Long-Term Safety of Certolizumab Pegol in Plaque Psoriasis: Pooled Analysis over 3 Years from Three Phase 3, Randomized, Placebo-Controlled Studies

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OBJECTIVE

- To report cumulative three-year safety data from three phase 3 trials of certolizumab pegol in plaque psoriasis.

BACKGROUND

- Certolizumab pegol (CZP) is an Fc-free, PEGylated, anti-tumor necrosis factor (TNF) biologic, which has been approved by the FDA and EMA for moderate to severe plaque psoriasis (PSO).[1,2]
- CZP has shown a safety profile consistent with the anti-TNF class in adults with PSO over 96 weeks in phase 3 trials.[3]
- Given that PSO is a chronic disease that can require management over much of a patient's lifetime, it is important to establish the long-term safety profile of treatments.[4]
- Here, we report cumulative safety data, pooled from three CZP in PSO phase 3 trials over 144 weeks, from a total of 995 patients.

METHODS

Patients and Study Design

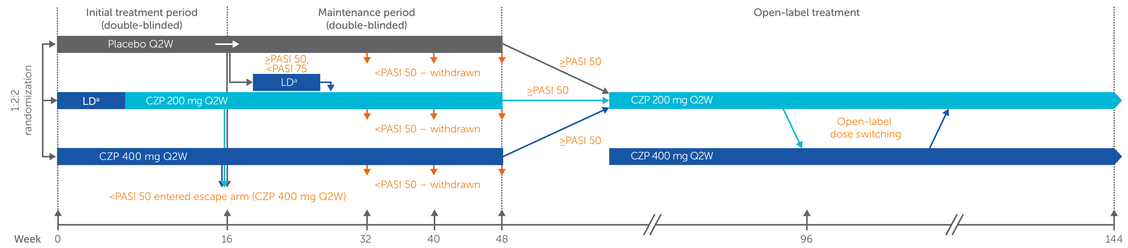
- Pooled safety data are presented for patients who received ≥1 dose of CZP during the 144 weeks of the CIMPASI-1 (NCT02326298), CIMPASI-2 (NCT02326272), or CIMPACT (NCT02346240) phase 3 studies **(Figure 1)**.
- Only 11 placebo-randomized patients continued on placebo after Week 16; placebo data are presented to Week 16 only.
- Inclusion criteria: ≥18 years of age with PSO for ≥6 months with Psoriasis Area and Severity Index (PASI) ≥12, ≥10% body surface area (BSA) affected, physician's global assessment (PGA) ≥3 on a 5-point scale; candidates for systemic PSO therapy, phototherapy and/or photochemotherapy.
- Exclusion criteria: previous treatment with CZP or >2 biologics; previous treatment with etanercept (ETN) (CIMPACT only); treatment with ETN within the first 12 weeks of enrolment (CIMPASI-1 and CIMPASI-2 only); history of primary failure to any biologic or secondary failure to >1 biologic; erythrodermic, guttate or generalized PSO types; history of or current, chronic or recurrent viral, bacterial or fungal infections.

Safety Assessments

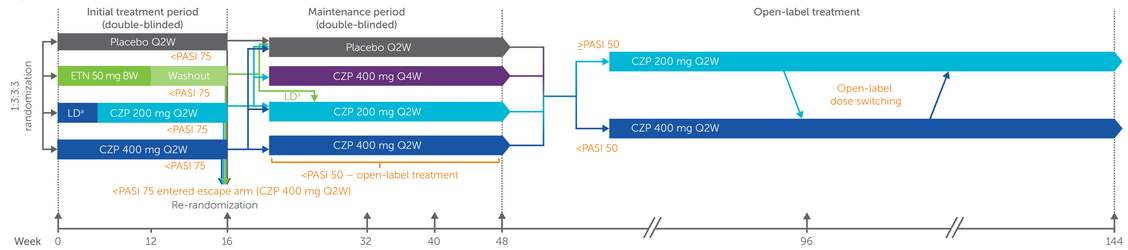
- Safety data were analyzed for the dose-combined CZP-treated group (All CZP) and separately for each CZP dose.
- For patients exposed to both doses of CZP over the course of the studies, treatment-emergent adverse events (TEAEs) were assigned to the dose being received at the time of onset, but each patient was counted in the All CZP group only once.
- TEAEs and serious TEAEs were classified using MedDRA version 18.1.
- Serious TEAEs were defined as those meeting one or more of the following criteria: life-threatening, leading to death, hospitalization, congenital anomalies/birth defects, medically significant (based upon medical judgement), infections requiring intravenous antibiotics, or leading to persistent or significant disability.
- Incidence rates (IR) were calculated as the number of new cases per 100 patient-years (PY).

Figure 1. CIMPASI-1, CIMPASI-2, and CIMPACT study designs

A) CIMPASI-1 and CIMPASI-2



B) CIMPACT



Dose adjustments were permitted during the open-label periods of all three studies, and were either mandatory or at the discretion of the investigator. Data collected during treatment with CZP 400 mg Q4W in CIMPACT were summarized under the CZP 200 mg Q2W treatment group.
[a]Loading dose of CZP 400 mg Q2W at Weeks 0, 2 and 4 or Weeks 16, 18, and 20. BW: twice per week; CZP: certolizumab pegol; ETN: etanercept; LD: loading dose; PASI: Psoriasis Area Severity Index; Q2W: every two weeks; Q4W: every four weeks.

Table 1. Pooled demographics and baseline characteristics for patients who received ≥1 dose CZP through Weeks 0–144

	All CZP[a] (N=995)	CZP 400 mg Q2W (n=728)	CZP 200 mg Q2W[b] (n=731)
Baseline demographics and disease characteristics			
Age, years, mean ± SD	45.6 ± 13.2	45.7 ± 13.1	45.3 ± 13.1
Male, n (%)	652 (65.5)	472 (64.8)	491 (67.2)
BMI, kg/m², mean ± SD	30.4 ± 7.0	30.6 ± 7.1	30.2 ± 6.7
PSO disease duration, years, mean ± SD	18.2 ± 12.5	18.2 ± 12.4	18.4 ± 12.6
PASI, mean ± SD	20.2 ± 7.8	20.2 ± 7.7	20.1 ± 7.8
Prior treatments			
Biologic therapy, n (%)	299 (30.1)	220 (30.2)	221 (30.2)
Anti-TNF	123 (12.4)	88 (12.1)	94 (12.9)
Anti-IL-17	149 (15.0)	106 (14.6)	109 (14.9)
Anti-IL-12/IL-23	49 (4.9)	43 (5.9)	30 (4.1)
Systemic therapy for PSO, n (%)	714 (71.8)	532 (73.1)	529 (72.4)

[a]Patients who received both CZP 200 mg Q2W and CZP 400 mg Q2W are only included once in the population count for the 'All CZP' group; [b]CZP 200 mg Q2W patients received a loading dose of CZP 400 mg at Weeks 0, 2, and 4 or Weeks 16, 18, and 20. BMI: body mass index; CZP: certolizumab pegol; IL: interleukin; PASI: Psoriasis Area Severity Index; PSO: psoriasis; Q2W: every two weeks; SD: standard deviation; TNF: tumor necrosis factor.

Table 2. Overview of TEAEs in CZP-treated patients to Week 144

	All CZP[a] (N=995)		CZP 400 mg Q2W (N=728)		CZP 200 mg Q2W[b] (N=731)	
Total exposure, PY	2,231		1,020		1,211	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Total TEAEs	847 (85.1)	144.9 (135.3, 155.0)	563 (77.3)	158.3 (145.5, 171.9)	557 (76.2)	134.1 (123.2, 145.7)
Total Serious TEAEs	154 (15.5)	7.5 (6.4, 8.8)	82 (11.3)	8.7 (6.9, 10.8)	76 (10.4)	6.7 (5.2, 8.3)
TEAEs leading to discontinuation	88 (8.8)	4.0 (3.2, 4.9)	48 (6.6)	4.7 (3.5, 6.3)	41 (5.6)	3.4 (2.5, 4.6)
Severe TEAEs	132 (13.3)	6.3 (5.3, 7.5)	70 (9.6)	7.2 (5.6, 9.1)	66 (9.0)	5.7 (4.4, 7.2)
TEAEs leading to death	7 (0.7)[c]	0.3 (0.1, 0.7)	3 (0.4)	0.3 (0.1, 0.9)	4 (0.5)	0.3 (0.1, 0.9)

[a]Patients who received both CZP 200 mg Q2W and CZP 400 mg Q2W are only included once in the population count for the 'All CZP' group; [b]CZP 200 mg Q2W patients received a loading dose of CZP 400 mg at Weeks 0, 2, and 4 or Weeks 16, 18, and 20; [c]One case each of acute myocardial infarction, cardiac arrest (due to liver failure and vasodilatory shock in association with hemorrhagic pancreatic necrosis), pneumonia *Legionella*, cirrhosis alcoholic, chronic obstructive pulmonary disease, craniocerebral injury, and multiple injuries, the first two of which were considered related to the study drug by the investigator. CI: confidence interval; CZP: certolizumab pegol; IR: incidence rate; PY: patient-years; Q2W: every two weeks; TEAE: treatment-emergent adverse event.

Table 3. Cumulative TEAEs over time at Weeks 16, 48, 96, and 144

		All CZP[a]	CZP 400 mg Q2W	CZP 200 mg Q2W[b]	Placebo
Week 16	Exposure, PY	211	105	107	47
	n/N (%)	414/692 (59.8)	217/342 (63.5)	197/350 (56.3)	97/157 (61.8)
	IR (95% CI)	319.1 (289.1, 351.4)	348.3 (303.5, 397.9)	292.1 (252.8, 335.9)	342.6 (277.8, 417.9)
Week 48	Exposure, PY	729	418	311	
	n/N (%)	709/962 (73.7)	444/627 (70.8)	321/460 (69.8)	–
	IR (95% CI)	219.6 (203.7, 236.4)	228.6 (207.8, 250.9)	221.2 (197.6, 246.7)	
Week 96	Exposure, PY	1,471	700	772	
	n/N (%)	820/995 (82.4)	528/711 (74.3)	514/726 (70.8)	–
	IR (95% CI)	172.7 (161.1, 184.9)	186.4 (170.9, 203.0)	161.4 (147.8, 176.0)	
Week 144	Exposure, PY	2,231	1,020	1,211	
	n/N (%)	847/995 (85.1)	563/728 (77.3)	557/731 (76.2)	–
	IR (95% CI)	144.9 (135.3, 155.0)	158.3 (145.5, 171.9)	134.1 (123.2, 145.7)	

[a]Patients who received both CZP 200 mg Q2W and CZP 400 mg Q2W are only included once in the population count for the 'All CZP' group; [b]CZP 200 mg Q2W patients received a loading dose of CZP 400 mg at Weeks 0, 2, and 4 or Weeks 16, 18, and 20. CZP: certolizumab pegol; IR: incidence rate; PY: patient-years; Q2W: every two weeks; TEAE: treatment-emergent adverse event.

Table 4. Selected TEAEs and Serious TEAEs of interest

	All CZP[a] (N=995)		CZP 400 mg Q2W (N=728)		CZP 200 mg Q2W[b] (N=731)	
Total exposure, PY	2,231		1,020		1,211	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Serious infections	32 (3.2)	1.5 (1.0, 2.1)	16 (2.2)	1.6 (0.9, 2.6)	16 (2.2)	1.3 (0.8, 2.2)
Active tuberculosis	1 (0.1)	0.0 (0.0, 0.3)	1 (0.1)[d]	0.1 (0.0, 0.6)	0 (0.0)	0 (0.0, 0.0)
Demyelinating-like disorders	2 (0.2)	0.1 (0.0, 0.3)	1 (0.1)[e]	0.1 (0.0, 0.6)	1 (0.1)[f]	0.1 (0.0, 0.5)
Major adverse cardiac events (MACE)[c]	9 (0.9)	0.4 (0.2, 0.8)	4 (0.5)[g]	0.4 (0.1, 1.0)	5 (0.7)[h]	0.4 (0.1, 1.0)
Congestive heart failure	1 (0.1)	0.0 (0.0, 0.3)	1 (0.1)	0.1 (0.0, 0.6)	0 (0.0)	0 (0.0, 0.0)
All malignancies	14 (1.4)	0.6 (0.3, 1.1)	8 (1.1)	0.8 (0.3, 1.6)	8 (1.1)	0.7 (0.3, 1.3)
Malignancies excluding NMSC	10 (1.0)	0.5 (0.2, 0.8)	4 (0.5)[i]	0.4 (0.1, 1.0)	7 (1.0)[j]	0.6 (0.2, 1.2)
NMSC	5 (0.5)	0.2 (0.1, 0.5)	4 (0.5)[k]	0.4 (0.1, 1.0)	1 (0.1)[l]	0.1 (0.0, 0.5)

[a]Patients who received both CZP 200 mg Q2W and CZP 400 mg Q2W are only included once in the population count for the 'All CZP' group; [b]CZP 200 mg Q2W patients received a loading dose of CZP 400 mg at Weeks 0, 2, and 4 or Weeks 16, 18, and 20; [c]Inclusive of fatal and non-fatal myocardial infarction, serious cerebrovascular events and congestive heart failure (regardless of seriousness); [d]Patient with negative QuantiFERON TB GOLD test and normal chest X-ray before study entry who was randomized to ETN, entered CZP 400 mg Q2W escape arm at Week 16, and was diagnosed 60 days after CZP initiation and discontinued the study; [e]One case of primary progressive multiple sclerosis (medical history indicated that symptoms pre-dated study entry); [f]One case of multiple sclerosis; [g]Includes one each of heart failure, congestive heart failure, acute coronary syndrome, extradural hematoma; [h]Includes one each of acute myocardial infarction, angina pectoris and cerebrovascular accident, and two transient ischemic attack; [i]Includes one each of adenocarcinoma of colon, anaplastic oligodendroglioma, prostate cancer, clear cell renal cell carcinoma; [j]Includes one each of breast cancer, glioblastoma, Hodgkin's disease, laryngeal cancer, non-small cell lung cancer, oropharyngeal squamous cell carcinoma, prostate cancer; [k]Includes three basal cell carcinomas and one keratoacanthoma; [l]One basal cell carcinoma. CI: confidence interval; CZP: certolizumab pegol; ETN: etanercept; IR: incidence rate; NMSC: non-melanoma skin cancer; PY: patient-years; Q2W: every two weeks; TEAE: treatment-emergent adverse event.

RESULTS

Patient Population

- Across all three studies, a total of 995 patients received ≥1 dose CZP through Weeks 0–144.
- Baseline characteristics were well balanced between the two treatment groups **(Table 1)**.

Incidence of TEAEs

- At Week 144, the IR of TEAEs and serious TEAEs was comparable between CZP dose groups **(Table 2)**.
- The most common TEAEs, reported in ≥10% of patients, were nasopharyngitis (IR: 14.2; 95% CI: 12.5, 16.0) and upper respiratory tract infection (IR: 7.9; 95% CI: 6.7, 9.3).
- The IR of TEAEs for CZP-treated patients did not increase with longer exposure **(Table 3)**.

Selected TEAEs and Serious TEAEs of Interest

- At Week 144 the overall incidences of selected TEAEs of interest and serious TEAEs of interest were low and were comparable between dose groups **(Table 4)**.
- There were 7 deaths, 2 of which were assessed by the investigator as related to the study drug **(Table 2)**.
- The IRs of serious infections and malignancies were low, and were comparable between dose groups **(Table 4)**.
- There was 1 case of active tuberculosis (TB) in a patient who lived in a country with a high TB prevalence **(Table 4)**.
- There were no reports of serious skin disorders or hypersensitivity reactions, and no cases of lupus or lupus-like events.

CONCLUSIONS

- No new safety signals were identified compared to previous studies in CZP.
- The risk of TEAEs did not increase with longer or higher CZP exposure.
- The safety profiles of the two CZP doses were similar.

References

1. Certolizumab Pegol Prescribing Information. Available at www.accessdata.fda.gov /scripts/cder/daf/index.cfm; **2.** Certolizumab Pegol Summary of Product Characteristics. Available at www.ema.europa.eu/ema; **3.** Blauvelt A *et al.* JEADV 2019;33(suppl 3):21–2; **4.** Gisondi P *et al.* Int J Mol Sci 2017;18:2427.

Author Contributions

Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: AB, CP, PvdK, RBW, ABG, RGL, FB, CA, MB, ML, KR; Drafting of the publication, or revising it critically for important intellectual content: AB, CP, PvdK, RBW, ABG, RGL, FB, CA, MB, ML, KR; Final approval of the publication: AB, CP, PvdK, RBW, ABG, RGL, FB, CA, MB, ML, KR.

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