Population PK and PASI Exposure-Response Modelling for Certolizumab Pegol in Patients with Chronic Plaque Psoriasis

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OBJECTIVES

- To characterise the pharmacokinetics of certolizumab pegol in patients with psoriasis, and the exposure-response relationship between certolizumab pegol and Psoriasis Area and Severity Index.

BACKGROUND

- Certolizumab pegol (CZP) is an Fc-free PEGylated anti-tumour necrosis factor (anti-TNF) antibody fragment.
- CZP is approved for several autoimmune diseases (rheumatoid arthritis, psoriatic arthritis, Crohn's disease [in the United States], axial spondyloarthritis) and has recently been approved for plaque psoriasis (PSO).[1]
- This poster describes the population pharmacokinetics of CZP and exposure-response for PASI in patients with PSO, using data from three Phase 3 trials.

METHODS

Data

- Clinical studies: three Phase 3 studies of CZP in PSO (CIMPASI-1 [NCT02326298], CIMPASI-2 [NCT02326272] and CIMPACT [NCT02346240]).
- Population: patients with moderate to severe PSO.
- Dosing regimens: placebo, or CZP 400 mg every 2 weeks (Q2W), or CZP 400mg at Weeks 0, 2 and 4 followed by CZP 200 mg Q2W. Patients with inadequate PASI response at Week 16 were transitioned to different CZP dosing regimens.
- PK data up to Week 48 and PASI data up to Week 16 were included.
- Route: subcutaneous.
- PK sampling at Weeks 0, 2, 4, 16, 24, 36 and 48.
- PASI observations at Weeks 0, 2, 4, 8, 12 and 16.
- Numbers in the analysis sets: 820 patients with 4,361 PK observations and 834 patients with 4,919 PASI observations.

PopPK and Exposure-Response Methodology

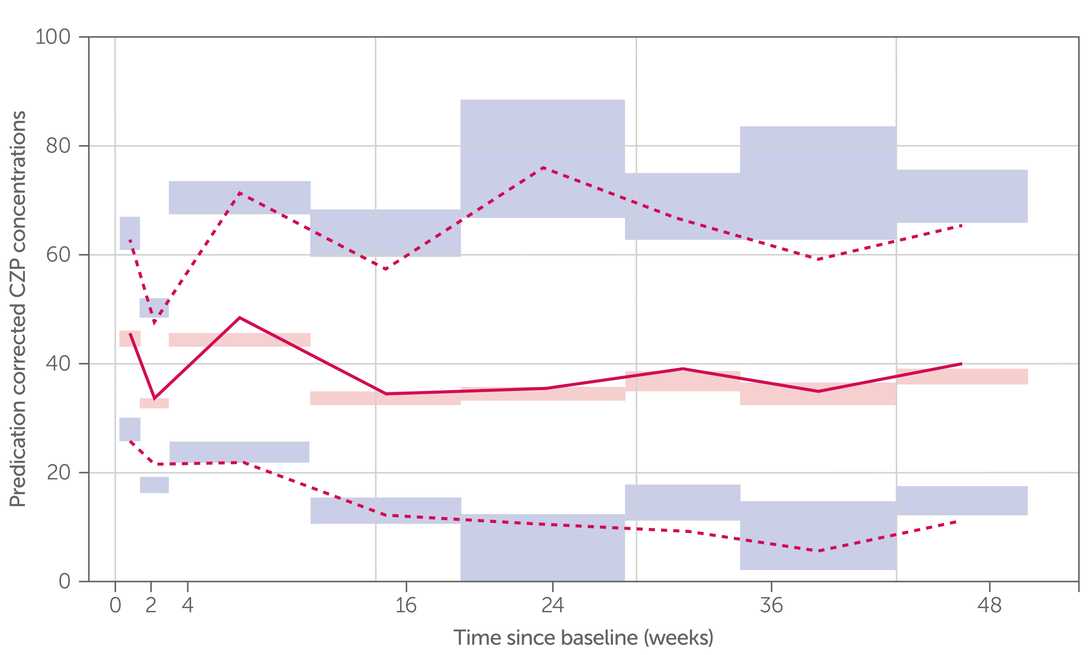
- A one-compartment model was used for the popPK, in line with previous knowledge of CZP PK.
- PASI was treated as a continuous variable. Logit transformation was used to account for the lower and upper bounds of the PASI scale.
- The covariates tested in the PK model were age, body weight, body surface area, body mass index, gender and anti-drug (CZP) antibodies (ADA).
- In the exposure-response model the following additional covariates were tested: baseline PASI, disease duration, prior biologic treatment and geographical region.
- The stepwise covariate modeling approach was used in the covariate motel with forward addition ($p<0.01$) followed by backward elimination ($p<0.001$).
- The models were developed in NONMEM Version 7.3.0. / PsN version 4.6.0.

Table 1. CZP population PK model parameters

	Value (RSE in %)	IIV (CV%) (RSE in %)
k_a (h^{-1})	0.251 (4.90)	–
CL/F (L/day)	0.338 (1.37)	22.2 (3.61)
V/F (L)	4.71 (2.17)	15.2 (16.3)
ADA impact on CL/F	2.31 (12.0)	–
WT impact on V/F	0.512 (11.1)	–
WT impact of CL/F	0.943 (3.86)	–
Covariance (CL/F-V/F)	0.101 (62.0)	–
Proportional Error (%)	16.8	7.90
Additive Error (µg/mL)	5.13	9.38

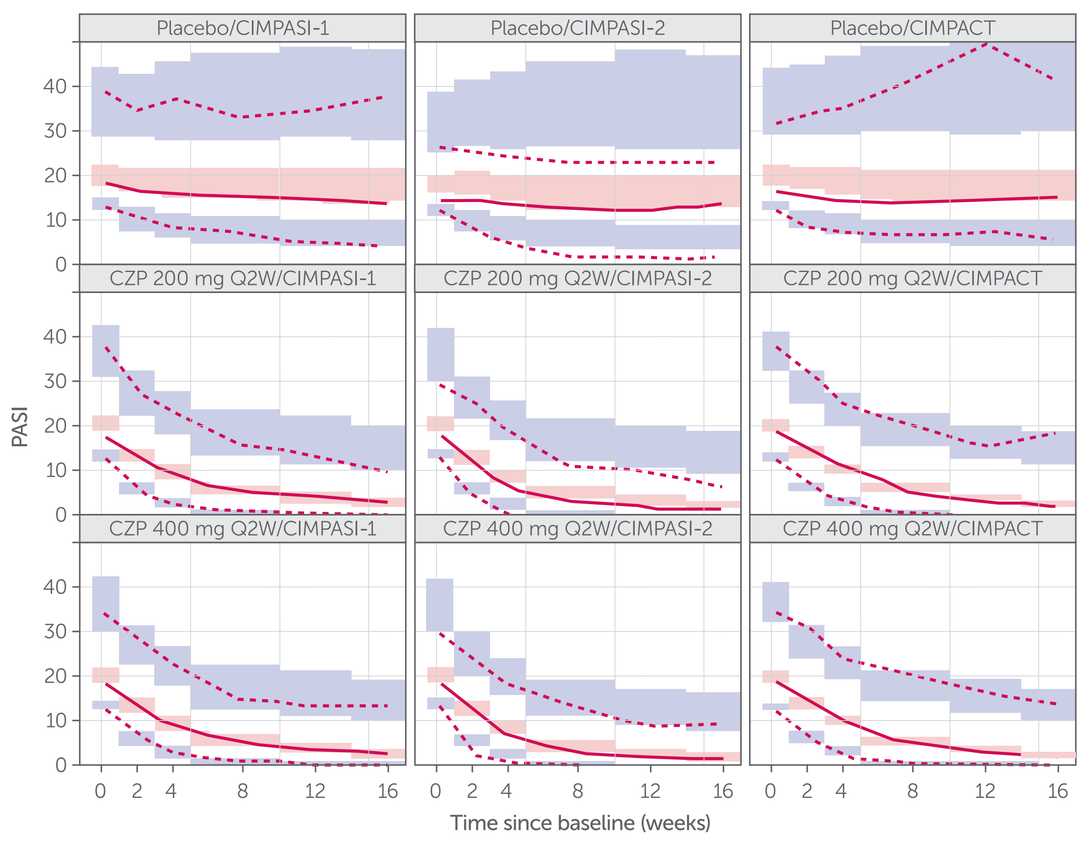
ADA: anti-drug (CZP) antibodies; IIV: interindividual variability; RSE: relative standard error; WT: body weight.

Figure 1. pcVPC for the popPK model



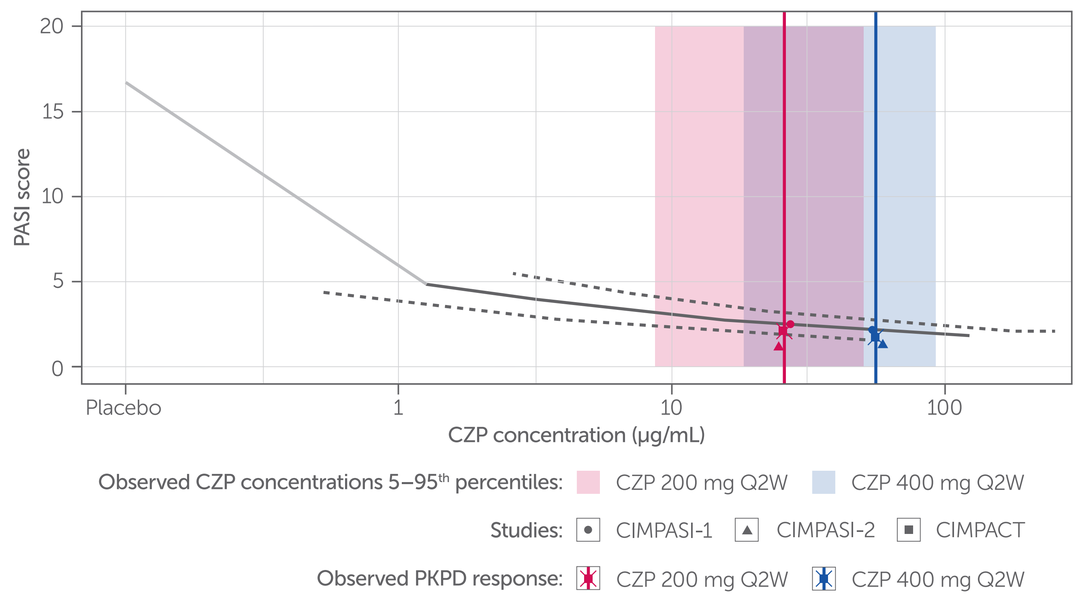
Solid and dashed lines represent the median and 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 95% CI of the median and 5th and 95th percentiles predicted by the model; pcVPC: prediction corrected visual predictive check.

Figure 2. VPC for the PASI exposure-response model



Solid and dashed lines represent the median and 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 95% CI of the median and 5th and 95th percentiles predicted by the model; pcVPC: prediction corrected visual predictive check.

Figure 3. Illustration of the predicted relationship between PASI score and CZP C_{trough} at Week 16



The solid line represents the predicted median of PASI score and the gray line is an extrapolation to placebo patients. The dotted lines represent the 95% CI of the predicted PKPD relationship. The symbols are the observed median PKPD responses by study and the crosses the observed median for all studies. The areas represent the 5-95th percentiles of the observed C_{trough} at week 16 and the vertical line the median.

RESULTS

Population PK Model

- One-compartment model with first order absorption and first order elimination from the central compartment.
- No deviation from dose proportionality.
- Body weight was a covariate of apparent clearance and apparent volume of distribution and the presence of anti-CZP antibodies increased the apparent clearance **(Table 1)**.

PASI Exposure-Response Model

- The relationship between CZP exposure and PASI was described with an indirect response model including the following components:
  - Placebo model accounting for both increase and decrease in PASI.
  - Drug model with a sigmoidal E_{max} function inhibiting the production of PASI response:

    $dPASI/dt = k_{in} \times (1\text{-}Drug_{effect}\text{-}Placebo_{effect}) - k_{out} \times PASI$
- EC_{90} was estimated as both dose regimens were at the upper part of the dose-exposure-response curve.
- The covariate analysis revealed that body weight was a significant covariate of PASI half-life with heavier patients taking longer to achieve maximum response **(Table 2)**.
- There were other statistically significant covariates but none were deemed to be clinically relevant.

Table 2. PASI exposure-response model parameters

	Value (RSE in %)	IIV (CV%) (RSE in %)
PASI baseline	19.0 (2.29)	91.0 (4.33)
PASI $t_{1/2}$ (days)	22.5 (4.94)	53.2 (5.85)
Placebo effect	0.143 (20.1)	71.3 (9.99)
EC_{90} (µg/mL)	11.1 (47.3)	515 (15.7)
Gamma	0.425 (17.2)	–
E_{max}	0.974 (0.228)	–
Prior biologics on baseline	0.340 (25.1)	–
Region NA on baseline	-0.323 (24.7)	–
Baseline on E_{max}	0.0711 (16.9)	–
WT on placebo	-0.00672 (31.4)	–
WT on PASI $t_{1/2}$	0.485 (28.1)	–
Region NA on PASI $t_{1/2}$	-0.192 (30.1)	–
Region WE on PASI $t_{1/2}$	0.216 (64.8)	–
ADA positivity on EC_{90}	47.7 (28.8)	–
Proportional error (%)	10.8 (6.93)	–
Additive error	0.233 (5.81)	–

ADA: anti-drug (CZP) antibodies; IIV: interindividual variability; NA: North America; RSE: relative standard error; WT: body weight.

CONCLUSIONS

- The popPK and PASI exposure-response models developed in these analyses characterise and describe well the observed CZP concentrations and PASI response from the Phase 3 studies in PSO.
- The two tested dose regimens were at the upper part of the dose-concentration-response curve.
- Body weight influences PASI half-life with heavier patients taking longer to achieve maximum response.

Author Contributions

Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: CS, MOM, PV, MZ; Drafting of the publication or revising it critically for important intellectual content: CS, MOM, PV, MZ; Final approval of the publication: CS, MOM, PV, MZ.

Author Disclosures

PV and **MZ:** Employees of UCB Pharma.

Acknowledgements

This study was funded by UCB Pharma. We thank the patients and the caregivers in addition to the investigators and their teams who contributed to the studies. Editorial services were provided by Helen Chambers, DPhil, Costello Medical, UK. All costs associated with development of this poster were funded by UCB Pharma.