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Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study

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ABSTRACT

Objectives There is a need for effective and safe treatment during pregnancy in women with chronic inflammatory diseases. This study evaluated placental transfer of certolizumab pegol (CZP), an Fc-free anti-tumour necrosis factor drug, from CZP-treated pregnant women to their infants.

Methods CRIB was a pharmacokinetic (PK) study of women ≥30 weeks pregnant receiving commercial CZP for a locally approved indication (last dose ≤35 days prior to delivery). Blood samples were collected from mothers, umbilical cords and infants at delivery, and infants again at weeks 4 and 8 post-delivery. CZP plasma concentrations were measured with a highly sensitive and CZP-specific electrochemiluminescence immunoassay (lower limit of quantification 0.032 µg/mL).

Results Sixteen women entered and completed the study. Maternal CZP plasma levels at delivery were within the expected therapeutic range (median [range] 24.4 [5.0–49.4] µg/mL). Of the 16 infants, 2 were excluded from the per-protocol set: 1 due to missing data at birth and 1 due to implausible PK data. Of the remaining 14 infants, 13 had no quantifiable CZP levels at birth (<0.032 µg/mL), and 1 had a minimal CZP level of 0.042 µg/mL (infant/mother plasma ratio 0.0009); no infants had quantifiable CZP levels at weeks 4 and 8. Of 16 umbilical cord samples, 1 was excluded due to missing data; 3/15 had quantifiable CZP levels (maximum 0.048 µg/mL).

Conclusions There was no to minimal placental transfer of CZP from mothers to infants, suggesting lack of *in utero* foetal exposure during the third trimester. These results support continuation of CZP treatment during pregnancy, when considered necessary.

Trial registration number NCT02019602; Results.

INTRODUCTION

Most chronic inflammatory diseases (CIDs) are more prevalent in women.[1] Disease onset tends to overlap with peak reproductive age, and women with CIDs are increasingly choosing to have children following diagnosis.[2] Adequate disease control is crucial to ensure the best foetal and maternal health, since high disease activity is associated with an increased risk of adverse pregnancy outcomes, including miscarriage, preterm delivery and low birth weight.[3–7] While disease activity may spontaneously improve during pregnancy, approximately 50% of women with rheumatic CIDs need effective therapeutic intervention and are faced with difficult questions regarding the impact of active disease on the foetus and the safety of different therapies during pregnancy.[8–12]

Anti-tumour necrosis factor (anti-TNF) drugs provide an effective therapeutic option that significantly improves the signs and symptoms of CIDs.[13] However, anti-TNF therapies are often discontinued after the first trimester to limit placental transfer of drug to the foetus.[14–16] Active transplacental transport of immunoglobulin G (IgG) from mother to infant is mediated by the neonatal fragment crystallisable (Fc) receptor (FcRn), a process that takes place mainly during the second and third trimesters of pregnancy.[15] Certolizumab pegol (CZP) is a PEGylated, Fc-free anti-TNF approved for the treatment of rheumatoid arthritis (RA), axial spondyloarthritis/ankylosing spondylitis (axSpA/AS), psoriatic arthritis (PsA), and Crohn's disease (CD). Because it lacks an IgG Fc region, unlike other anti-TNFs, CZP does not bind FcRn and is consequently not expected to undergo FcRn-mediated transfer across the placenta.[17] Preclinical data and findings from two investigator-initiated studies of pregnant women treated with anti-TNFs support the hypothesis that there is minimal placental transfer of CZP in humans.[18–21] However, the enzyme-linked immunosorbent assay (ELISA) used to measure CZP plasma levels in these studies was not specific for CZP, and it was not developed to measure the low CZP concentrations expected from placental transfer. Consequently, there is a need for more accurate and robust information to guide therapeutic decision making in women with CIDs regarding CZP treatment during pregnancy.

CRIB is the first industry-sponsored study designed to evaluate placental transfer of CZP from mothers to infants, by using a highly sensitive and specific assay to accurately measure the CZP plasma concentration in mothers, umbilical cords and infants at delivery, and in infants again at weeks 4 and 8 post-delivery.
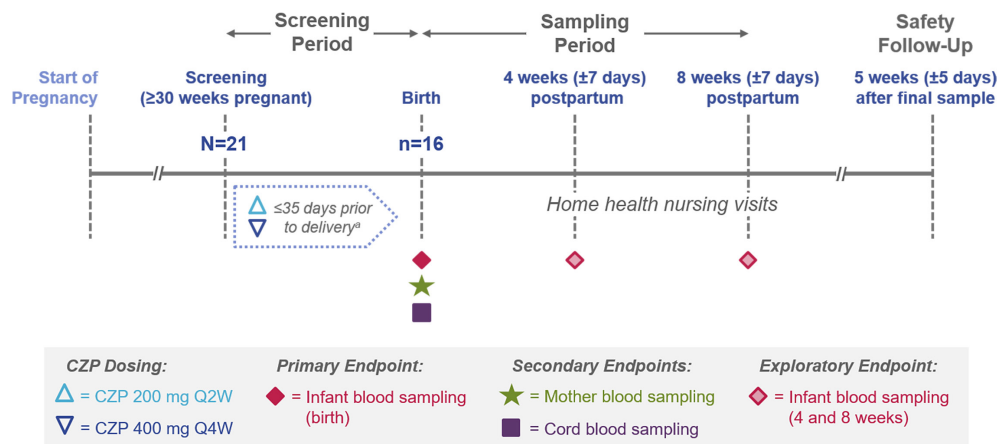
METHODS

Study design and patients

CRIB (ClinicalTrials.gov, NCT02019602) was a prospective, postmarketing, multicentre, pharmacokinetic (PK) study designed to evaluate placental

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Figure 1 CRIB study design.
aLast certolizumab pegol (CZP) dose given within 35 days prior to delivery.

transfer of CZP from mothers to infants (figure 1). This study was conducted between January 2014 and November 2016 across 11 sites in France, Netherlands, Switzerland and the USA and was approved by local Institutional Review Boards. All women provided informed consent to participate and, together with the designated holder of parental rights, to enrol their infant in the study.

Eligible women were ≥30 weeks pregnant at the time of informed consent. Since CRIB was a postmarketing study, all women enrolled were being treated with commercial CZP for a locally approved indication (RA, axSpA/AS, PsA, and CD), as prescribed by their treating physicians. Patients were required to receive a CZP dose within 35 days prior to delivery. The decision to continue CZP treatment during pregnancy was made by the treating physicians prior to and independently from study participation. CZP was not provided by the study sponsor.

Patients with any pregnancy-related, clinically significant abnormality noted on obstetric ultrasound or other imaging assessment, with significant laboratory abnormalities during pregnancy, or with any evidence suggesting chronic or acute uteroplacental insufficiency were ineligible to participate. Mothers who had received treatment with any biologic or any anti-TNF other than CZP during pregnancy were excluded, as were mothers who were taking or had taken any medication with a strong risk of human foetal teratogenicity during pregnancy. Also excluded were mothers with a positive or indeterminate tuberculosis (TB) test at screening, with active or latent TB infection or at high risk for TB infection.

Study procedures
Mothers received commercial CZP on either the 2-weekly dose (CZP 200 mg every 2 weeks [Q2W]) or 4-weekly dose regimen (CZP 400 mg every 4 weeks [Q4W]), per their prescribers' discretion.

Maternal blood samples (≤4 mL per sample) were collected within 24 hours before or after delivery. Umbilical cord samples (≤4 mL per sample) were collected within 1 hour of birth. Infant blood samples (≤1.2 mL per sample) were collected within 24 hours after birth and at weeks 4 and 8 postpartum (figure 1). Samples collected at delivery/birth were obtained in the hospital setting, while in-home nursing visits at weeks 4 and 8 minimised the burden on mothers.

CZP concentration was measured in all plasma samples. Volume permitting, anti-CZP antibodies and total polyethylene glycol (PEG) levels (intact CZP, deconjugated PEG or other

sources of PEG) were also measured. CZP and anti-CZP levels were measured at Covance Inc. (Chantilly, VA, USA). Total PEG levels were measured at Intertek Pharmaceutical Services (Manchester, UK).

CZP concentrations were measured using an electrochemiluminescence immunoassay validated in human plasma.[22] The assay was developed for optimal sensitivity and specificity: CZP was captured by a TNF-coated multiarray electrode and detected with an anti-PEG antibody, prior to reading on a MESO SCALE DISCOVERY platform (MSD; Rockville, MD, USA).[22] The assay is CZP-specific and >10 times more sensitive (lower limit of quantification [LLOQ] 0.032 μg/mL) than the previous ELISA used in other CZP PK studies.[20 23 24] Anti-CZP antibodies were measured using a previously validated ELISA (samples were positive if anti-CZP antibody levels were >2.4 units/mL).[24] Total PEG concentration was determined by nuclear magnetic resonance spectroscopy (LLOQ 2.5 μg/mL).

Study endpoints
The primary endpoint was the concentration of CZP in the infants' plasma at birth. CZP and anti-CZP antibody levels in the mothers' plasma and umbilical cords were secondary endpoints. Exploratory endpoints included CZP levels in the infants' plasma at weeks 4 and 8, anti-CZP antibody levels in the infants' plasma at birth and weeks 4 and 8, and PEG concentrations in the plasma of mothers, cords and infants.

Safety analyses included all mothers who received at least one dose of CZP, including screen failures, and infants of all mothers who entered the sampling period. Adverse events (AEs) were captured from the time of informed consent until the safety follow-up (5 weeks±5 days after final sample/withdrawal) and were coded using MedDRA V.18.1.

Statistical analysis
No formal sample size calculations were performed, as no statistical hypotheses were tested. The planned sample size was 20 mother–infant pairs. All PK variables were based on observed values; no imputation was used.

RESULTS
Patient disposition and baseline characteristics
A total of 21 CZP-treated pregnant women were screened. Five women discontinued screening, one due to serious AEs (SAEs) of placental insufficiency and premature baby, and four due

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
Caesarean 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)
Head circumference at birth,[b] cm	34.5 (32.5, 37.0)
Normal APGAR score (7 to 10),[c] n	
At 1 min	16
At 5 min	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.
APGAR, Appearance, Pulse, Grimace, Activity, Respiration; CZP, certolizumab pegol; max, maximum; min, minimum; Q2W, every 2 weeks; Q4W, every 4 weeks.

Figure 2 Plasma CZP concentrations in mothers and infants (n=14 mother–infant pairs[a]). [a]Two of 16 infants were excluded from the final per-protocol set: one due to missing data at birth and one due to implausible PK data (ie, data not consistent with a paediatric CZP PK model, based on the expected range of clearance, volume of distribution and subsequent elimination half-life; see online supplementary appendix); [b]Infant samples were collected within 24 hours post-delivery, while mother samples could be collected within 24 hours before or after delivery; [c]±7 days (two samples missing); [d]±7 days. BLQ, below the LLOQ (<0.032 µg/mL); CZP, certolizumab pegol; LLOQ, lower limit of quantification.

to ineligibility. Based on preliminary PK and safety analyses, which showed consistent data for the initial mother–infant pairs enrolled in the study, a final enrolment of 16 pregnant women was deemed sufficient to assess the primary objective.
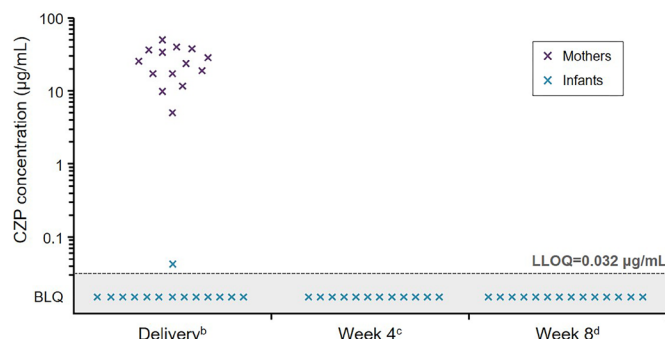
All 16 mothers who entered the sampling period completed the study (no missed visits); 15 were on CZP 200 mg Q2W and one on CZP 400 mg Q4W. Median time between the last CZP dose and delivery was 11 days (range 1–27 days). Baseline characteristics of all participating mothers and their infants are shown in table 1. The gestational age and weight at birth of the 16 infants were within the expected range for healthy infants.

CZP plasma concentrations
Median CZP plasma level at delivery for all 16 participating mothers was 24.4 µg/mL (range 5.0–49.4 µg/mL). Of the 16 umbilical cord samples, one was excluded (sample not collected). Of the 15 remaining cord samples, only three had quantifiable CZP levels (0.035 µg/mL, 0.040 µg/mL, and 0.048 µg/mL); the maximum cord/mother plasma ratio for these three cords was 0.0025.

Of the 16 infants, two were excluded from the per-protocol set: one due to missing data at birth and one due to implausible PK data. The latter infant exhibited a high plasma CZP concentration at birth (0.485 µg/mL), while the week 4 and week 8 sample results were below the assay LLOQ (<0.032 µg/mL). Using two different PK modelling approaches, there was a very low probability (<0.1%) of an infant with this CZP concentration at birth to display levels below the LLOQ at week 4 (see online supplementary appendix for full investigation).

Of the 14 infants in the per-protocol set, 13 had no quantifiable CZP plasma levels at birth (<0.032 µg/mL), and one infant had a minimal CZP level at birth of 0.042 µg/mL (infant/mother plasma ratio 0.0009). No infants had quantifiable CZP plasma levels at week 4 (two samples missing) and week 8 (figure 2; online supplementary table 1). Nine mothers continued CZP postpartum and breastfed their infants; none of these infants had quantifiable CZP plasma levels.

PEG plasma concentrations
Median PEG plasma level at delivery for all 16 mothers was 30.0 µg/mL (range 10.1–59.9 µg/mL). Of 15 available umbilical cord samples, 14 had no quantifiable PEG; the remaining cord had 9.8 µg/mL PEG (corresponding CZP level was below LLOQ). Infant data were not interpretable, due to PEG contamination of the blood collection tubes (see online supplementary appendix).

Safety and immunogenicity analyses
Safety follow-up (up to 5 weeks±5 days after final sample/withdrawal) included the 21 CZP-exposed mothers screened and the 16 infants of all participating mothers. Overall, 15 mothers (71.4%) experienced 34 AEs, and 5 infants (31.3%) experienced 13 AEs; most AEs were mild to moderate (table 2). Two mothers reported severe AEs (arrested labour and prolonged labour), which were also classified as SAEs. All SAEs in the mothers were resolved, except for delivery of a premature baby. A severe AE of infection was reported in one infant, which was also an SAE (table 2). This infant had an unspecified infection indicated by elevated white blood cell count with no clinical signs. All infant SAEs were resolved. No congenital malformations were observed. No anti-CZP antibodies were detected in the mothers, umbilical cords or infants at any time point during the study.

DISCUSSION
Women diagnosed with CIDs during their reproductive years may need effective treatment to control disease activity during pregnancy.[1–7] However, the limited data published so far leave women and treating physicians in a difficult situation when deciding whether to continue anti-TNF therapy during pregnancy.[8–12 14–16] Although some recent treatment recommendations in rheumatology and gastroenterology state that CZP can be continued throughout pregnancy,[25–27] implementation in clinical practice varies greatly across the different specialities involved in the care of pregnant women. Disease flares during pregnancy are associated with an increased risk of miscarriage,

Table 2 Safety overview

n (%)[a]	Mothers (n=21)[b]	Infants (n=16)
Any TEAEs	15 (71.4)	5 (31.3)
Mild TEAEs	4 (19.0)	2 (12.5)
Moderate TEAEs	9 (42.9)	2 (12.5)
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 labour	None
2	**Arrested labour**	None
3	**Prolonged labour**	None
4	Gestational diabetes Polyhydramnios	None
5	None	Hypoglycaemia **Infection**
6	Perineal abscess	None
7	Vaginal laceration	Macrosomia Meconium in amniotic fluid

TEAEs were defined as any adverse event (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 five screen failures).
[c]Serious TEAEs were classified using the United States Food and Drug Administration regulatory definition of serious AEs.
TEAE, treatment-emergent adverse event; SF, screen failure; N/A, not applicable.

preterm delivery and low birth weight,[3–7] and may be more deleterious to neonatal outcomes than any potential risks associated with anti-TNF therapy.[14 16] Therefore, disease activity should be controlled through optimised medical therapy throughout pregnancy, taking into consideration the possible influence of anti-TNFs on the immune response of the *in utero* exposed infant.

CRIB was the first industry-sponsored PK study evaluating placental transfer of a biologic, CZP, from mothers to their infants. Maternal CZP plasma concentrations were within the expected therapeutic range,[23 24] confirming that all mothers in the CRIB study were adequately exposed to CZP at the time of delivery. Using the new, highly sensitive and CZP-specific assay, 13 of 14 infants had no quantifiable CZP plasma levels at birth. In the single infant with a measurable level at birth, the CZP concentration was 0.09% of the maternal CZP plasma level, which is unlikely to have any clinical relevance. At weeks 4 and 8 postpartum, there were no quantifiable CZP levels in the infants' plasma. Umbilical cord data were in agreement with the infant plasma results. AEs in the mothers were consistent with the known safety profile of CZP, and events expected during pregnancy in unexposed women with these underlying CIDs. AEs experienced by the infants did not show any patterns or clusters of events suggesting a specific safety signal in children.[28]

To date, two investigator-initiated studies on placental transfer of anti-TNFs have been published: one in women with CD by Mahadevan *et al.* (maternal, cord and infant samples collected at birth)[20] and one in women with RA and axSpA by Förger *et al.* (maternal and cord samples collected at birth).[19] CRIB greatly expands on the available data, because it was designed to evaluate placental transfer of CZP and to further understand the PK profile of CZP at 4 and 8 weeks in the *in utero* exposed infant,

in the event of placental transfer. Furthermore, to enhance the accuracy of CZP measurement, a new electrochemiluminescence assay was developed.[22] This technology offered significantly improved specificity and sensitivity over the ELISA previously used by Mahadevan *et al.* and Förger *et al.*[20 23 24]

ELISAs provide a relatively simple, high-throughput method of measuring drug concentrations in human blood. Using this type of assay, Mahadevan *et al.* showed low levels of placental transfer of CZP (median cord/mother percentage 3.9%), compared to adalimumab (median cord/mother percentage 153%) and infliximab (median cord/mother percentage 160%).[20] Förger *et al.* reported similar findings for CZP (maximum cord/mother percentage 3.8%).[19] Although the ELISA used in these two studies conforms to regulatory guidelines and has been validated to measure the therapeutic range of CZP concentrations typically seen in treated adults, it was not developed to measure the low CZP concentrations expected from placental transfer (LLOQ of the ELISA 0.41 μg/mL). Furthermore, the detection reagent used was an anti-human kappa light chain antibody, which is not specific for CZP and can detect other TNF-binding antibodies, such as other therapeutic anti-TNF antibodies, or naturally occurring autoantibodies to TNFα, which can be found both in patients with CIDs and otherwise healthy individuals.[29] By contrast, the new electrochemiluminescence assay used in CRIB is highly specific for CZP, since it uses a TNF-coated electrode to capture CZP and an anti-PEG antibody as the detection reagent. In addition, at an LLOQ of 0.032 μg/mL, the new assay is over 10 times more sensitive than the previous ELISA.[22] Consequently, this assay enabled us to provide much more accurate data regarding placental transfer of CZP, which can be translated with greater confidence into evidence-based clinical practice.

One limitation of the CRIB study is the fact that the PK profile of CZP in pregnant women was not fully characterised during pregnancy, since maternal samples were collected only at delivery. It would be valuable to measure maternal CZP concentrations earlier in pregnancy and to investigate the potential impact of the loading dose (CZP 400 mg at weeks 0, 2 and 4) in women initiating CZP treatment while pregnant. Further research is needed to answer these questions.

It has been suggested that TNFα may play a role in the normal development of the immune system.[30] However, TNFα-deficient mice generated by gene targeting have normal secondary lymphoid organs, suggesting that TNFα is not necessary for lymphoid organogenesis.[31] Surprisingly, these mice lack primary B cell follicles in the spleen, although this functional defect can be rescued by complementation of TNFα expression.[31 32] While rodents develop B cell follicles and germinal centres early in pregnancy, in humans, this process starts in the third trimester and continues through week 8 postpartum.[33] The results of the CRIB study suggest no to minimal placental transfer of CZP during the third trimester, and the minimal level detected in one infant at birth (<0.1% of the adult therapeutic level) can be assumed to have no effect on immune system development. Furthermore, a study in pregnant macaque monkeys examined the effect of the anti-TNF golimumab during organogenesis and the perinatal/postnatal period. Golimumab, which has an Fc portion and is therefore expected to actively cross the placenta, was found at high concentrations in neonatal macaques and persisted for 6 months postpartum. However, there were no significant repercussions on lymphoid organ development and immune function, suggesting once again that TNFα may be dispensable for the immune system development during pregnancy.[34]

Humans are born with an immature immune system and have an increased risk of infection compared to adults, relying on innate immune responses and maternal antibodies transferred across the placenta and via breast milk.[30] So far, few studies have examined the long-term safety of anti-TNFs in antenatally exposed children.[35 36] With the exception of CZP, all approved anti-TNFs (infliximab, adalimumab, golimumab and etanercept) contain an IgG1 Fc region, which enables FcRn-mediated transport across the placenta.[20 30] In a prospective study of infants born to mothers who received anti-TNFs during pregnancy, adalimumab and infliximab could be detected in infant blood until 12 months of age, due to IgG recycling in neonates via FcRn.[35] This has raised concerns regarding the potential risk of infection and the challenges of vaccinating infants exposed to anti-TNFs *in utero*. By contrast, in CRIB, there were no quantifiable CZP levels in the infants' plasma at weeks 4 and 8 after birth, and AEs experienced by the infants did not suggest a specific safety signal. While these results can be considered reassuring, long-term observational studies are needed to fully characterise the safety profile of CZP in the infants of exposed mothers.

In addition to the influence of anti-TNFs on the neonatal immune system, it is also important to take into account the potential impact of intrauterine exposure earlier in pregnancy, particularly during the first trimester, before the placenta is fully formed and when organogenesis takes place. Recent systematic reviews and meta-analyses have found no association of anti-TNF exposure during the first trimester with adverse pregnancy outcomes.[25 37 38] Furthermore, evidence gathered through pharmacovigilance reporting supports the conclusion that maternal CZP exposure during the first trimester does not appear to increase the risk of adverse neonatal outcomes or major congenital malformations.[39] Of note, 10 of the 14 infants in CRIB were born to mothers exposed during the first trimester.

In conclusion, our data indicate no to minimal placental transfer of CZP from mothers to infants, suggesting a lack of *in utero* foetal exposure during the third trimester. Combined with the evidence currently available regarding pregnancy outcomes in women exposed to CZP during the first trimester, which indicate no increased rate of major congenital malformations,[39] the results of the CRIB study support the continuation of CZP treatment throughout pregnancy when considered necessary to control disease activity.

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