# Safety of Certolizumab Pegol in Chronic Plaque Psoriasis: Cumulative Data over 48 Weeks' Exposure from Phase 3, Multicenter, Randomized, Placebo-Controlled Studies

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## OBJECTIVE

- To assess cumulative 48-week safety data from all phase 3 trials in the clinical development program of certolizumab pegol for the treatment of moderate-to-severe chronic plaque psoriasis.

## SYNOPSIS

- Plaque psoriasis (PSO) is a chronic, immune-mediated, inflammatory disease affecting ~3% of adults in the US,[1,2] and ~2–6% in Europe.[3]
- Certolizumab pegol (CZP), the only Fc-free, PEGylated, anti-tumor necrosis factor (TNF) biologic, is approved for the treatment of adults with rheumatoid arthritis, psoriatic arthritis, Crohn's disease (US), ankylosing spondylitis and non-radiographic axial spondyloarthritis (EU).
- CZP has demonstrated promising results in the treatment of adults with moderate-to-severe PSO in phase 2[4] and phase 3 trials, where clinical and patient reported improvements were shown over 16 weeks of treatment and maintained through 48 weeks.[5,6,7]

## METHODS

### Patients

- Data were pooled from three ongoing phase 3 trials of CZP in adults with PSO: CIMPASI-1 [NCT02326298], CIMPASI-2 [NCT02326272], and CIMPACT [NCT02346240].
- The trials enrolled adults with PSO ≥6 months with Psoriasis Area Severity Index [PASI] ≥12, ≥10% body surface area [BSA] affected, and physician's global assessment [PGA] ≥3 on a 5-point scale.
- For the initial period (Weeks 0–16), patients were randomized to subcutaneous CZP 400 mg every two weeks (Q2W), 200 mg Q2W (following 400 mg loading dose at Weeks 0, 2 and 4), placebo Q2W, or etanercept (ETN) 50 mg twice weekly (BIW) for 12 weeks in CIMPACT **(Figure 1)**.
- At Week 16, patients entered the double-blind maintenance period (Weeks 16–48). In CIMPASI-1 and CIMPASI-2 those classed as responders (PASI 50) continued at the same dose. In CIMPACT, responders (PASI 75) were re-randomized to CZP or placebo **(Figure 1)**.

### Safety Assessments

- 48-week safety data were pooled across studies for patients receiving ≥1 dose of CZP during the initial and/or maintenance periods of the studies, with up to 48 weeks of exposure as of the cut off dates 20 October 2016 (CIMPASI-1), 16 August 2016 (CIMPASI-2), 5 December 2016 (CIMPACT).
- 16-week safety data were pooled across studies for patients receiving ≥1 dose of CZP during the initial period of the studies.
- Adverse events (AEs) and serious adverse events (SAEs) were classified according to the Medical Dictionary for Regularity Activities (MedDRA) v.18.1.
- An SAE was defined as an AE meeting one or more of the following criteria: death, life-threatening, significant or persistent disability/incapacity, congenital anomaly/birth defect, important medical event, initial or prolonged inpatient hospitalization.
- Incidence rates (IR) were calculated as incidence of new cases per 100 patient-years (PY).

## RESULTS

### Patient Population

- Across all three studies, a total of 962 patients received ≥1 dose CZP during Weeks 0–48: 460 received CZP 200 mg Q2W and 627 received 400 mg CZP Q2W.
- Baseline demographics are shown in **Table 1**.

### Incidence of Adverse Events and Serious Adverse Events

- Over 48 weeks of CZP treatment, 709 patients (73.7%) experienced ≥1 AE **(Table 2)**.
  - All CZP (n=962), IR=219.6 (95% confidence interval [CI]=203.7–236.4)
  - CZP 200 mg Q2W (n=460), IR=221.2 (95% CI=197.6, 246.7)
  - CZP 400 mg Q2W (n=627), IR=228.6 (95% CI= 207.8, 250.9)
- IR of AEs did not increase with longer exposure duration. In patients with up to 16 weeks of exposure, AE IRs were:
  - All CZP (n=692), IR=319.1 (95% CI=289.1–351.4)
  - CZP 200 mg Q2W (n=350), IR=292.1 (95% CI=252.8–335.9)
  - CZP 400 mg Q2W (n=342), IR=348.3 (95% CI=303.5–397.9)
  - Placebo (n=157), IR=342.6 (95% CI=277.8, 417.9)
- Over 48 weeks of CZP treatment, IR was similar across both the CZP 200 mg Q2W and CZP 400 mg Q2W dose groups **(Table 2)**.
- 64 CZP-treated patients (6.7%) reported SAEs across the 48 weeks **(Table 2)**.
- 1 death occurred during the 48-week period due to a motor vehicle accident **(Table 2)**.

### Adverse Events of Interest

- Selected SAEs are shown in **Table 4**.
- The rate of serious infections was low **(Table 4)**, comparable with other anti-TNFs in this indication.
  - There was 1 case of active tuberculosis (TB) in a patient who received ETN during the initial 16-week period before switching to CZP 400 mg Q2W **(Table 4)**. TB was diagnosed 172 days after ETN initiation, 60 days after CZP initiation. The patient discontinued the study.
  - No other opportunistic infections were reported.
- There were no reports of serious skin disorders such as Steven Johnson or lupus.
- Overall, 9 patients experienced Fungal Infections (High Level Term), IR=1.2 (95% CI=0.6, 2.4), including 1 case of fungal skin infection and 1 case of oral fungal infection, both in patients receiving CZP 400 mg Q2W.
- There were 3 reports of oral candidiasis, 1 in a patient receiving CZP 200 mg Q2W, IR=0.3 (95% CI=0.0, 1.8) and 2 reports in patients receiving CZP 400 mg Q2W, IR=0.5 (95% CI=0.1, 1.7). There was 1 case of skin candida in a patient receiving CZP 400 mg Q2W, IR=0.2 (95% CI=0.0, 1.3).
- Malignancies were reported in 4 patients receiving CZP 400 mg Q2W **(Table 4)**, including 1 case of anaplastic oligodendroglioma, 2 cases of basal cell carcinoma and 1 case of keratoacanthoma.

### Table 2. Overview of AEs and SAEs during Weeks 0–48 across CIMPASI-1, CIMPASI-2 and CIMPACT

| | All CZP (N=962) | | CZP 200 mg Q2W (N=460) | | CZP 400 mg Q2W (N=627) | |
|---|---|---|---|---|---|---|
| | IR/100 PY (95% CI) | n (%) | IR/100 PY (95% CI) | n (%) | IR/100 PY (95% CI) | n (%) |
| Total AEs | 219.6 (203.7, 236.4) | 709 (73.7) | 221.2 (197.6, 246.7) | 321 (69.8) | 228.6 (207.8, 250.9) | 444 (70.8) |
| Severe | 7.5 (5.6, 9.8) | 53 (5.5) | 6.2 (3.8, 9.7) | 19 (4.1) | 8.3 (5.8, 11.6) | 34 (5.4) |
| Drug-related | 29.6 (25.5, 34.1) | 187 (19.4) | 28.5 (22.6, 35.6) | 78 (17.0) | 31.4 (25.9, 37.7) | 115 (18.3) |
| AEs leading to withdrawal | 5.0 (3.5, 6.9) | 36 (3.7) | 3.9 (2.0, 6.8) | 12 (2.6) | 5.8 (3.7, 8.6) | 24 (3.8) |
| Total SAEs | 9.1 (7.0, 11.6) | 64 (6.7) | 7.6 (4.8, 11.4) | 23 (5.0) | 10.1 (7.3, 13.8) | 41 (6.5) |
| AEs leading to death | 0.1 (0.0, 0.8) | 1 (0.1) | 0 | 0 | 0.2 (0.0, 1.3) | 1 (0.2) |

Patients who received both CZP 200 mg Q2W and CZP 400 mg Q2W are included in the population count for the 'All CZP' group. Total exposure for all CZP patients from Baseline to Week 48=730 PY.

### Table 3. Most commonly reported AEs (≥3% patients) during Weeks 0–48 across CIMPASI-1, CIMPASI-2 and CIMPACT

| | All CZP (N=962) | | CZP 200 mg Q2W (N=460) | | CZP 400 mg Q2W (N=627) | |
|---|---|---|---|---|---|---|
| | IR/100 PY (95% CI) | n (%) | IR/100 PY (95% CI) | n (%) | IR/100 PY (95% CI) | n (%) |
| Nasopharyngitis | 28.5 (24.5, 33.0) | 181 (18.8) | 29.3 (23.2, 36.4) | 80 (17.4) | 29.7 (24.3, 35.8) | 109 (17.4) |
| Upper repiratory tract infection | 13.3 (10.7, 16.3) | 91 (9.5) | 13.4 (9.5, 18.3) | 39 (8.5) | 13.9 (10.5, 18.2) | 55 (8.8) |
| Hypertension | 6.5 (4.8, 8.7) | 46 (4.8) | 6.0 (3.6, 9.5) | 18 (3.9) | 6.9 (4.6, 10.0) | 28 (4.5) |
| Headache | 6.1 (4.4, 8.2) | 43 (4.5) | 6.0 (3.5, 9.4) | 18 (3.9) | 6.4 (4.2, 9.4) | 26 (4.1) |
| Arthralgia | 5.1 (3.5, 7.0) | 36 (3.7) | 6.3 (3.8, 9.8) | 19 (4.1) | 4.2 (2.4, 6.6) | 17 (2.7) |

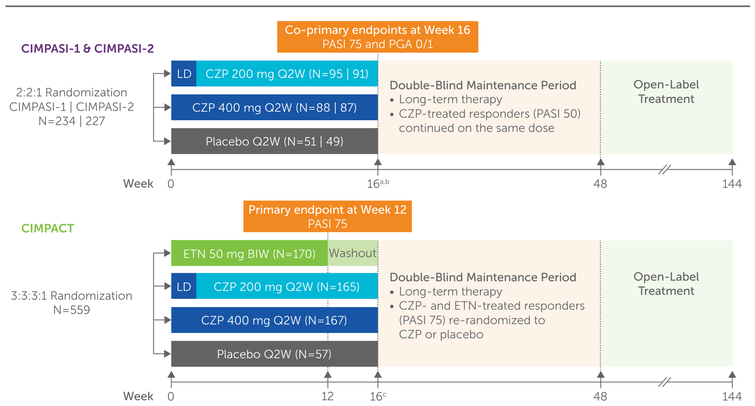
Patients who received both CZP 200 mg Q2W and CZP 400 mg Q2W are included in the population count for the 'All CZP' group. Total exposure for all CZP patients from Baseline to Week 48=730 PY.

### Table 4. Selected AEs and SAEs of interest during Weeks 0–48 across CIMPASI-1, CIMPASI-2 and CIMPACT

| | All CZP (N=962) | | CZP 200 mg Q2W (N=460) | | CZP 400 mg Q2W (N=627) | |
|---|---|---|---|---|---|---|
| | IR/100 PY (95% CI) | n (%) | IR/100 PY (95% CI) | n (%) | IR/100 PY (95% CI) | n (%) |
| Serious infections | 1.5 (0.8, 2.7) | 11 (1.1) | 1.0 (0.2, 2.8) | 3 (0.7)[a] | 1.9 (0.8, 3.8) | 8 (1.3)[b] |
| Active tuberculosis | 0.1 (0.0, 0.8) | 1 (0.1) | 0 | 0 | 0.2 (0.0, 1.3) | 1 (0.2) |
| Primary progressive multiple sclerosis | 0.1 (0.0, 0.8) | 1 (0.1) | 0 | 0 | 0.2 (0.0, 1.3) | 1 (0.2)[c] |
| Congestive heart failure | 0.1 (0.0, 0.8) | 1 (0.1) | 0 | 0 | 0.2 (0.0, 1.3) | 1 (0.2) |
| Malignancies (excluding non-melanoma skin cancer) | 0.1 (0.0, 0.8) | 1 (0.1) | 0 | 0 | 0.2 (0.0, 1.3) | 1 (0.2)[d] |
| Non-melanoma skin cancer | 0.4 (0.1, 1.2) | 3 (0.3) | 0 | 0 | 0.7 (0.2, 2.1) | 3 (0.5)[e] |

Patients who received both CZP 200 mg Q2W and CZP 400 mg Q2W are included in the population count for the 'All CZP' group. Total exposure for all CZP patients from Baseline to Week 48=730 PY. [a]Gastroenteritis, pancreas infection and pneumonia. [b]*Escherichia coli* sepsis and pyelonephritis in the same patient; abdominal abscess and haematoma in the same patient related to a bicycle accident; endophthalmitis, pneumonia, sepsis, tuberculosis, each in 1 patient; erysipelas in 2 patients. [c]Primary progressive multiple sclerosis was an incidental finding during evaluation for low back pain (no AEs during study) and considered unrelated to treatment by the Investigator. [d]Anaplastic oligodendroglioma. [e]Two cases of basal cell carcinoma and 1 keratoacanthoma.

### Figure 1. Study design for CIMPASI-1, CIMPASI-2 and CIMPACT phase 3 trials




[a]In CIMPASI-1/-2, PASI 50 non-responders 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 then CZP 200 mg Q2W; [c]In CIMPACT, PASI 75 non-responders at Week 16 entered the Escape Arm for treatment with open label CZP 400 mg Q2W. ETN: etanercept; LD: loading dose; PASI: psoriasis area and severity index; PGA: physician global assessment.

### Table 1. Pooled demographics and baseline characteristics for patients exposed to CZP during Weeks 0–48 across CIMPASI-1, CIMPASI-2 and CIMPACT

| | All CZP (N=962) | CZP 200 mg Q2W (N=460) | CZP 400 mg Q2W (N=627) |
|---|---|---|---|
| Patient Characteristics | | | |
| Age, years, mean (SD) | 45.6 (13.1) | 45.6 (13.2) | 45.4 (12.9) |
| Male, n (%) | 633 (65.8) | 312 (67.8) | 403 (64.3) |
| Caucasian, n (%) | 906 (94.2) | 438 (95.2) | 587 (93.6) |
| BMI, mean (SD) | 30.4 (7.1) | 30.5 (6.8) | 30.4 (7.1) |
| Disease duration, years, mean (SD) | 18.3 (12.4) | 18.6 (12.8) | 17.9 (12.0) |
| Prior Treatment, n (%) | | | |
| Biologic therapy | | | |
| 0 | 674 (70.1) | 322 (70.0) | 443 (70.7) |
| 1 | 220 (22.9) | 105 (22.8) | 139 (22.2) |
| 2 | 67 (7.0) | 33 (7.2) | 44 (7.0) |
| ≥3 | 1 (0.1) | 0 | 1 (0.2) |
| Anti-TNF | 119 (12.4) | 57 (12.4) | 71 (11.3) |
| Anti-IL-17 | 142 (14.8) | 78 (17.0) | 89 (14.2) |
| Anti-IL-12/IL-23 | 47 (4.9) | 15 (3.3) | 39 (6.2) |

Patients who received both CZP 200 mg Q2W and CZP 400 mg Q2W are included in the population count for the All CZP group. BMI: body mass index; IL: interleukin; SD: standard deviation.

## CONCLUSIONS

- Across all available safety data for patients treated with CZP for up to 48 weeks in phase 3 clinical trials of PSO, the safety profile was as expected for this therapeutic class.
- Number and type of AEs and SAEs reported was similar between CZP 400 mg Q2W and 200 mg Q2W treatment groups, and overall IR for AEs did not increase with treatment duration.
- These studies show that CZP, an anti-TNF biologic, affords a novel treatment option for psoriasis patients.

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