQI 0/1 and absolute PASI thresholds (Figures 3c and 4c).

The PASI 75 response among the subset of these patients who achieved PASI 75 after 16 weeks of CZP treatment (week 32 of the study) was maintained over the following 128 weeks, with 82% achieving PASI 75 at week 144 (Figure 5c). Of the patients who achieved PASI 75 at week 32, 65% also achieved PASI 90 (Figure 5c). This rate increased to 76% at week 48 and was maintained through the open-label period, with 72% of week 32 PASI 75 responders achieving PASI 90 at week 144 (Figure 5c). A similar trend was observed for PASI 90 response in patients who achieved PASI 90 at week 16 (Figure 6c).

DLQI 0/1 responder rates in the subset of patients who achieved PASI 75 after 16 weeks of treatment increased over 2 years of further treatment, from 59% at week 32 to 73% at week 144 (Figure 5c). In week 32 PASI 90 responders, the DLQI 0/1 rate was maintained from 75% at week 32 to 77% at week 144 (Figure 6c).

Discussion

During the 3-year CIMPASI-1 and CIMPASI-2 phase III trials, patients treated with CZP showed sustained and durable improvements in the signs and symptoms of plaque psoriasis. Psoriasis is a chronic disease that is likely to require patients to remain on continuous treatment for many years.[7] Long-term data from clinical trials can help guide clinical decision-making for patients and healthcare professionals.[1] Although multiyear sustained efficacy has previously been reported for other indications in which CZP is approved, including rheumatoid arthritis, psoriatic arthritis, Crohn's disease and axial spondyloarthritis,[10,11,19–22] this had yet to be demonstrated in psoriasis beyond 48 weeks, prior to this publication.

The results of these trials suggest that for some patients, CZP 400 mg Q2W may offer greater long-term benefits than CZP 200 mg Q2W. At week 48, numerically higher responder rates were observed in the CZP 400 mg Q2W-randomized group, compared with the CZP 200 mg Q2W group, for all reported outcomes.[16] However, after mandatory dose reduction at week 48, responder rates among the patients initially randomized to the higher dose gradually reduced, and week 144 responses were similar between the two populations (PASI 75 rates around 70%, for example). These data suggest that some patients may require continuous treatment with CZP 400 mg Q2W to maintain optimal response.

Further evidence of the long-term benefits of CZP 400 mg Q2W is provided by the placebo-randomized patients who received open-label CZP 400 mg Q2W from week 16. A numerically greater proportion of these patients achieved the

most stringent outcomes of PASI 90, PGA 0/1 and DLQI 0/1 at week 144, compared with patients who underwent mandatory dose reduction to CZP 200 mg Q2W at week 48.

Long-term data have also been reported for other biologics approved for the treatment of psoriasis. In a 160-week phase III trial of adalimumab, 53% and 33% of patients who received continuous adalimumab for 144 weeks achieved PASI 75 and PASI 90, respectively.[23] In the same trial, among patients who achieved PASI 75 after both 16 and 33 weeks of adalimumab treatment, 76% maintained their responses over a further 108 weeks.[23] For secukinumab, a PASI 75 responder rate of 77% has been reported after 152 weeks of treatment, and a PASI 90 rate of 58%.[24] Here, long-term treatment with CZP resulted in similar responses to those seen with secukinumab, with PASI 75 and PASI 90 responder rates at week 144 of 71–76% and 43–59%, respectively.

As with all clinical trials, CIMPASI-1 and CIMPASI-2 had strict inclusion criteria that may affect the generalizability of these results to clinical practice, and these data should be viewed alongside long-term data from treatment registries, for which inclusion criteria are broader, to better understand the real-world efficacy. The CIMPASI-1 and CIMPASI-2 trial designs did not include study arms where patients were mandated to remain on the same treatment dose for 3 years. The study protocols denoted ranges of PASI response during the open-label period under which dose adjustments were either mandatory or at the investigator's discretion. These adjustments introduced some limitations on interpretation of data and comparison between dose regimens. However, of the patients who entered the open-label period, around two-thirds or more remained on the stated treatment for the remainder of the trial. In addition, while dose adjustments provided some limitations on data interpretation, the trials may be seen to have benefited from more closely emulating potential real-world treatment patterns.

These results demonstrate the long-term therapeutic benefit of CZP for the treatment of moderate-to-severe plaque psoriasis. After rapid improvements during the initial phase of the trials, PASI 75 responses remained high in patients dosed with either CZP 200 mg Q2W or CZP 400 mg Q2W. However, for the more stringent outcomes of PASI 90, PGA 0/1 and DLQI 0/1, numerically higher responder rates were generally observed within the patient population receiving CZP 400 mg Q2W, suggesting that some additional benefits may be obtained from the higher dose.

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Appendix

Conflicts of interest

K.B.G. has received honoraria and/or research support from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dermira Inc., Eli Lilly, Janssen, Novartis, Pfizer, Sun Pharma and UCB Pharma. R.B.W. has served as a speaker, advisor and/or clinical study investigator for AbbVie, Almirall, Arena Pharmaceuticals, Avillion, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Janssen, LEO Pharma, Novartis, Ortho, Sanofi Genzyme, Sun Pharma and UCB Pharma. A.B.G. has current consulting or advisory board agreements with AbbVie, Allergan, Avotres Therapeutics, Beiersdorf, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dermira Inc., Dr. Reddy's Laboratories, Eli Lilly, Incyte, Janssen, LEO Pharma, Novartis, Sun Pharma, UCB Pharma, Valeant and XBiotech (no personal compensation); and has received research and educational grants from Boehringer Ingelheim, Incyte, Janssen, Novartis, UCB Pharma and XBiotech. A.B. has served as a scientific adviser and/or clinical study investigator for AbbVie, Aclaris, Allergan, Almirall, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Dermira Inc., Eli Lilly and Company, FLX Bio, Forte, Galderma, Janssen, LEO Pharma, Novartis, Ortho, Pfizer, Regeneron, Sandoz, Sanofi Genzyme, Sun Pharma and UCB Pharma; and as a paid speaker for AbbVie. D.T. has received honoraria for participation on ad boards, as a speaker or for consultancy from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dignity, Dr. Reddy's Laboratories, Eli Lilly, Galapagos, GSK, Janssen, LEO Pharma, Morphosis, MSD, Novartis, Pfizer, Sandoz-Hexal, Pfizer, Regeneron/Sanofi and UCB Pharma; and research grants from Celgene and Novartis. C.L. is treasurer of the International Psoriasis Council; a Fellow of the American Academy of Dermatology; a Member of the American Dermatological Association and Adjunct Professor of Dermatology at St Louis University School of Medicine; has a private practice in St Louis, MO; has received consulting and advisory board honoraria from AbbVie, Amgen, Boehringer Ingelheim, Dermira Inc., Eli Lilly, Janssen, LEO Pharma, Pfizer, Sandoz, UCB Pharma and Vitae; has acted as an investigator for AbbVie, Actavis, Amgen, Boehringer Ingelheim, Celgene, Coherus, Corrona, Dermira Inc., Eli Lilly, Galderma, Glenmark, Janssen, LEO Pharma, Merck, Novartis, Novella, Pfizer, Sandoz, Stiefel and Wyeth; and has acted as a speaker (with honoraria) for AbbVie, Celgene, Eli Lilly and Novartis. Y.P. has acted as an investigator (research grants) for AbbVie, Baxter, Boehringer Ingelheim, Celgene, Centocor/Janssen, Eli Lilly, EMD Serono, GSK, LEO Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Takeda and UCB Pharma; and as a speaker (with honoraria) for AbbVie, Celgene, Janssen, Eli Lilly, LEO Pharma, Novartis, Regeneron and Sanofi Genzyme. M.B., F.B. and C.E. are employees of UCB Pharma. K.R. has served as an advisor and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Centocor, Covagen, Dermira Inc., Eli Lilly, Forward Pharma, Fresenius Medical Care, Galapagos, GSK, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Medac, Merck Sharp & Dohme, Miltenyi Biotec, Novartis, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB Pharma, Valeant and Xenoport.

Appendix

Data sharing

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 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 www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a prespecified time, typically 12 months, on a password-protected portal.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1 Dose adjustment during the open-label period.
Table S1 Summary of results.
Table S2 Summary of results in patients who achieved ≥ 75% improvement in Psoriasis Area and Severity Index after 16 weeks of certolizumab pegol treatment.
Table S3 Summary of results in patients who achieved ≥ 90% improvement in Psoriasis Area and Severity Index after 16 weeks of certolizumab pegol treatment.
Powerpoint S1 Journal Club Slide Set.