# Lack of Placental Transfer of Certolizumab Pegol During Pregnancy: Results from CRIB, a Prospective, Postmarketing, Multicenter, Pharmacokinetic Study

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## OBJECTIVE

- To accurately measure the level of placental transfer of certolizumab pegol (CZP) from mothers to infants using a highly sensitive CZP-specific assay.

## BACKGROUND

- Women affected by chronic inflammatory diseases, such as psoriatic disease, need effective and safe treatments during pregnancy.[1,2]
- Adequate disease control is important to reduce the risk of adverse pregnancy outcomes.[3]
- Anti-TNFs are efficacious, but because most cross the placenta, treatment is often stopped during pregnancy.[4,5]
- Certolizumab pegol (CZP), due to its Fc-free molecular structure, is not expected to undergo active placental transfer compared to other antibody-based anti-TNFs.[6,7]
- CRIB (NCT02019602) is the first prospective, industry-sponsored study designed to evaluate placental transfer of CZP from the mother to her infant.

## METHODS

### Patients and Study Design

- CRIB was a pharmacokinetic (PK) study of pregnant women receiving commercial CZP for an approved indication.
- The **primary endpoint** was the concentration of CZP in the infants' plasma at birth (Figure 1).
- Key inclusion criteria:
  - Patients were ≥30 weeks pregnant with a singleton or twins at the time of informed consent.
  - Patients were being treated with CZP as per the locally approved label and prescriber's discretion.
  - Patients started or decided to continue CZP treatment independently from and prior to participating in this study and in accordance with the treating physician.
  - Patients received a CZP dose within 35 days prior to delivery.
- Key exclusion criteria:
  - Patients had any pregnancy-related, clinically significant abnormality noted on obstetric ultrasound or other imaging assessment, or had significant laboratory abnormalities during their pregnancy.
  - Patients were taking or had taken any medication with strong positive evidence of human fetal risk of teratogenicity during pregnancy.
  - Patients had received treatment with any biological therapeutic agent, including anti-TNFs other than CZP, during pregnancy.

### Detection of CZP and Anti-CZP Antibodies

- CZP concentrations in blood were measured using a highly sensitive, CZP-specific electrochemiluminescence immunoassay (Figure 2):
  - **Sensitivity:** >10 times more sensitive than the previous assay used in other CZP PK studies (lower limit of quantification [LLOQ]: 0.032 µg/mL).[8]
  - **Specificity:** Requires binding of CZP to TNF and detection with an anti-PEG antibody.[8]
- The presence of anti-CZP antibodies in blood was determined using a previously validated enzyme-linked immunosorbent assay (ELISA). Samples were defined as positive if anti-CZP antibody levels were >2.4 units/mL.[9]

### Study Assessments

- Blood samples were collected from the mothers, umbilical cords, and infants at delivery, and from infants again at Weeks 4 and 8 post-delivery (Figure 1).
- Safety analyses included all mothers who received at least one dose of CZP, and the infants of participating mothers. Adverse events (AEs) were coded according to the MedDRA v18.1.

### Statistical Analyses

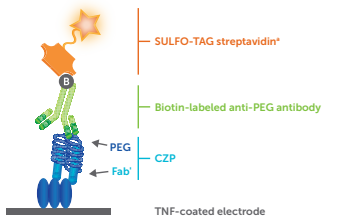
- No formal sample size calculations were performed, as no statistical hypotheses were tested. All PK variables were based on the observed values; no imputation for missing data was used.

## RESULTS

### Baseline Characteristics

- 21 CZP-treated pregnant women were screened; 5 women discontinued screening. Based on preliminary PK and safety analyses, which showed consistent data for the initial mother/infant pairs enrolled, the study concluded with a final enrollment of 16 pregnant women, which was deemed sufficient to assess the primary objective.
- Of the 16 mothers who entered the sampling period, 15 were on CZP 200 mg Q2W and 1 on 400 mg Q4W (Table 1).
- The gestational age and weight at birth of the 16 infants were within the expected range for healthy infants (Table 1).

### Figure 2. CZP-specific immunoassay




*The SULFO-TAG label emits light upon electrochemical stimulation initiated at the electrode surface. PEG: polyethylene glycol; Fab': fragment antigen-binding; TNF: tumor necrosis factor.

### Table 1. Baseline characteristics of mothers and infants

| Median (min, max), unless stated otherwise | Mothers (n=16)[a] |
|---|---|
| Age, years | 31 (18, 40) |
| Mother's indication for CZP treatment, n | |
| Rheumatoid arthritis | 11 |
| Crohn's disease | 3 |
| Psoriatic arthritis | 1 |
| Axial spondyloarthritis/ankylosing spondylitis | 1 |
| Delivery type, n | |
| Vaginal | 14 |
| Cesarean section | 2 |
| **Median (min, max), unless stated otherwise** | **Infants (n=16)** |
| Female, n (%) | 10 (62.5) |
| Gestational age at birth, weeks | 39.9 (37.7, 41.7) |
| Weight at birth, kg | 3.3 (2.6, 4.0) |
| Length at birth,[b] cm | 49.5 (46.0, 55.9) |
| Normal APGAR score (7 to 10) at 1 and 5 minutes,[c] n | 16 |

[a]Mothers who entered the sampling period. [b]n=15 (1 infant with missing data); [c]APGAR scores range from 0 to 10; scores of 7 to 10 are considered normal. Min: minimum; max: maximum; APGAR: Appearance, Pulse, Grimace, Activity, Respiration.

### CZP Plasma Concentrations

- In all mothers enrolled (n=16), CZP plasma levels at delivery were within the expected therapeutic range (median [range]: 24.4 [5.0–49.4] µg/mL).
- Two infants were excluded from the per protocol analysis set: 1 due to missing data at birth, and 1 due to implausible PK data at birth (i.e. data not consistent with a pediatric CZP PK model, based on the expected range of clearance, volume of distribution, and subsequent elimination half-life).
- Of the remaining 14 infants, 13 had no quantifiable CZP plasma levels at birth (<0.032 µg/mL); 1 infant had a minimal CZP level at birth of 0.042 µg/mL (infant/mother plasma ratio: 0.0009) (Figure 3).
- None of the 14 infants had quantifiable CZP plasma levels at Weeks 4 and 8 (Figure 3). Of note, 9 of these infants were breastfed while their mothers were taking CZP.
- Of the 16 umbilical cord samples, 1 was excluded due to missing data. Of the remaining 15 cords, 3 had quantifiable CZP levels (maximum: 0.048 µg/mL).

### Safety and Immunogenicity Analysis

- AEs in the mothers were consistent with the known safety profile of CZP and pregnancy profile of these underlying diseases (Table 2).
- Serious AEs (SAEs) in the mothers were mild to moderate, except one case of arrested labor and one case of prolonged labor. Six SAEs led to hospitalization; all were resolved except for delivery of a premature baby (Table 2).
- AEs experienced by the infants did not show any patterns or clusters of events suggesting a specific safety signal in children (Table 2).
- Four SAEs were reported in two infants; all were mild to moderate except the infection. All SAEs were resolved (Table 2).
- No anti-CZP antibodies were detected in the mothers, umbilical cords, or infants at any time point during the study.

### Table 2. Safety overview

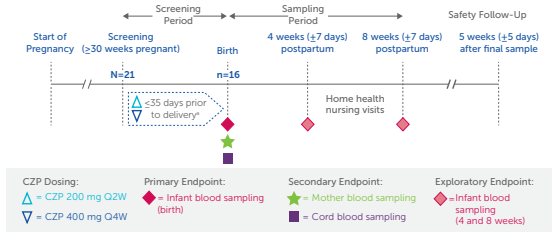
| n (%)[a] | Mothers (n=21)[b] | Infants (n=16) |
|---|---|---|
| Any TEAEs | 15 (71.4) | 5 (31.3) |
| Severe TEAEs | 2 (9.5) | 1 (6.3) |
| Discontinuation due to TEAEs | 2 (9.5) | 0 |
| Drug-related TEAEs | 3 (14.3) | 1 (6.3) |
| Serious TEAEs[c] | 7 (33.3) | 2 (12.5) |
| Deaths | 0 | 0 |
| **Serious TEAEs by mother-infant pair** | | |
| **SF** | Placental insufficiency, Premature baby | N/A |
| **1** | Arrested labor | *None* |
| **2** | **Arrested labor** | *None* |
| **3** | **Prolonged labor** | *None* |
| **4** | Gestational diabetes Polyhydramnios | *None* |
| **5** | *None* | Hypoglycemia **Infection** |
| **6** | Perineal abscess | *None* |
| **7** | Vaginal laceration | Macrosomia Meconium in amniotic fluid |

TEAEs were defined as any AE captured from the time of informed consent until the Safety Follow-Up; **bold text** indicates severe TEAEs. [a]Number of mothers or infants reporting at least one AE for the indicated category. [b]Safety set for mothers (includes 5 screen failures). [c]Serious TEAEs were classified using the FDA definition of serious AEs. TEAE: treatment-emergent adverse event; SF: screen failure; N/A: not applicable.

## CONCLUSIONS

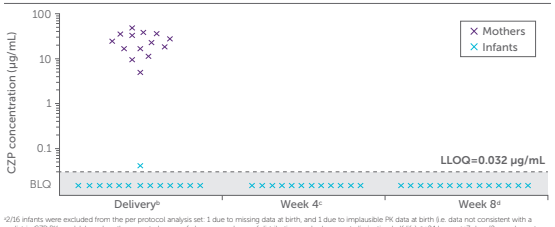
- Using a highly sensitive and CZP-specific assay, CZP levels were below LLOQ (<0.032 µg/mL) in 13/14 infant blood samples at birth and in all infant blood samples at Weeks 4 and 8.
- This indicates no to minimal placental transfer of CZP from mothers to infants, suggesting a lack of *in utero* fetal exposure during the third trimester.
- No new safety signals were identified in the mothers. AEs experienced by the infants did not show any patterns or clusters of events suggesting a specific safety signal in children.
- Combined with evidence from early exposure,[10] these data support continuation of CZP treatment throughout pregnancy, if anti-TNF therapy is considered necessary.

### Figure 1. CRIB study design




*Last CZP dose given within 35 days prior to delivery. Q2W: every 2 weeks; Q4W: every 4 weeks.

### Figure 3. Plasma CZP concentrations in mothers and infants (n=14 mother-infant pairs[a])




[a]2/16 infants were excluded from the per protocol analysis set: 1 due to missing data at birth, and 1 due to implausible PK data at birth (i.e. data not consistent with a pediatric CZP PK model, based on the expected range of clearance, volume of distribution, and subsequent elimination half-life). [b]+24 hours; [c]+7 days (2 samples not collected); [d]+7 days. BLQ: below LLOQ (<0.032 µg/mL).

**References**

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**Author Contributions**

Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: ABK, XM, BA, AF, FF, AM, R-MF, AvT, LS, JS, MT, EH, MW, EC; Drafting of the publication, or revising it critically for important intellectual content: ABK, XM, BA, AF, FF, AM, R-MF, AvT, LS, JS, MT, EH, MW, EC; Final approval of the publication: ABK, XM, BA, AF, FF, AM, R-MF, AvT, LS, JS, MT, EH, MW, EC.

**Disclosures**

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