Maintenance of Response With Certolizumab Pegol for the Treatment of Chronic Plaque Psoriasis: Results of a 32-Week Re-Randomized Maintenance Period from an Ongoing Phase 3, Multicenter, Randomized, Active- and Placebo-Controlled Study (CIMPACT)

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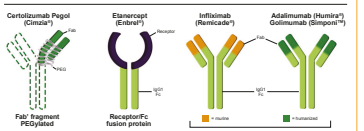
INTRODUCTION

- Psoriasis affects ~3% of adults in the US[1,2] and ~2-6% of adults in Europe[3]; onset can begin at any age, though most patients develop the disease in the third decade of life[4]
- Therapy for patients with plaque psoriasis varies according to the severity of the disease, with limited or mild psoriasis treated with topical therapies and/or phototherapy and more severe disease treated with photochemotherapy, cyclosporine, methotrexate, or biological agents such as tumor necrosis factor (TNF) inhibitors, anti-IL17s, and anti-IL12/23s
- Certolizumab pegol (CZP) is the only PEGylated, Fc-free, anti-TNF biologic (**Figure 1**) and is currently under investigation for the treatment of moderate-to-severe chronic plaque psoriasis
- Previously presented data through Week 16 of 3 ongoing, randomized, double-blind, placebo-controlled trials have demonstrated clinically meaningful efficacy and a safety profile consistent with anti-TNF therapy[5,6]
- CIMPACT (NCT02346240) is designed to assess the efficacy and safety of treatment with CZP compared with placebo and etanercept (ETN) in adult patients with moderate-to-severe chronic plaque psoriasis; results through Week 48 for patients initially treated with CZP are presented here

Figure 1. Structure of TNF Blocking Agents



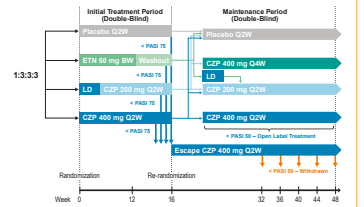
Fab: fragment antigen-binding; Fc: fragment crystallizable; IgG: immunoglobulin G; PEG: polyethylene glycol

METHODS

Study Design

- CIMPACT is an ongoing phase 3, randomized, multinational, parallel-group, placebo- and active-controlled trial
- Patients were randomized 3:3:1:3 to CZP 400 mg every 2 weeks (Q2W), CZP 200 mg Q2W (after an initial loading dose of 400 mg at Weeks 0, 2, and 4), or placebo Q2W for 16 weeks or ETN twice weekly for 12 weeks (**Figure 2**)
- At Week 16, CZP- and ETN-treated PASI 75 responders were re-randomized and continued for 32 weeks of maintenance treatment:
  - From CZP 400 mg Q2W to 400 mg Q2W, 200 mg Q2W, or placebo Q2W
  - From CZP 200 mg Q2W to 400 mg every 4 weeks (Q4W), 200 mg Q2W, or placebo Q2W
  - From ETN to CZP 200 mg Q2W (after loading dose) or placebo Q2W
- At Week 16, placebo-treated PASI 75 responders continued placebo Q2W for 32 weeks of maintenance treatment
- At Week 16, PASI 75 nonresponders entered an Escape Arm for treatment with CZP 400 mg Q2W

Figure 2. Study Design



BW, twice weekly; 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 50, ≥50% reduction in psoriasis area and severity index (PASI); PASI 75, ≥75% reduction in PASI; Q2W, every 2 weeks; Q4W, every 4 weeks

Patients

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

Study Assessments

- The primary endpoint was PASI 75 (≥75% reduction in PASI; CZP vs placebo) responder rate at Week 12
- Secondary endpoints included:
  - PGA 0/1 ('clear' or 'almost clear' with ≥2-category improvement; CZP vs placebo), PASI 90 (≥90% reduction in PASI; CZP vs placebo), and PASI 75 (CZP vs ETN) responder rates at Week 12; PASI 75, PGA 0/1, and PASI 90 responder rates (CZP vs placebo) at Week 16
  - PASI 75 responder rate at Week 48 for Week 16 PASI 75 responders
- Other efficacy variables included:
  - PGA 0/1 and PASI 90 responder rates at Week 48 for Week 16 PASI 75 responders
- Safety evaluation included treatment-emergent adverse events (TEAEs), physical examinations, clinical laboratory parameters, and blood pressure monitoring

Statistical Analysis

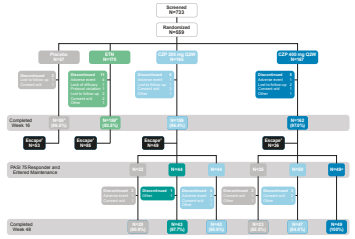
- Week 12 and Week 16 PASI 75, PGA 0/1, and PASI 90 responder rates were analyzed via a logistic regression model with factors for treatment, region, and prior biologic exposure (yes/no); the Markov chain Monte Carlo (MCMC) method[7] for multiple imputation was used to account for missing data
- Multiplicity was controlled for the primary and secondary endpoints via a fixed-sequence testing procedure
- Week 48 PASI 75, PGA 0/1, and PASI 90 responder rates were based on nonresponse imputation and are summarized using descriptive statistics

RESULTS

Patient Disposition, Demographics, and Baseline Characteristics

- Of 559 patients randomized, 535 (95.7%) completed Week 16 (**Figure 3**)
- Of 234 CZP-treated PASI 75 responders who were re-randomized into the Maintenance Period of the trial, 222 (94.9%) completed Week 48 (**Figure 3**)
- Patient demographics and Baseline characteristics were similar between groups (**Table 1**)

Figure 3. Patient Disposition



*Placebo-treated PASI 75 responders at Week 16 (N=2) continued placebo
†ETN-treated PASI 75 responders at Week 16 (N=74) were re-randomized to placebo (N=24) or CZP 200 mg Q2W (N=50)
‡PASI 75 nonresponders at Week 16 entered the escape arm for treatment with CZP 400 mg Q2W
§Two patients completed Week 16 but did not enter Maintenance Period (1 loss to follow-up, 1 consent withdrawn)
CZP 400 mg Q4W: BW, twice per week; CZP, certolizumab pegol; ETN, etanercept; PASI 75, ≥75% reduction in psoriasis area and severity index; Q2W, every 2 weeks; Q4W, every 4 weeks; wd, withdrawn

Table 1. Patient Demographics and Baseline Disease Characteristics

	Placebo (N=57)	ETN (N=170)	CZP 200 mg Q2W (N=165)	CZP 400 mg Q2W (N=167)
Demographics				
Age (years), 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 Central/Eastern Europe Western Europe	10 (17.5) 36 (63.2) 11 (19.3)	29 (17.1) 111 (65.3) 30 (17.6)	26 (15.8) 107 (64.8) 32 (19.4)	27 (16.2) 109 (65.3) 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/m²), 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 (years), 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
BSA (%), mean ± SD	24.3 ± 13.8	27.5 ± 15.5	28.1 ± 16.7	27.6 ± 15.3
PGA, n (%) 3: moderate 4: severe	40 (70.2) 17 (29.8)	115 (67.6) 55 (32.4)	114 (69.1) 51 (30.9)	113 (67.7) 54 (32.3)
DLQI, mean ± SD	13.2 ± 7.6	14.1 ± 7.4	12.8 ± 7.0	15.3 ± 7.3
Prior biologic use,* n (%) anti-TNF anti-IL17	11 (19.3) 5 (8.8) 8 (14.0)	51 (30.0) 8 (4.7) 39 (22.9)	44 (26.7) 4 (2.4) 38 (23.0)	48 (28.7) 4 (2.4) 35 (21.0)

*Patients may have had exposure to >1 prior biologic but ≤2 per exclusion criteria
BMI, body mass index; BSA, body surface area; CZP, certolizumab pegol; DLQI, Dermatology Life Quality Index; ETN, etanercept; IL, interleukin; PASI, psoriasis area and severity index; PGA, physician's global assessment; Q2W, every 2 weeks; SD, standard deviation; TNF, tumor necrosis factor

Efficacy

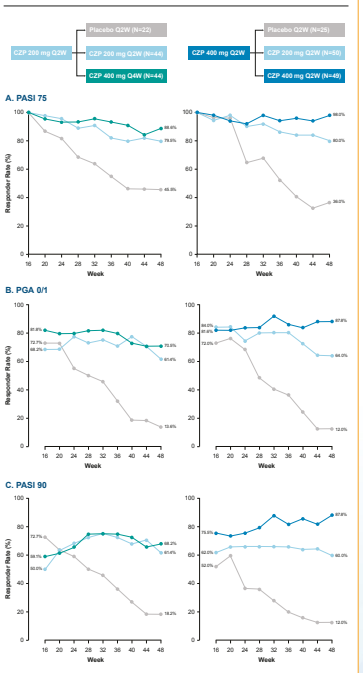
Baseline to Week 16

- At Week 12, PASI 75 responder rates were higher for CZP 400 mg Q2W and CZP 200 mg Q2W versus placebo (66.7% and 61.3% vs 5.0%; p<0.0001 for both)
- Also at Week 12, responder rates were greater for CZP 400 mg Q2W and CZP 200 mg Q2W versus placebo for PGA 0/1 (50.3% and 39.8% vs 1.9%; p<0.0001 and p=0.0004, respectively) and PASI 90 (34.0% and 31.2% vs 0.2%, p<0.0001 for both)
- At Week 16, responder rates were greater for CZP 400 mg Q2W and CZP 200 mg Q2W versus placebo for PASI 75 (74.7% and 68.2% vs 3.8%), PGA 0/1 (58.4% and 48.3% vs 3.4%), and PASI 90 (49.1% and 39.8% vs 0.3%) (p<0.0001 for all)
- CZP 400 mg Q2W achieved superiority to ETN at Week 12 (p=0.0152); CZP 200 mg Q2W achieved noninferiority to ETN at Week 12 (95% confidence interval: -2.9–18.9, within the prespecified noninferiority margin of 10%)

Week 16 to Week 48

- Among Week 16 PASI 75 responders, Week 48 PASI 75 (**Figure 4A**), PGA 0/1 (**Figure 4B**), and PASI 90 (**Figure 4C**) responder rates were greater in the patients re-randomized to CZP compared with placebo, with the highest rates seen among patients receiving CZP 400 mg Q2W in both the Initial and Maintenance Periods

Figure 4. PASI 75, PGA 0/1, and PASI 90 Responder Rates From Week 16 to Week 48 in Week 16 PASI 75 Responders



Missing data were imputed using nonresponse imputation
CZP, certolizumab pegol; PASI 75, ≥75% reduction in psoriasis area and severity index (PASI); PASI 90, ≥90% reduction in PASI; PGA 0/1, 'clear' or 'almost clear' with ≥2-category improvement in physician's global assessment (5-point scale); Q2W, every 2 weeks; Q4W, every 4 weeks

Safety

- From Baseline to Week 12, TEAE/serious TEAE incidence rates per 100 patient-years were 309.2/10.6 for CZP 400 mg Q2W, 299.5/2.7 for CZP 200 mg Q2W, 393.3/41.0 for placebo, and 295.6/2.7 for ETN
- From Baseline to Week 48
  - Percentage of patients experiencing any TEAE was similar between CZP 400 mg Q2W and CZP 200 mg Q2W groups and few patients discontinued due to TEAEs (**Table 2**)
  - Serious TEAEs were infrequent in the CZP groups (**Table 2**)
    - From Baseline to Week 48, incidence rates of serious infections and infestations per 100 patient-years were 2.9 for CZP 400 mg Q2W and 1.9 for CZP 200 mg Q2W
    - 1 patient in the Escape Arm, after 22 weeks of CZP 400 mg Q2W (combined Initial and Maintenance Periods), was diagnosed with primary progressive multiple sclerosis during evaluation for low back pain. The subject reported a 2-year history of recurrent falls (none during study), and an MRI revealed lesions consistent with MS; this event was unrelated to treatment according to the Investigator

Table 2. Adverse Events From Baseline to Week 48 by CZP Dose Taken at Time of TEAE

	CZP 200 mg Q2W[a,b] (N=265)	CZP 400 mg Q2W[b] (N=354)
TEAEs, n (%) [incidence rate[c]] Any Drug-related[d] Serious	175 (66.0) [214.0] 40 (15.1) 12 (4.5) [7.7]	230 (65.0) [201.3] 58 (16.4) 23 (6.5) [11.3]
Discontinuations due to TEAE, n (%)	4 (1.5)	11 (3.1)
Deaths, n (%)	0	0
Most frequently reported TEAEs (≥5% in any group), n (%) [incidence rate[c]]		
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]
TEAEs of interest, n (%) [incidence rate[c]]		
Infections and infestations	108 (40.8) [93.8]	132 (37.3) [79.7]
Serious infections and infestations	3 (1.1) [1.9][e]	6 (1.7) [2.9][f]
Multiple sclerosis	0	1 (0.3) [0.5][g]
Microscopic colitis	0	1 (0.3) [0.5]
Depression	4 (1.5) [2.5]	1 (0.3) [0.5]
Malignancy	0	2 (0.6) [1.0][h]

[a]Patients who switched doses could have been counted in both CZP doses
[b]Patients receiving CZP 400 mg Q4W were included in the CZP 200 mg Q2W group (same cumulative monthly dose)
[c]Incidence of new cases per 100 patient-years
[d]Incidence rate not calculated
[e]Gastroenteritis, pancreas infection, and pneumonia
[f]Escherichia coli sepsis and pyelonephritis in the same subject, endophthalmitis, pneumonia, sepsis, erysipelas, and tuberculosis
[g]Primary progressive multiple sclerosis; incidental finding during evaluation for low back pain and considered unrelated to treatment according to the Investigator
[h]Anaplastic oligodendroglioma, keratoacanthoma
CZP, certolizumab pegol; TEAE, treatment-emergent adverse event; Q2W, every 2 weeks

CONCLUSIONS

- CZP 400 mg Q2W and CZP 200 mg Q2W demonstrated statistically significant and clinically meaningful improvements in signs and symptoms of moderate-to-severe chronic plaque psoriasis versus placebo at Weeks 12 and 16
- CZP 400 mg Q2W was superior and CZP 200 mg Q2W was noninferior to ETN for PASI 75 responder rate at Week 12
- Among CZP-treated Week 16 PASI 75 responders, those who were re-randomized to CZP continued to have clinically meaningful responses in PASI 75, PGA 0/1, and PASI 90 through Week 48 that were well above the responses observed for those re-randomized to placebo
  - Across efficacy endpoints, treatment with CZP 400 mg Q2W in both the Initial and Maintenance Periods provided greater efficacy than either reducing the dose to CZP 200 mg Q2W after PASI 75 was achieved or treatment with CZP 200 mg Q2W in both the Initial and Maintenance Periods
  - The maintenance dosing regimens of CZP 200 mg Q2W and CZP 400 mg Q4W (same cumulative monthly dose) provided similar efficacy
  - Patients initially treated with CZP and re-randomized to placebo had a considerable loss of efficacy over time; no episodes of rebound were reported
- The safety profile of CZP appears to be consistent with the known safety profile of anti-TNF therapy in patients with moderate-to-severe chronic plaque psoriasis; no new safety signals were identified with either dose through 48 weeks of treatment

References

1. Rachakonda et al. *J Am Acad Dermatol.* 2014;70(3):512-6. **2.** Kurd et al. *J Am Acad Dermatol.* 2009;60(2):218-24. **3.** Danielsen et al. *Br J Dermatol.* 2013;168(6):1303-10. **4.** Farber et al. *Dermatologica.* 1974;148(1):1-18. **5.** Gottlieb et al. Oral presentation at: 75th Annual Meeting of the American Academy of Dermatology; March 3-7, 2017; Orlando, FL. Abstract 5077. **6.** Lebwohl et al. Poster presentation at: 13th Annual Maui Derm for Dermatologists; March 20-24, 2017; Maui, HI. Abstract 3120. **7.** Sun. Application of Markov Chain Monte-Carlo Multiple imputation method to deal with missing data from the mechanism of MNAR in sensitivity analysis for a longitudinal clinical trial. In: Chen et al. *Monte-Carlo Simulation-Based Statistical Modeling.* Singapore, Springer; 2017:233-52.

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