Pharmacokinetics of Certolizumab Pegol in Pregnancy: Results from the Open-Label, Phase 1b CHERISH Study

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Objective

To investigate the longitudinal pharmacokinetics and safety of the use of certolizumab pegol during pregnancy and postpartum by measuring plasma certolizumab pegol concentration and monitoring treatment-emergent adverse events.

Background

- Approximately 50% of women of childbearing age with autoimmune diseases such as rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), psoriatic arthritis, plaque psoriasis (PSO) and Crohn's Disease require therapeutic intervention during pregnancy.[1] However, there are limited data on the pharmacokinetics (PK) of tumour necrosis factor inhibitors (TNFis) during pregnancy.
- Certolizumab pegol (CZP), a PEGylated Fc-free TNFi, may be used in adults for the treatment of these autoimmune diseases and has shown no to minimal placental transfer. We report results from the first longitudinal assessment of CZP PK during pregnancy.

Methods

- CHERISH (NCT04163016) was a multicenter, longitudinal, interventional, prospective, open-label phase 1b exploratory study evaluating the impact of pregnancy on the PK of CZP.
- Study design and sampling periods are illustrated in **Figure 1**.
  - All participants were receiving a stable maintenance dose of commercial CZP for an approved indication for at least 12 weeks prior to enrolment.
- The primary outcome was predose (≤4 hours before dosing) and postdose (7±1 days after the dose was administered) plasma CZP concentrations analysed by linear mixed effects model with fixed effects for disease phenotype, gestational week, trimester, and whether the sample was predose or postdose (binary indicator) in participants who received ≥1 commercial dose of CZP after enrolment (pharmacokinetic per protocol set).
  - Differences in overall plasma CZP concentrations during pregnancy versus (vs) postpartum were also adjusted for individual serum albumin, body mass index (BMI), and C-reactive protein (CRP).
  - Adjusted mean differences and 95% confidence intervals were estimated.
- Anti-CZP antibody positivity was also assessed (electrochemiluminescence immunoassay method).
- Safety was assessed in participants dosed with commercial CZP at screening (safety set).

Results

- Of the 21 enrolled participants (CZP 200 mg every two weeks [Q2W], n=15; CZP 400 mg Q2W, n=1; CZP 400 mg Q4W, n=5), 16 (76.2%) completed the study.
  - Baseline characteristics are reported in **Table 1**.
- The range of plasma CZP concentrations observed (**Figure 2**) was within the range of plasma concentrations observed in CZP studies of non-pregnant patients with PSO, axSpA and RA.[2–4]
- Plasma CZP concentrations were lower during pregnancy relative to postpartum; the reduction in plasma CZP concentration associated with pregnancy was consistent across trimesters 1 through 3 (**Figure 3**).
  - Mean differences in overall plasma CZP concentrations during pregnancy vs postpartum were reduced when accounting for individual serum albumin and BMI, but not CRP (**Table 3**).
- The safety profile observed in this study was consistent with the known safety profile of CZP (**Table 2**).[5]
  - 17 (81.0%) participants had a TEAE; the most common maternal TEAE was infections and infestations (n=12 [57.1%]).
  - No participant deaths, infant illnesses, or other safety concerns were reported.
- At enrolment, 85.7% were anti-CZP antibody positive, consistent with overall PSO, axSpA and RA populations.[6]
  - There was no clear change in anti-CZP antibody positivity over the course of pregnancy.

Conclusions

CZP PK data in pregnant patients show that CZP plasma concentration was reduced during pregnancy versus postpartum but was within the range observed in non-pregnant patients and remained consistent throughout pregnancy. The safety profile of CZP was consistent with the known safety profile of CZP in the general patient population. Findings in this study support continuation of CZP dosing during pregnancy.

Summary

Longitudinal pharmacokinetics and safety of certolizumab pegol during pregnancy and postpartum were assessed.

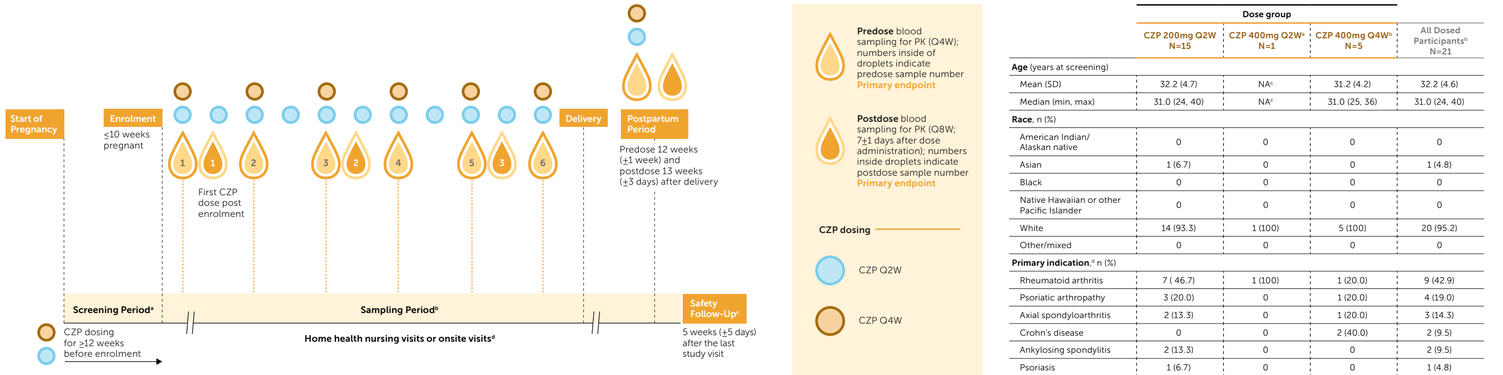
The range of plasma **CZP concentrations** observed was **within the range** of plasma concentrations observed in CZP studies of non-pregnant patients.

Plasma CZP concentrations were lower during pregnancy relative to postpartum; these differences were **reduced** when accounting for individual serum albumin and BMI, but not CRP.

The safety profile observed in this study was consistent with the known safety profile of CZP.

Findings in this study support continuation of CZP dosing during pregnancy.

Figure 1 Study design and sampling schedule



[a] WoCBA patients already on CZP could register interest in the study. After confirmation of pregnancy and consent to participate, women were eligible to enrol in the study once they had stable maintenance dosing for at least 12 weeks. [b] Pregnancy Period: PK samples were collected prior to the subsequent dose (predose) Q4W starting with the first dose after enrolment. Further, postdose (7±1 day after dose administration) PK samples were collected Q8W throughout the pregnancy. It was expected that there would be approximately 6 predose and 3 postdose PK samples collected per participant (if there were no discontinuations) over the pregnancy. Postpartum Period: A predose sample 12 weeks (±1 week) postpartum was collected during the Postpartum Period. If possible, 1 postdose sample 1 week (±1 day) after the 12 weeks postpartum dose was also collected. [c] Safety follow-up: All participants were contacted via telephone 5 weeks (±5 days) after final study visit. If any participant withdrew early, they completed the safety follow-up. [d] Timing and the number of visits across the pregnancy varied for individual participants.

Table 1 Baseline demographics and disease characteristics (enrolled set)

	Dose group			
	CZP 200mg Q2W N=15	CZP 400mg Q2W[a] N=1	CZP 400mg Q4W[b] N=5	All Dosed Participants[b] N=21
Age (years at screening)				
Mean (SD)	32.2 (4.7)	NA[c]	31.2 (4.2)	32.2 (4.6)
Median (min, max)	31.0 (24, 40)	NA[c]	31.0 (25, 36)	31.0 (24, 40)
Race, n (%)				
American Indian/ Alaskan native	0	0	0	0
Asian	1 (6.7)	0	0	1 (4.8)
Black	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
White	14 (93.3)	1 (100)	5 (100)	20 (95.2)
Other/mixed	0	0	0	0
Primary indication,[d] n (%)				
Rheumatoid arthritis	7 (46.7)	1 (100)	1 (20.0)	9 (42.9)
Psoriatic arthropathy	3 (20.0)	0	1 (20.0)	4 (19.0)
Axial spondyloarthritis	2 (13.3)	0	1 (20.0)	3 (14.3)
Crohn's disease	0	0	2 (40.0)	2 (9.5)
Ankylosing spondylitis	2 (13.3)	0	0	2 (9.5)
Psoriasis	1 (6.7)	0	0	1 (4.8)

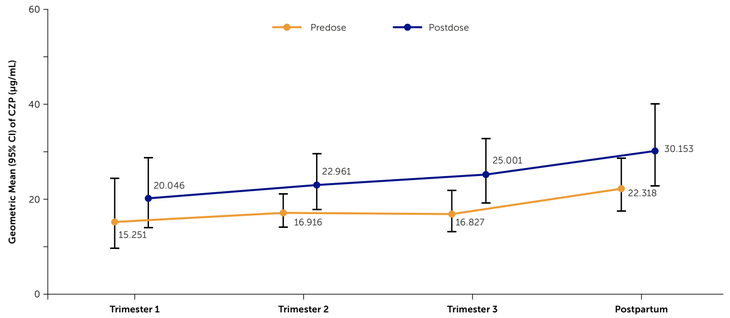
[a] One participant had their dose reduced from CZP 400mg Q2W to CZP 200mg Q2W. This participant was only counted once under the initial dose group. [b] One participant was not dosed while enrolled in the study; this participant subsequently re-enrolled and was included in the CZP 400mg Q4W group and the All Dosed Participants group. [c] Not applicable replaced summary statistics when the sample size satisfied the N=3 or N<3 rule. [d] This summary included medical conditions that were identified as the "Primary Condition" for CZP treatment on the case report form.

Table 2 Incidence of TEAEs (safety set)

n (%) [events]	Dose group			
	CZP 200mg Q2W N=15	CZP 400mg Q2W[a] N=1	CZP 400mg Q4W[b] N=5	All Dosed Participants[b] N=21
Any TEAEs	13 (86.7) [57]	1 (100) [1]	3 (60.0) [8]	17 (81.0) [66]
Serious TEAEs	4 (26.7) [4]	0	1 (20.0) [1]	5 (23.8) [5]
Severe TEAEs	2 (13.3) [2]	0	0	2 (9.5) [2]
Permanent withdrawal of CZP due to TEAEs	0	0	0	0
TEAEs requiring dose change	0	1 (100) [1]	0	1 (4.8) [1]
Drug-related TEAEs	1 (6.7) [1]	0	0	1 (4.8) [1]
Discontinuation due to TEAEs	1 (6.7) [1]	0	0	1 (4.8) [1]
All deaths (TEAEs leading to death)	0	0	0	0

[a] One participant had their dose reduced from CZP 400mg Q2W to CZP 200mg Q2W. This participant was only counted once under the initial dose group. [b] One participant was not dosed while enrolled in the study; this participant subsequently re-enrolled and was included in the CZP 400mg Q4W group and the All Dosed Participants group.

Figure 2 Plasma concentrations of CZP 200 mg Q2W (µg/mL) by trimester and postpartum



Pharmacokinetic per protocol set (patients treated with 200 mg Q2W only). Data points represent geometric means (µg/mL). Error bars represent geometric 95% CIs. Trimester 1 defined as ≤12 weeks and 6 days' gestation, trimester 2 defined as 13–28 weeks and 6 days' gestation, trimester 3 defined as ≥29 weeks' gestation.

Figure 3 Forest plot of mean changes relative to postpartum of CZP plasma concentrations (µg/mL) by trimester (mixed model)

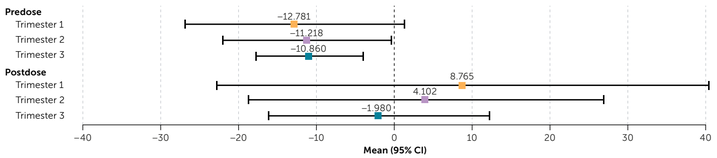


Table 3 Mean plasma concentration of CZP (µg/mL) change relative to postpartum by trimester (mixed models)

Adjusted mean difference (95% CI)	Trimester 1 vs postpartum (N=20)	Trimester 2 vs postpartum (N=20)	Trimester 3 vs postpartum (N=20)
Overall	−8.920 (−24.362, 6.521)	−7.308 (−18.951, 4.335)	−8.488 (−15.814, −1.162)
Adjusted for Albumin	−2.623 (−21.920, 16.673)	−0.712 (−17.418, 15.995)	−2.499 (−15.757, 10.759)
Adjusted for CRP	−8.754 (−24.730, 7.221)	−7.278 (−19.248, 4.693)	−8.611 (−16.143, −1.079)
Adjusted for BMI	−4.420 (−21.251, 12.412)	−3.182 (−16.389, 10.025)	−4.408 (−13.885, 5.069)

Pharmacokinetic per protocol set. Includes participants from the 200mg Q2W and 400 mg Q4W dosing regimens. Data from a linear mixed effects model adjusted for disease phenotype, gestational week, trimester (trimester 1, 2, 3 or postpartum), and whether the sample was predose or postdose (binary indicator), with study participant as the random effect. Data points represent adjusted mean changes differences (µg/mL). Error bars represent 95% CIs. Trimester 1 defined as ≤12 weeks and 6 days gestation, trimester 2 defined as 13–28 weeks and 6 days' gestation and trimester 3 defined as ≥29 weeks' gestation.

axSpA: axial spondyloarthritis; **BMI:** Body Mass Index; **CI:** confidence interval; **CRP:** C-reactive protein; **CZP:** certolizumab pegol; **Min:** minimum; **Max:** maximum; **NA:** not applicable; **PK:** pharmacokinetics; **PsA:** psoriatic arthritis; **PSO:** plaque psoriasis; **Q2W:** every 2 weeks; **Q4W:** every 4 weeks; **Q8W:** every 8 weeks; **RA:** rheumatoid arthritis; **SD:** standard deviation; **TEAE:** treatment-emergent adverse event; **TNFi:** tumour necrosis factor inhibitor; **vs:** versus; **WoCBA:** women of childbearing age.

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