CLINICAL STUDY REPORT SYNOPSIS: UP0017

Name of company: UCB, Inc.	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: CIMZIA®	**Volume**: Not applicable	
Name of active ingredient: Certolizumab pegol	**Page:** Not applicable	

Title of study: A Multicenter, Postmarketing Study to Evaluate the Placental Transfer of Certolizumab Pegol in Pregnant Women Receiving Treatment with CIMZIA® (Certolizumab Pegol)

Investigators: Eleven Investigators enrolled pregnant women in this study.

Study sites: Eleven sites enrolled at least 1 pregnant woman in this study.

Publications (references): None at the time of reporting

Study period: Approximately 2 years and 10 months **First subject enrolled:** 09 Jan 2014 **Last subject completed:** 21 Nov 2016	**Phase of development:** Postmarketing Phase 1b

Objectives: The primary objective of this clinical study was to assess whether there was transfer of certolizumab pegol (CZP) across the placenta to infants from mothers by evaluating the concentration of CZP in the plasma of infants at birth.

The secondary objectives were to assess the concentration of CZP and levels of anti-CZP antibodies in the plasma of mothers at delivery and to assess the concentration of CZP and levels of anti-CZP antibodies in the plasma of umbilical cords at birth.

The exploratory objectives were:

- To assess the concentration of polyethylene glycol (PEG) in the plasma of infants
- To assess the concentration of PEG in the plasma of mothers
- To assess the concentration of PEG in the plasma of umbilical cords
- To assess the levels of anti-CZP antibodies in the plasma of infants at birth
- To assess the concentrations of CZP and PEG, and levels of anti-CZP antibodies in the plasma of infants 4 weeks and 8 weeks after birth

Methodology: This was a multicenter, postmarketing, prospective study evaluating the placental transfer of CZP by measuring the plasma concentration of CZP from blood samples taken from in the infant, mother, and umbilical cord at delivery/birth. Additionally, blood samples were collected from the infant at Week 4 and Week 8 after birth.

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This study only included pregnant women who started or decided to continue treatment with CZP for an approved indication in accordance with their treating physician prior to participating in the study. The CZP was not provided by the Sponsor. The CZP was to be administered in accordance with the current approved prescribing information; however, deviations were noted after study close relating to prescribing practice by the treating physicians for patients with Crohn's disease (CD). To be eligible to participate in the study, subjects must have been ≥30 weeks pregnant at the start of the Screening Period and expected to receive CZP until at least 35 days prior to their expected delivery (date of injection counted as Day 1).

The study consisted of 3 periods with an expected maximum duration of up to 25 weeks for each subject.

Screening Period: Up to 10 weeks, from the time of maternal informed consent to participate (pregnancy week ≥30), and consent for participation of her infant (including paternal consent according to local regulations, where applicable), up to the start of intervention (sampling at delivery/birth).

Sampling Period: Up to 8 weeks (±7 days), from the first sample (at delivery/birth) to the final blood sample taken at Week 8.

Safety Follow-Up Period: 5 weeks (±5 days), from the final blood sample to the Safety Follow-Up contact.

Additionally, there was a Prescreening Period where pregnant women taking CZP could register their interest in the study at any time after conception and the start of CZP therapy.

The end of the study was defined as the date of the last follow-up visit/contact of the last subject (and/or her infant) in the study.

The levels of CZP in the plasma were measured by a validated CZP-specific immunoassay (electrochemiluminescence; lower limit of quantification [LLOQ]=0.032µg/mL) which measures intact CZP and deconjugated fragment antigen binding (Fab'). The concentrations of total PEG were determined by a validated assay using ^{1}H nuclear magnetic resonance (NMR) spectroscopy (which measures intact CZP-PEG, deconjugated PEG, or other sources of PEG). The levels of anti-CZP antibodies in the plasma were measured by a validated assay to assess levels of antibodies to CZP (enzyme-linked immunosorbent assay; LLOQ=0.630 units/mL).

Number of subjects (planned and analyzed): Approximately 30 pregnant subjects were planned to be screened in order to enroll 20 pregnant subjects. The planned enrollment of 20 pregnant subjects (and their infants) was independent of any statistical considerations. On the basis of preliminary pharmacokinetic (PK) and safety results, consistent data were observed for the initial mother/infant pairs enrolled in the study. Therefore, the study concluded with a final

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enrollment of 16 mother/infant pairs. A total of 21 mothers were screened and 16 mothers completed the study. All 21 mothers screened received at least 1 dose of CZP ≤35 days prior to delivery and were included in the Safety Set for Mothers (SS-M) and 16 infants were included in the Safety Set for Infants (SS-I) (consisting of all infants born to mothers in the SS-M). The infants of the 5 mothers who discontinued during the Screening Period were not included in the SS-I as these mothers were screen failures. A total of 16 mothers provided the CZP concentration samples at delivery and were included in the Pharmacokinetic Set for Mother (PKS-M) and 16 infants provided at least 1 CZP concentration sample and were included in the Pharmacokinetic Set for Infants (PKS-I). Of the 16 infants in the SS-I, 15 had umbilical cords from which a CZP concentration sample was obtained at birth and were included in the Pharmacokinetic Set for Umbilical Cords (PKS-U). Of the 16 infants in the SS-I, 2 had at least 1 important protocol deviation and, therefore, 14 infants were included in the Pharmacokinetic Per-Protocol Set for Infants (PK-PPS-I).

Diagnosis and main criteria for inclusion: This study enrolled female subjects ≥18 years of age who were being treated with CZP per the current approved prescribing information at the Screening Visit (Visit 1), who were ≥30 weeks pregnant with a singleton or twins at the time of informed consent, and who expected to receive CZP until at least 35 days prior to her expected delivery (date of injection counted as Day 1). Subjects must have started or decided to continue treatment with CZP independently from and prior to participating in this study and in accordance with the treating physician. At Visit 2 (delivery/birth; prior to first sample from the infant) the subjects must have delivered a live born infant at or near term (≥34 weeks gestation), received CZP within 35 days before delivery (date of injection counted as Day 1), and must have not received contraindicated medication.

Subjects were not permitted to enroll in the study if they had any pregnancy-related clinically significant abnormality noted on obstetric ultrasound, or other imaging assessment, or the subject had significant laboratory abnormalities during her pregnancy, as judged by the Investigator; were taking or had taken any medication with strong positive evidence of a human fetal risk of teratogenicity (eg, methotrexate or leflunomide) during pregnancy; received treatment with any biological therapeutic agent, or other anti-tumor necrosis factors with the exception of CZP, during pregnancy; had a positive or indeterminate QuantiFERON®-tuberculosis (TB) GOLD In-Tube test at Screening or had a known TB infection, at high risk of acquiring TB infection, or latent TB (LTB) infection.

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Test product: This study only included pregnant women who started or decided to continue treatment with CZP for an approved indication in accordance with their treating physician prior to participating in the study. The CZP was not provided by the Sponsor. The CZP dose and administration schedule were to be per the physician's instructions.

Duration of treatment: The expected maximum duration was up to 25 weeks for each subject.

Reference therapy: None

Criteria for evaluation:

Pharmacokinetics: The primary PK variable was the plasma concentration of CZP in the infant at birth.

The secondary PK variables were:

- The plasma concentration of CZP in the mother at delivery
- The ratio between plasma concentration of CZP between the infant and mother at delivery/birth
- The plasma concentration of CZP in the umbilical cord at birth

The exploratory PK variables were:

- The plasma concentration of total PEG in the infant at birth
- The plasma concentration of total PEG in the mother at delivery
- The plasma concentration of total PEG in the umbilical cord at birth
- The ratio between plasma concentration of total PEG in the infant and mother at delivery/birth
- The ratio between plasma concentration of PEG in the mother and umbilical cord at delivery/birth
- The plasma concentration of total PEG in the infant at 4 weeks and 8 weeks after birth
- The ratio between plasma concentration of CZP in the mother and umbilical cord at birth/delivery
- The plasma concentration of CZP in the infant at 4 weeks and 8 weeks after birth

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Immunological: The secondary immunological variables were:

- The plasma level of anti-CZP antibodies in the mother at delivery
- The plasma level of anti-CZP antibodies in the umbilical cord at birth

The exploratory immunological variables were:

- The plasma level of anti-CZP antibodies in the infant at birth
- The plasma level of anti-CZP antibodies in the infant at 4 weeks and 8 weeks after birth
- The ratio between plasma level of anti-CZP antibodies between infant and mother at delivery/birth

Safety: The safety variable was as follows:

- Treatment-emergent adverse events (TEAEs) of both mother and infant from time of informed consent through Safety Follow-Up

Statistical methods: In general, summary statistics (n [number of available measurements], arithmetic mean, standard deviation [SD], median, minimum, and maximum) for quantitative variables and frequency tables for qualitative data were presented. For CZP concentrations and PEG levels, summary statistics included geometric mean, geometric coefficient of variation (CV), 95% confidence interval (CI), arithmetic mean, arithmetic SD, median, minimum, and maximum.

Values that were below the limit of quantification (BLQ) were set to half the LLOQ if applicable in calculations. Descriptive statistics were calculated if at least two-thirds of the values were above the LLOQ and if the number of values above the LLOQ ≥4. If this was not the case, only median, minimum, and maximum results were presented.

All summaries of PK variables were based on the observed values. No imputation was used for missing values.

The PK and immunological Baseline for mothers (Day 0) was defined as the day of blood sampling within 24 hours before or after delivery.

The PK and immunological Baseline for infants (Day 0) was defined as the day of blood sampling within 24 hours after birth.

The Baseline for non-PK data was defined as Visit 1 (Screening).

The SS-M consisted of all participating mothers who received at least 1 dose of CZP ≤35 days prior to delivery. The SS-I consisted of all infants born to mothers in the SS-M. Safety variables

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used the SS-M and SS-I as appropriate. The PKS-I consisted of all infants from the SS-I analysis set who provided at least 1 CZP concentration sample. The PKS-M consisted of all mothers from the SS-M analysis set who provided the CZP concentration sample at delivery. The PKS-U consisted of all umbilical cords of infants from the SS-I analysis set from which a CZP concentration sample was obtained at birth. The PK-PPS-I consisted of all infants from the SS-I analysis set who provided a CZP concentration sample at birth and had no important protocol deviations that would have impacted the primary PK analysis. The primary PK variable used the PK-PPS-I analysis set. Other PK variables used the relevant PK analysis set for mothers, infants, and umbilical cords.

There was no inferential statistical analysis of the primary PK variable. The primary PK variable was also summarized and listed using the PKS-I as a sensitivity analysis. There were 3 subgroup analyses of the primary PK variable using the PKS-I analysis set. These subgroups were the following:

- Dose regimen (200mg every 2 weeks [Q2W], 2×200mg every 4 weeks [Q4W), loading dose of 400mg every Q2W).
- Mother's indication (note that if a subject was diagnosed with more than 1 indication then the first indication that was diagnosed was used for the indication of mother; all diagnoses for each mother were noted).
- Breastfeeding status (breastfeeding and taking CZP, not breastfeeding and/or not taking CZP).

The plasma concentrations of CZP and total PEG and the levels of anti-CZP antibodies were listed separately by mother, infant, and umbilical cord using the PKS-M, PKS-I, and PKS-U analysis sets, respectively. Additionally, the ratio of the CZP concentration between the infant and mother and between the mother and the umbilical cord was produced and summarized.

Anti-CZP antibody status was defined for each visit as follows:

- Results ≤2.4 units/mL were defined as anti-CZP antibody negative.
- Results >2.4 units/mL were defined as anti-CZP antibody positive.

Additionally, the overall antibody status was defined as positive if an infant had any value >2.4 units/mL throughout the sampling period.

The plasma levels of anti-CZP antibodies in the mother at delivery, in the umbilical cord at birth, and in the infant at birth, 4 weeks (Week 4), and 8 weeks (Week 8) after birth were summarized. The ratio between the plasma levels of anti-CZP antibodies between the infant and mother at birth was also summarized.

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Adverse events in this study were considered as TEAEs, since mothers were required to be receiving CZP as part of the inclusion criteria. Treatment-emergent AEs were captured for both mother and infant from the time of informed maternal consent through to the Safety Follow-Up.

Summary and conclusions:

Subject disposition: A total of 21 mothers entered the Screening Period and 16 mothers completed the Screening Period. Five mothers discontinued during the Screening Period. One mother discontinued Screening due to SAEs of placental insufficiency and premature baby. Four mothers discontinued Screening due to ineligibility (including 1 mother who reported an ongoing TEAE of LTB that met Exclusion Criterion 11). All 16 mothers who completed the Screening Period, entered, and also completed the Sampling Period.

Of note, the 5 mothers who discontinued during the Screening Period were included in the SS-M. Per the study design, all mothers received at least 1 dose of CZP ≤35 days prior to delivery and were, therefore, included in the SS-M. Safety monitoring, including TEAE reporting, began once the Informed Consent form was signed. Thus, although the 5 mothers discontinued during the Screening Period, any TEAEs reported during that period are included in the safety data. However, the 5 mothers who discontinued during the Screening Period were not included in the PKS-M.

Pharmacokinetic results:

- Thirteen of the 14 infants in the PK-PPS-I had no quantifiable plasma CZP levels at birth (<0.032µg/mL) and 1 had a quantifiable plasma CZP level of 0.0422µg/mL.
- No infants had quantifiable plasma CZP levels at Week 4 and Week 8.
- No differences in infant plasma CZP levels were observed by mother's dose regimen, mother's indication, or breastfeeding status.
- Maternal CZP plasma concentrations at delivery were within the range expected given the variability of time since their last maintenance dose of CZP (range of plasma CZP concentration: 4.96 to 49.4µg/mL).
- The median CZP ratio between infants at birth relative to their mothers was low (0.07634% [range: 0.0403% to 0.323%]); the CZP ratio between the 1 infant with quantifiable plasma CZP at birth relative to its mother was 0.0855%.
- Twelve of the 15 umbilical cords in the PKS-U had no quantifiable plasma CZP levels at birth and 3 had quantifiable plasma CZP levels of ≤0.0477µg/mL.

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- The values for total PEG levels in the infants are not interpretable; the median plasma concentration of total PEG in the mothers at delivery was 29.95µg/mL (range: 10.1µg/mL to 59.9µg/mL); 14 of the 15 umbilical cords in the PKS-U had no quantifiable plasma concentrations of total PEG.

Immunological results:

- The levels of anti-CZP antibodies were BLQ for all mothers, umbilical cords, and infants at all time points during the study.
- None of the mothers, umbilical cords, or infants were positive for anti-CZP antibodies at any time point during the study.

Safety results: The TEAEs observed in the mothers are in alignment with the events expected in pregnant patients with these underlying diseases and with the known safety profile of CZP. Clinical events experienced by the infants in this study did not show any patterns or clusters of events suggesting a specific safety signal.

- Treatment-emergent AEs were reported in 15 mothers (71.4%) and were most commonly reported in the SOC of Pregnancy, puerperium and perinatal conditions (6 mothers [28.6%]). The most commonly reported TEAEs (by PT) were rheumatoid arthritis (3 mothers [14.3%]), vaginal laceration (2 mothers [9.5%]), and arrested labor (2 mothers [9.5%]).
- Treatment-emergent AEs were reported in 5 infants (31.3%) and were most commonly reported in the SOC of Pregnancy, puerperium and perinatal conditions (4 infants [25.0%]). The most commonly reported TEAEs (by PT) were gastroesophageal reflux disease, Candida infection, and umbilical cord around neck (2 infants [12.5%] each).
- In the mothers, most TEAEs reported were mild or moderate in intensity. Two mothers reported severe TEAEs (arrested labor and prolonged labor) that were also SAEs; in the infants, all TEAEs reported were mild or moderate in intensity, with the exception of 1 TEAE of infection that was severe in intensity and also an SAE.
- Three mothers (14.3%) reported drug-related TEAEs and most were in the SOC of Infections and infestations. In the infants, 1 TEAE of infection (severe in intensity; reported term infection NOS) was considered drug related per the Investigator and was also an SAE.
- Seven mothers (33.3%) reported SAEs during the study, mainly in the SOC of Pregnancy, puerperium and perinatal conditions; SAEs were reported in 2 infants (12.5%) during the study (hypoglycemia and infection in 1 infant, and macrosomia and meconium in amniotic fluid in 1 infant).

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- Two mothers (9.5%) discontinued due to TEAEs during the Screening Period (1 mother reported SAEs of placental insufficiency and premature baby, and 1 mother reported a TEAE of LTB).
- No deaths and no clinically relevant TEAEs of interest were reported during this study.
- There were no clinically significant findings identified for vital sign parameters and physical examination.

Conclusions:

- There was no to minimal placental transfer of CZP from mother to infant.
- Maternal CZP plasma concentrations at delivery were within the expected therapeutic range observed from nonpregnant women receiving a maintenance dose regimen, indicating that pregnant women were adequately exposed to CZP.
- There was no detectable development of anti-CZP antibodies in either the mothers or the infants.
- No new safety signals were identified in either the mothers or the infants.

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