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Stable plasma concentration of certolizumab pegol is associated with persistent clinical improvement among patients with moderate to severe plaque psoriasis: Data from CIMPASI-1 and CIMPASI-2

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Objective

To report certolizumab pegol (CZP) plasma concentrations in parallel with skin clearance and quality of life over 3 years of treatment.

Background

- CZP is an Fc-free, PEGylated, anti-tumour necrosis factor biologic that has shown sustained clinical improvements in patients with moderate to severe plaque psoriasis.[1–3]
- High plasma concentrations of biologic therapies are associated with improved clinical outcomes, and are desirable for durable efficacy during long-term treatment.[4]
- On the basis of phase III clinical trial data in patients with psoriasis, a population exposure–response relationship has been established between plasma concentration of CZP and Psoriasis Area and Severity Index (PASI) with an EC90 (concentration of drug that induces 90% maximal response) of 11.1 µg/mL.[5]
- Here, plasma levels of CZP are reported alongside mean PASI and Dermatology Life Quality Index (DLQI) scores over 3 years of treatment.

Methods

- Data were pooled from the CIMPASI-1 and CIMPASI-2 phase 3 trials (**Figure 1**).[1]
- CZP plasma concentrations (geometric mean and median), and PASI and DLQI (mean and median) are reported through Week 144 for patients initially randomised to CZP 200 mg or 400 mg every 2 weeks (Q2W) and for those randomised to placebo who entered the CZP 400 mg Q2W escape arm at Week 16.
- Data are reported as observed case (OC), with patients included as part of a dosage group at a given week if they received the stated CZP dose at that visit (they may have received a higher or lower dose in previous weeks).

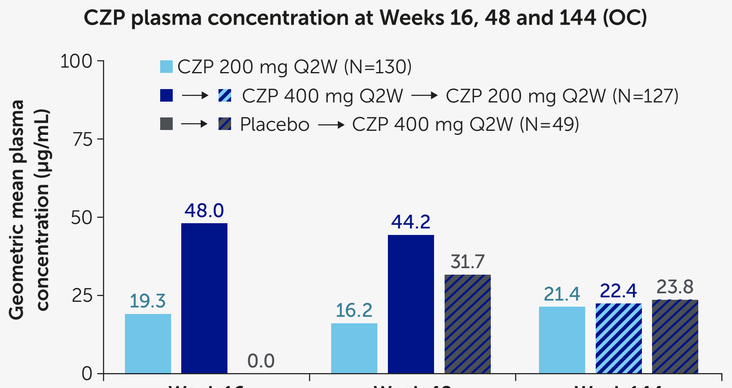
Results

- At baseline, 186 patients were randomised to CZP 200 mg Q2W and 175 to CZP 400 mg Q2W, while 72 placebo-randomised patients entered the CZP 400 mg Q2W escape arm at Week 16 (**Table 1**).
- For all randomisation groups, plasma concentrations of CZP increased rapidly after treatment initiation and occurred in parallel with improvements in PASI and DLQI scores (**Figure 2A–C**; **Table 2**).
- For patients randomised to CZP 200 mg Q2W, geometric mean plasma concentrations increased rapidly in response to a loading dose of CZP 400 mg at Weeks 0, 2 and 4 and concentrations observed at Week 16 were stable through Week 144 (**Figure 2A**).
- CZP plasma concentrations were higher through Week 48 for patients randomised to CZP 400 mg Q2W, and decreased to levels comparable to those seen in the CZP 200 mg Q2W group following Week 48 dose reduction to 200 mg Q2W (**Figure 2B**).
- Plasma levels of CZP increased following initiation of CZP 400 mg Q2W treatment at Week 16 in patients initially randomised to placebo and were maintained thereafter through Week 144 (**Figure 2C**).

Conclusions

CZP plasma levels remained stable and above the established EC90 of 11.1 µg/mL over 3 years of treatment, and were observed to occur in parallel with clinical and quality of life improvements.

Summary



Results and conclusions

Plasma levels of CZP were maintained and stable over 3 years:

- Week 16 CZP plasma levels were maintained over 3 years for patients initially randomised to CZP 200 mg Q2W.
- For placebo-randomised patients who entered the CZP 400 mg Q2W escape arm at Week 16, plasma levels of CZP increased following initiation of CZP treatment and were maintained thereafter through Week 144.
- In parallel, improvements in PASI and DLQI were observed in the first 16 weeks of treatment, which were maintained over 3 years.

Table 2 Median CZP plasma concentrations, PASI and DLQI scores over 3 years (OC)

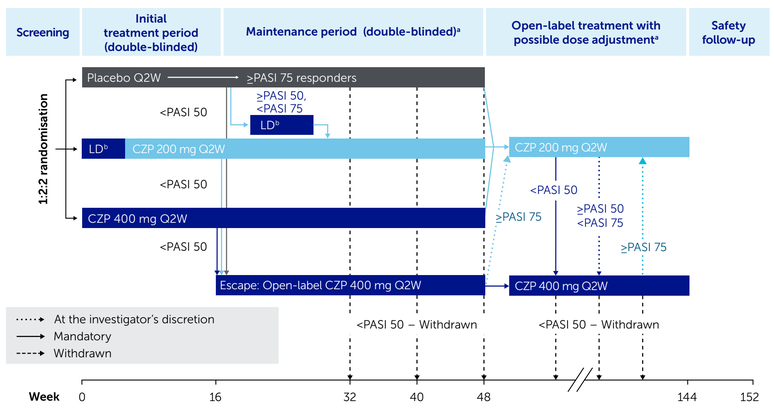
	CZP 200 mg Q2W[a] (N=130)			CZP 400 mg Q2W[b] (N=127)			Placebo escapers[c] (N=49)		
	Week 0	Week 16	Week 144	Week 0	Week 16	Week 144	Week 0	Week 16	Week 144
Median plasma concentration, µg/mL	0.00	25.40	23.08	0.00	57.43	22.42	0.00	0.00	41.82
PASI, median	16.65	1.60	0.60	18.20	1.70	0.80	17.60	16.80	1.60
DLQI, median	14.00	1.00	1.00	14.00	1.00	1.00	12.00	9.00	1.00

Pharmacokinetic set. [a]CZP 400 mg at Weeks 0/2/4; [b]CZP 200 mg from Week 48 onwards; [c]CZP 400 mg Q2W from Week 16 onwards.

Table 1 Baseline characteristics

	CZP 200 mg Q2W (N=186)	CZP 400 mg Q2W (N=175)	Placebo escapers (N=72)
Age (years), mean ± SD	45.6 ± 13.2	45.0 ± 12.9	46.7 ± 13.1
Caucasian, n (%)	173 (93.0)	160 (91.4)	64 (88.9)
Male, n (%)	125 (67.2)	103 (58.9)	48 (66.7)
Weight (kg), mean ± SD	95.1 ± 23.4	92.0 ± 24.8	91.6 ± 21.6
BMI, mean ± SD	32.0 ± 7.8	31.2 ± 7.9	31.1 ± 7.2
Duration of psoriasis (years), mean ± SD	17.7 ± 12.9	18.5 ± 12.6	16.9 ± 11.9
PASI, mean ± SD	19.2 ± 7.2	19.6 ± 7.3	18.3 ± 6.3
BSA (%), mean ± SD	23.5 ± 14.9	23.6 ± 14.3	22.4 ± 13.8
PGA, n (%)			
3: moderate	128 (68.8)	126 (72.0)	53 (73.6)
4: severe	58 (31.2)	49 (28.0)	19 (26.4)
DLQI, mean ± SD	14.3 ± 7.4	13.7 ± 6.9	12.9 ± 7.4
Any prior systemic therapy for psoriasis, n (%)	131 (70.4)	124 (70.9)	52 (72.2)
Prior biologic therapy, n (%)	62 (33.3)	59 (33.7)	23 (31.9)
anti-TNF	44 (23.7)	40 (22.9)	14 (19.4)
anti-IL-17	16 (8.6)	8 (4.6)	4 (5.6)
anti-IL-12/23	3 (1.6)	10 (5.7)	6 (8.3)

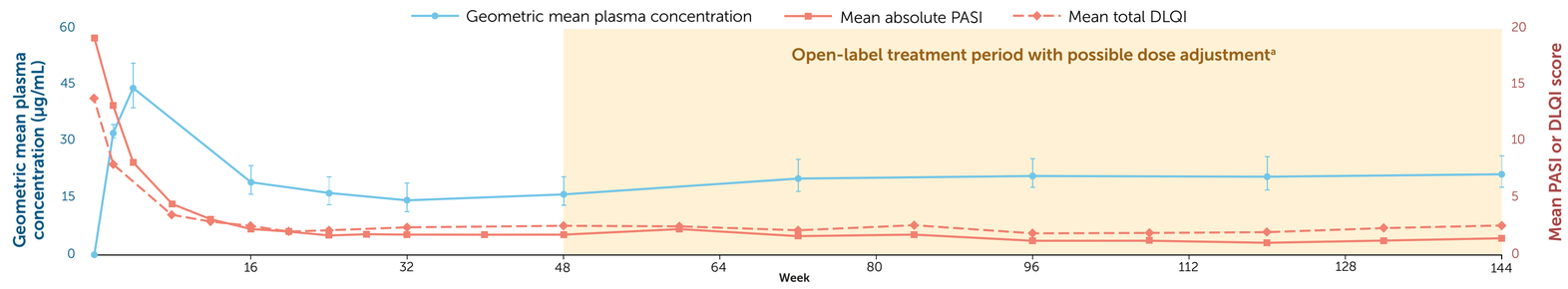
Figure 1 Study design (CIMPASI-1 and CIMPASI-2)



[a]Dose adjustments were mandatory or at the investigator's discretion, based on PASI response; [b]Loading dose of CZP 400 mg Q2W at Weeks 0, 2 and 4 or Weeks 16, 18 and 20.

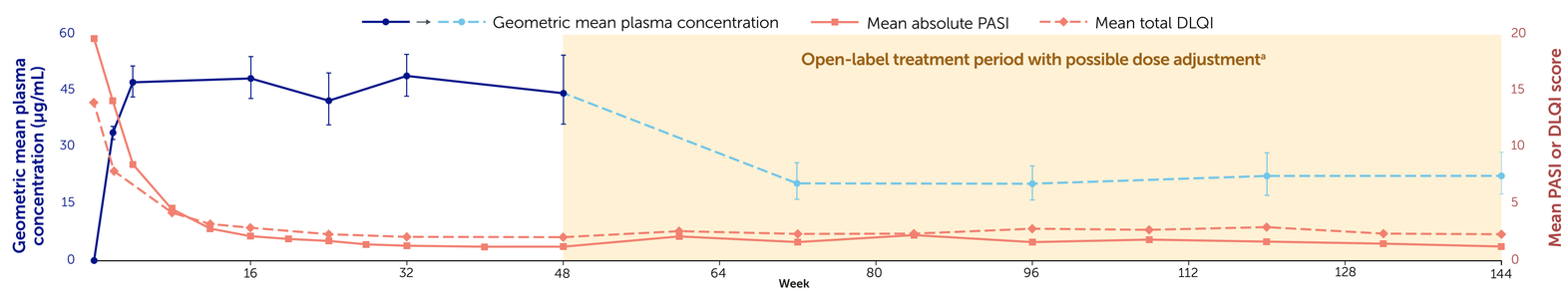
Figure 2 Geometric mean CZP plasma levels versus mean PASI and DLQI (OC)

A) CZP 200 mg Q2W (400 mg at Weeks 0/2/4; N=130)



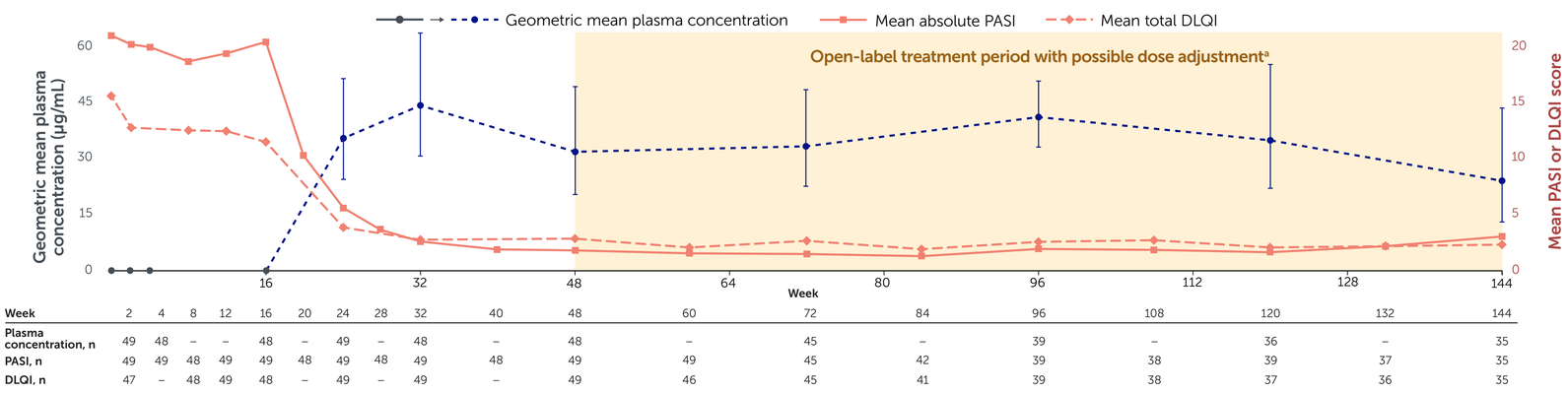
Week	2	4	8	12	16	20	24	28	32	40	48	60	72	84	96	108	120	132	144
Plasma concentration, n	128	128	–	–	126	–	123	–	125	–	128	–	110	–	92	–	79	–	72
PASI, n	129	129	128	129	130	128	127	128	127	130	130	128	110	103	95	91	83	74	73
DLQI, n	129	–	124	128	130	–	126	–	126	–	130	124	109	98	93	91	83	72	73

B) CZP 400 mg Q2W (200 mg from Week 48 onwards; N=127)



Week	2	4	8	12	16	20	24	28	32	40	48	60	72	84	96	108	120	132	144
Plasma concentration, n	126	127	–	–	124	–	122	–	120	–	125	–	110	–	91	–	76	–	68
PASI, n	127	127	127	126	127	124	124	126	125	124	127	125	92	105	92	86	81	73	69
DLQI, n	126	–	126	124	127	–	124	–	124	–	127	121	109	102	92	85	81	71	69

C) Placebo to CZP 400 mg Q2W open-label escape arm at Week 16 (N=49)



Week	2	4	8	12	16	20	24	28	32	40	48	60	72	84	96	108	120	132	144
Plasma concentration, n	49	48	–	–	48	–	49	–	48	–	48	–	45	–	39	–	36	–	35
PASI, n	49	49	48	49	49	48	49	48	49	48	49	49	45	42	39	38	39	37	35
DLQI, n	47	–	48	49	48	–	49	–	49	–	49	46	45	41	39	38	37	36	35

Pharmacokinetic set. [a]Dose adjustments were mandatory or at the investigator's discretion, based on PASI response. During the OLE, only patients receiving the stated dose (CZP 200 mg Q2W in Figure 2A and 2B and CZP 400 mg Q2W in Figure 2C) were included in the analysis at a given week. Geometric mean (the root of the product of a set of values) plasma concentrations are reported. Errors bars represent 95% confidence intervals.

BMI: body mass index; **BSA:** body surface area; **CZP:** certolizumab pegol; **DLQI:** Dermatology Life Quality Index; **EC90:** the concentration of drug that induces 90% maximal response; **IL:** interleukin; **OC:** observed case; **PASI:** Psoriasis Area and Severity Index; **PASI 50/75:** ≥50/≥75% improvement from baseline in PASI; **PGA:** Physician's Global Assessment; **Q2W:** every 2 weeks; **SD:** standard deviation; **TNF:** tumour necrosis factor.

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