Certolizumab Pegol for the Treatment of Patients with Moderate-to-Severe Chronic Plaque Psoriasis: An Overview of 3 Randomized Controlled Trials

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Introduction

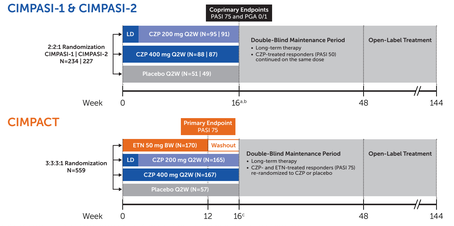
- Certolizumab pegol (CZP), the only Fc-free, PEGylated, anti-TNF biologic, has demonstrated promising results in three ongoing, phase 3, randomized, double-blind, placebo-controlled clinical trials in adults with moderate-to-severe chronic plaque psoriasis (CIMPASI-1,[1,2] CIMPASI-2,[1,2] and CIMPACT[3,4])
- CZP does not bind the neonatal Fc receptor for IgG (FcRn) and consequently shows minimal placental transfer from mothers to infants[5]
- CZP is approved for the treatment of adults with rheumatoid arthritis, psoriatic arthritis, Crohn's disease (US only), ankylosing spondylitis, and axial spondyloarthritis (EU only)
- Pooled efficacy and safety results from the first 16 weeks of three 144-week multinational, randomized, double-blind clinical trials evaluating CZP versus placebo are reported here

Methods

Study Design

- CIMPASI-1 (NCT02326298), CIMPASI-2 (NCT02326272), and CIMPACT (NCT02346240) are ongoing phase 3, multicenter, double-blind, placebo-controlled (and active-controlled; CIMPACT only) trials
- Patients were randomized to CZP 400 mg every 2 weeks (Q2W), CZP 200 mg Q2W (following 400 mg loading doses at Weeks 0, 2, and 4), or placebo Q2W for 16 weeks (or etanercept [ETN] twice weekly for 12 weeks in CIMPACT only; ETN data are not included in this pooled analysis) (**Figure 1**)

Figure 1. Study Design



[a]In CIMPASI-1 and CIMPASI-2, PASI 50 nonresponders at Week 16 entered the Escape Arm for treatment with open-label CZP 400 mg Q2W
[b]Upon entering the Maintenance Period, placebo-treated PASI 75 responders (≥75% reduction in PASI) continued blinded placebo treatment and placebo-treated PASI 50–74 responders (≥50% but <75% reduction in PASI) received CZP 400 mg loading dose at Weeks 16, 18, and 20 and then CZP 200 mg Q2W
[c]In CIMPACT, PASI 75 nonresponders at Week 16 entered the Escape Arm for treatment with open-label CZP 400 mg Q2W
BW, twice weekly; CZP, certolizumab pegol; ETN, etanercept; LD, CZP 400 mg loading dose at Weeks 0, 2, and 4; PASI 50, ≥50% reduction in psoriasis area and severity index (PASI); PASI 75, ≥75% reduction in PASI; PGA 0/1, 'clear'/'almost clear' with ≥2-category improvement in physician's global assessment; Q2W, every 2 weeks

Patients

- Eligible patients were ≥18 years of age with moderate-to-severe chronic psoriasis for ≥6 months (psoriasis area severity index [PASI] ≥12, body surface area affected [BSA] ≥10%, and physician's global assessment [PGA] ≥3 on a 5-point scale) and candidates for systemic psoriasis therapy, phototherapy, and/or photochemotherapy
- Patients were excluded if they had previous treatment with CZP (or ETN in CIMPACT) or >2 biologics (including anti-TNF); had a history of primary failure to any biologic or secondary failure to >1 biologic; or had erythrodermic, guttate, or generalized pustular forms of psoriasis

Study Assessments

- Coprimary endpoints for the pooled analysis were PASI 75 (≥75% reduction in PASI) and PGA 0/1 ('clear'/'almost clear' with ≥2-category improvement) responder rates at Week 16; PASI 90 (≥90% reduction in PASI) responder rate at Week 16 was a key secondary endpoint; Dermatology Life Quality Index (DLQI) 0/1 responder rate and change from Baseline (CfB) in DLQI versus placebo at Week 16 were also assessed
- Safety evaluation included assessment of treatment-emergent adverse events (TEAEs)

Statistical Analyses

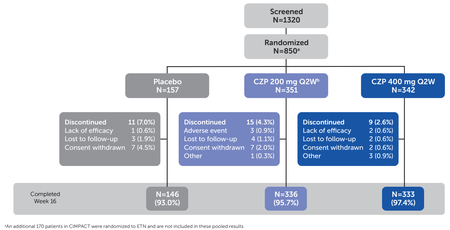
- PASI 75, PGA 0/1, and PASI 90 responder rates were analyzed via a logistic regression model with treatment group, region, study, prior biologic exposure (yes/no), and the interactions study*region and study*prior biologic exposure (yes/no) as factors using Markov chain Monte Carlo methodology for multiple imputation to address missing data
- CfB in DLQI scores are adjusted least squares mean differences from an analysis of covariance (ANCOVA) model with treatment group, region, study, prior biologic exposure (yes/no), and the interactions study*region and study*prior biologic exposure (yes/no) as factors and Baseline DLQI score as a covariate using last observation carried forward (LOCF) imputation
- DLQI 0/1 responder rates were summarized descriptively with counts and percentages, where missing data were imputed using nonresponder imputation (NRI)
- P-values were not adjusted for multiplicity

Results

Disposition, Demographics, and Baseline Disease Characteristics

- Of 850 patients randomized to CZP or placebo in CIMPASI-1, CIMPASI-2, or CIMPACT, 815 patients (95.9%) completed 16 weeks of treatment (333 [97.4%] for CZP 400 mg Q2W, 336 [95.7%] for CZP 200 mg Q2W, and 146 [93.0%] for placebo; **Figure 2**)
- Patient demographics and Baseline disease characteristics were similar between treatment groups (**Table 1**) and across trials (data not shown) including Baseline PASI and PGA scores
- Across the overall population, approximately one-third of study participants reported prior biologic use (**Table 1**)

Figure 2. Patient Disposition (Week 16)



[a]An additional 170 patients in CIMPACT were randomized to ETN and are not included in these pooled results
[b]CZP 200 mg Q2W patients received loading dose of CZP 400 mg at Weeks 0, 2, and 4
CZP, certolizumab pegol; ETN, etanercept; Q2W, every two weeks

Table 1. Patient Demographics and Baseline Disease Characteristics

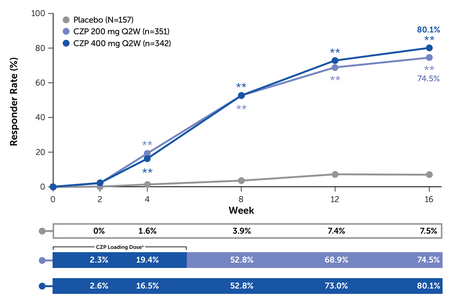
	Placebo (N=157)	CZP 200 mg Q2W[a] (N=351)	CZP 400 mg Q2W (N=342)
Demographics			
Age (years), mean ± SD	46.0 ± 13.3	46.1 ± 13.4	45.2 ± 12.6
Male, n (%)	95 (60.5)	238 (67.8)	210 (61.4)
White, n (%)	146 (93.0)	331 (94.3)	322 (94.2)
Geographic region, n (%)			
North America	71 (45.2)	136 (38.7)	133 (38.9)
Europe	86 (54.8)	215 (61.3)	209 (61.1)
Weight (kg), mean ± SD	92.2 ± 25.8	92.6 ± 22.3	89.2 ± 22.7
BMI (kg/m²), mean ± SD	31.2 ± 7.8	31.0 ± 7.1	30.1 ± 7.1
Baseline Disease Characteristics			
Duration of psoriasis at screening (years), mean ± SD	17.7 ± 12.7	18.5 ± 13.1	18.2 ± 12.0
Concurrent psoriatic arthritis (self-reported), n (%)	25 (15.9)	59 (16.8)	65 (19.0)
PASI, mean ± SD	18.8 ± 6.8	20.3 ± 8.1	20.2 ± 7.5
DLQI,[a] mean ± SD	13.4 ± 7.7	13.6 ± 7.2	14.5 ± 7.1
BSA (%), mean ± SD	23.5 ± 13.6	25.6 ± 15.9	25.5 ± 14.9
PGA, n (%)			
3: moderate	112 (71.3)	242 (68.9)	239 (69.9)
4: severe	45 (28.7)	109 (31.1)	103 (30.1)
Any prior systemic psoriasis treatment, n (%)	111 (70.7)	249 (70.9)	247 (72.2)
Prior biologic use,[b] n (%)	40 (25.5)	106 (30.2)	107 (31.3)
anti-TNF	24 (15.3)	49 (14.0)	43 (12.6)
anti-IL17	13 (8.3)	54 (15.4)	43 (12.6)

[a]For DLQI: Placebo, N=154; CZP 200 mg Q2W, N=346; CZP 400 mg Q2W, N=340
[b]Patients may have had exposure to ≤1 prior biologic but ≥2 per-exclusion criteria; 1 patient in the CZP 400 mg Q2W group in CIMPASI-2 had prior exposure to 3 biologics, which was a protocol violation
[c]CZP 200 mg Q2W patients received loading dose of CZP 400 mg at Weeks 0, 2, and 4
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; TNF, tumor necrosis factor

Pooled Efficacy

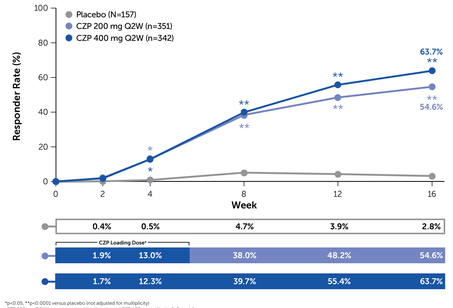
- At Week 16, PASI 75 and PGA 0/1 responder rates were significantly greater in the pooled CZP 400 mg Q2W and pooled CZP 200 mg Q2W groups versus placebo, with clinically meaningful differences observed as early as Week 4 for both CZP doses versus placebo (**Figure 3** and **Figure 4**)
- Similarly, Week 16 PASI 90 responder rates were significantly greater in the CZP 400 mg Q2W and CZP 200 mg Q2W groups versus placebo, with clinically meaningful differences observed as early as Week 8 for both CZP doses versus placebo (**Figure 5**)
- Meaningful improvements in quality of life, measured by CfB in DLQI and DLQI 0/1 responder rates, were observed in CZP-treated patients versus placebo at Week 16 (**Figure 6**)

Figure 3. Pooled PASI 75 Responder Rates From Baseline to Week 16



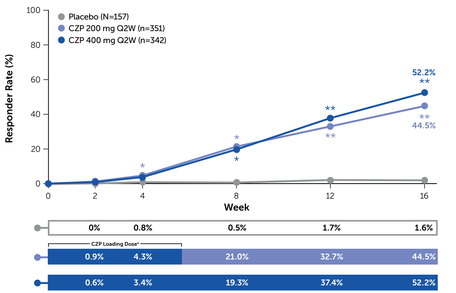
*p<0.0001 versus placebo (not adjusted for multiplicity)
CZP 200 mg Q2W patients received loading dose of CZP 400 mg at Weeks 0, 2, and 4
Responder rates are the adjusted predicted probabilities based on logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), and the interactions study*region and study*prior biologic exposure (yes/no) where missing data were imputed using multiple imputation (MCMC method)
CZP, certolizumab pegol; LD, loading dose of CZP 400 mg Q2W at Weeks 0, 2, and 4; MCMC, Markov chain Monte Carlo; PASI 75, ≥75% reduction in psoriasis area and severity index; Q2W, every 2 weeks

Figure 4. Pooled PGA 0/1 Responder Rates From Baseline to Week 16



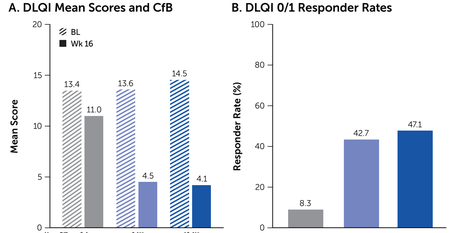
*p<0.05, **p<0.0001 versus placebo (not adjusted for multiplicity)
CZP 200 mg Q2W patients received loading dose of CZP 400 mg at Weeks 0, 2, and 4
Responder rates are the adjusted predicted probabilities based on logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), and the interactions study*region and study*prior biologic exposure (yes/no) where missing data were imputed using multiple imputation (MCMC method)
CZP, certolizumab pegol; MCMC, Markov chain Monte Carlo; PGA 0/1, 'clear'/'almost clear' with ≥2-category improvement in physician's global assessment; Q2W, every 2 weeks

Figure 5. Pooled PASI 90 Responder Rates From Baseline to Week 16



*p<0.05, **p<0.0001 versus placebo (not adjusted for multiplicity)
[a]CZP 200 mg Q2W patients received loading dose of CZP 400 mg at Weeks 0, 2, and 4
Responder rates are the adjusted predicted probabilities based on logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), and the interactions study*region and study*prior biologic exposure (yes/no) where missing data were imputed using multiple imputation (MCMC method)
CZP, certolizumab pegol; MCMC, Markov chain Monte Carlo; PASI 90, ≥90% reduction in psoriasis area and severity index; Q2W, every 2 weeks

Figure 6. Pooled DLQI Scores at Baseline and Week 16 and DLQI 0/1 Responder Rates at Week 16



**p<0.0001 vs placebo based on adjusted least squares mean difference from an ANCOVA model with treatment group, region, study, prior biologic exposure (yes/no), and the interactions study*region and study*prior biologic exposure (yes/no) as factors and Baseline DLQI score as a covariate using LOCF imputation (p-values not adjusted for multiplicity); for DLQI 0/1 responder rates, missing data were imputed using nonresponder imputation (NRI)
[a]CZP 200 mg Q2W patients received loading dose of CZP 400 mg at Weeks 0, 2, and 4
BL, Baseline; CfB, change from BL; CZP, certolizumab pegol; DLQI, Dermatology Life Quality Index; LOCF, last observation carried forward; NRI, nonresponder imputation; Q2W, every 2 weeks

Pooled Safety

- The safety profile for both CZP doses was consistent with the anti-TNF class in psoriasis; based on the known safety profile of CZP,[6] no new safety signals were observed (**Table 2**)
  - The incidence of TEAEs was generally similar between CZP 400 mg Q2W and placebo groups, and was lower in the CZP 200 mg Q2W group versus placebo; TEAEs infrequently led to discontinuation
- Serious TEAEs and serious infections and infestations were infrequent across treatment groups (CZP 400 mg Q2W: 4.7% and 0.6%, respectively; CZP 200 mg Q2W: 1.4% and 0%; placebo: 4.5% and 0%) (**Table 2**)
  - Two serious infections were reported in the CZP 400 mg Q2W group – hematoma infection and abdominal abscess in 1 patient following a bicycle accident, and pneumonia in 1 patient
- No deaths were reported in any of the three studies through Week 16 (**Table 2**)

Table 2. Treatment-Emergent Adverse Events (Safety Set)

	Placebo (N=157)	CZP 200 mg Q2W[a] (N=350)	CZP 400 mg Q2W (N=342)
TEAEs, n (%)			
All	97 (61.8)	197 (56.3)	217 (63.5)
Serious	7 (4.5)	5 (1.4)	16 (4.7)
Discontinuations due to TEAE, n (%)	0	4 (1.1)	4 (1.2)
Deaths, n (%)	0	0	0
Frequent and other TEAEs of interest, n (%)			
Infections and infestations	53 (33.8)	108 (30.9)	124 (36.3)
Latent tuberculosis	0	0	0
Active tuberculosis	0	0	0
Candida infections	0	1 (0.3)[b]	0
Oral fungal infection	0	0	1 (0.3)
Fungal skin infection	0	0	1 (0.3)[c]
Nasopharyngitis	19 (12.1)	42 (12.0)	43 (12.6)
Upper respiratory tract infection	11 (7.0)	17 (4.9)	23 (6.7)
Serious infections	0	0	2 (0.6)[d]
Non-melanoma skin cancer	0	0	1 (0.3)[e]
Malignancy (excluding non-melanoma skin cancer)	0	0	0
Depression	0	2 (0.6)	2 (0.6)

[a]CZP 200 mg Q2W patients received loading dose of CZP 400 mg at Weeks 0, 2, and 4
[b]Vulvovaginal candidiasis
[c]Reported as fungal infection preferred term in the database
[d]Hematoma infection and abdominal abscess in 1 patient (bicycle accident), and pneumonia in 1 patient
[e]Basal cell carcinoma
Safety Set includes all randomized patients who received ≥1 dose of study medication
CZP, certolizumab pegol; TEAE, treatment-emergent adverse event; Q2W, every 2 weeks

Conclusions

- In the phase 3 program, certolizumab pegol (CZP) 400 mg Q2W and CZP 200 mg Q2W were each associated with statistically significant, clinically meaningful improvements in moderate-to-severe chronic plaque psoriasis
  - Clinically meaningful differences in PASI 75 and PGA 0/1 responder rates versus placebo were observed as early as Week 4
  - Greater improvement in quality of life as measured by CfB in DLQI and DLQI 0/1 responder rate was seen for both CZP dose groups compared with placebo at Week 16
  - Responder rates were numerically greater for patients treated with CZP 400 mg Q2W versus 200 mg Q2W
- In the phase 3 program, the safety profile for CZP was consistent with the anti-TNF class in psoriasis; based on the known safety profile of CZP, no new safety signals were observed
  - Serious TEAEs were infrequent across treatment groups

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Author Disclosures

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