CLINICAL STUDY REPORT SYNOPSIS: UP0016

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 Concentration of Certolizumab Pegol in the Breast Milk of Mothers Receiving Treatment with CIMZIA® (Certolizumab Pegol)

Investigators: 6 Investigators enrolled mothers in this study

Study sites: 6 sites enrolled at least 1 mother in this study

Publications (references): None at the time of reporting

Study period: Approximately 1 year and 4 months **First subject enrolled:** 08 Sep 2014 **Last subject completed:** 12 Jan 2016	**Phase of development:** Postmarketing Phase 1b

Objectives: The primary objectives of this clinical study were to determine the concentrations of certolizumab pegol (CZP) in human breast milk and to calculate the daily infant dose of maternal CZP.

[redacted]

Methodology: This was a multicenter, postmarketing, prospective study of CZP concentration in breast milk of lactating mothers prescribed commercial CZP by their treating physician in accordance with the current approved prescribing information.

This study enrolled eligible subjects who were receiving CZP while lactating and who were on an established CZP dose regimen at the start of the Sampling Period. Subjects were considered participants in the study at this point. In addition to a traditional site-based approach to enrollment, this study utilized an open enrollment model with oversight by a central Investigator. This IRB approved open enrollment model provided interested and qualified subjects access to study participation, even though they were located remotely from traditional study sites.

The CZP was not provided by the Sponsor. The decision of the subject to administer CZP was made in accordance with her treating physician and was to be completely independent of the decision to participate in this study. The subjects must have decided, in consultation with their treating physician, and independent of participation in the study, whether or not to breastfeed or feed expressed breast milk to their infant(s). In terms of this study, subjects were not required to breastfeed their infants, as long as they were lactating.

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For qualifying subjects, the study consisted of a Screening Period of up to 10 weeks, a 2-week or a 4-week mature breast milk Sampling Period (based on whether the mother was dosing with CZP every 2 weeks [Q2W] or every 4 weeks [Q4W], respectively), and a Safety Follow-Up contact (via remote contact) 5 weeks (±5 days) after the final sample was obtained.

Screening Period: Up to 10 weeks duration. This period commenced with the subject's informed consent to participate (including paternal consent according to local regulations, where applicable) and ended immediately prior to collection of the first sample.

Sampling Period: 2 to 4 weeks duration based on the CZP dosing regimen (Q2W or Q4W), starting at least 6 weeks after delivery and once the subject was on an established dosing regimen of CZP (ie, at least the third dose of CZP).

Safety Follow-Up Period: 5 weeks (±5 days) after the final sample was obtained.

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[s]) in the study.

The concentration of CZP was measured using a sensitive validated immunoassay method (electrochemiluminescence; lower limit of quantification [LLOQ]=0.032µg/mL). The concentrations of total PEG (ie, PEG present as intact CZP or in deconjugated form) was determined by a validated assay using nuclear magnetic resonance spectroscopy with an LLOQ of 0.5µg/mL.

Number of subjects (planned and analyzed): Approximately 25 mothers were planned to be screened in order to enroll 16 mothers. A total of 19 mothers were screened and 17 mothers completed the study. Eighteen mothers were included in the Safety Set for Mothers (SS-M) and 17 infants (consisting of all infants of mothers in the SS-M) were included in the Safety Set for Infants (SS-I). Note that 1 mother was a screen failure (discontinuation due to a Treatment-emergent adverse event [TEAE]), but was included in the SS-M; her infant was not included in the SS-I. Seventeen mothers were included in the Pharmacokinetic Per-Protocol Set (PK-PPS).

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). Subjects must have delivered term infants(s) (at least 37 weeks gestation) and agreed to use only the emollient or nipple cream provided by the Sponsor for use during the Sampling Period. The decision to treat with CZP or to breastfeed must have been made independently from and prior to the subject consenting to participate in this study. At Visit 2 (just prior to sampling) the subjects must have been at least 6 weeks postpartum and on an established dosing regimen of CZP (at least the third dose of CZP since starting/restarting

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CZP).

Subjects were not permitted to enroll in the study if they had received treatment with any biological therapeutic agent, or other anti- tumor necrosis factor agents with the exception of CZP, within 5 half-lives prior to obtaining the first sample; 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 infection.

Test product: This study only included women who were receiving treatment with CZP in accordance with their treating physician prior to participating in the study. The CZP was not provided by the Sponsor. [redacted]

Duration of treatment: The total duration of subject participation in this study was variable, depending on whether the subject was on a CZP Q2W or Q4W dosing regimen; the maximum duration of participation was approximately 19 weeks.

Reference therapy: None

Criteria for evaluation:

Pharmacokinetics: The primary pharmacokinetic (PK) variables were:

- The concentration of CZP in the breast milk of lactating mothers on an established dosing regimen of CZP on Day 0 (predose) of the Sampling Period, just prior to next scheduled dose of CZP, and on Days 2, 4, 6, 8, 10, 12, and 14 (predose if Q2W dosing), relative to CZP administration on Day 0. In addition, in mothers on a CZP Q4W dosing regimen, the concentration of CZP in breast milk was also evaluated on or about Day 28 (ie, prior to and on the same day of the next scheduled administration of CZP).
- The calculated daily infant dose of CZP in breast milk on Days 2, 4, 6, 8, 10, 12, and 14 (predose if Q2W dosing), and on or about Day 28 (predose) (as applicable) and the estimated average daily infant dose (determined from the dosing interval; 14 or 28 days).

The exploratory PK variable was the concentration of total PEG in the breast milk on Day 0 (predose), and on Days 2, 4, 6, 8, 10, 12, and 14, and on or about Day 28 (as applicable).

Safety: The safety variables were:

- TEAEs of the mother from time of informed consent through Safety Follow-Up
- TEAEs of the infant(s) from time of mother's informed consent through Safety Follow-Up

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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 and PEG concentrations, in general summary statistics included geometric mean, geometric coefficient of variation, 95% confidence intervals, arithmetic mean, arithmetic SD, median, minimum, and maximum, unless otherwise specified. All summaries of PK variables were based on the observed values.

Baseline for all assessments was defined as the predose measurement at Day 0 of the Sampling Period.

The SS-M consisted of all participating mothers who had received at least 1 dose of CZP. The SS-I consisted of all infants of mothers in the SS-M. Safety variables used the SS-M and SS-I as appropriate. The Pharmacokinetic Set for Mothers (PKS-M) consisted of all subjects in the SS-M with at least 1 valid postdose measurement of CZP concentration in breast milk. The PPK-PPS consisted of all subjects with a valid CZP concentration measurement in breast milk with no important protocol deviations affecting the primary variable. The primary PK and exploratory PK variables used the PK-PPS. Supportive summaries used the PKS-M. However, the PK-PPS and PKS-M analysis sets were identical; therefore, no summaries using the PKS-M analysis sets were produced.

No inferential statistical analysis of the PK variables was planned.

If milk sampling measurements were deemed to be below the limit of quantification (BLQ), then for calculation of the derived statistics this sample result was set to half the LLOQ. Descriptive and summary statistics were calculated if at least two-thirds of the values on a given day were above the LLOQ. If this was not the case, only median, minimum, and maximum were presented.

The amount of CZP that the infant may potentially have consumed daily was calculated on Day 2, 4, 6, 8, 10, 12, and 14, and on or about Day 28 based on the standardized mean milk consumption for a fully breastfed 2-month-old infant of 150mL/kg/day.

For the calculation of PK parameters, concentrations that were BLQ were treated per standard procedures for plasma concentrations, ie, replaced by 0 before t_{max} and treated as missing after t_{max}. For the calculation of the amount/dose, BLQ concentrations were replaced by 0.

The following PK parameters were computed for CZP, if possible:

- AUC_{τ}: Area under the curve over a dosing interval (14 or 28 days)
- C_{av}: Average concentration over a dosing interval, equal to $Cav=AUC\tau/\tau$

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- C_{max}: Maximum observed drug concentration
- t_{max}: Time of the maximum observed concentration
- λ_z: First-order terminal elimination rate constant, calculated from a semi-log plot of the milk concentration vs time curve (Q4W dosing regimen only)
- $t_{1/2}$: First-order terminal elimination half-life, calculated as 0.693/λz

The estimated average daily infant dose that corresponds to the average amount of CZP that the infant may potentially consume daily over the dosing interval was calculated.

Adverse events in this study were considered as TEAEs if they were identified after the mother had received at least 1 administration of CZP. 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 19 mothers entered the Screening Period and 17 mothers completed the Screening Period. One mother was prescribed CZP prior to entering the Screening Period, but never received any doses of CZP and was therefore, not eligible for the study. One mother discontinued during the Screening Period due to a TEAE of herpes zoster; this mother was included in the SS-M, but her infant was not included in the SS-I. No mothers were rescreened. All 17 mothers who completed the Screening Period, entered and also completed the Sampling Period. All 17 mothers completed Safety Follow-Up.

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Pharmacokinetic results:

- The breast milk concentration of CZP was low or BLQ at all time points during the study; the highest concentration measured at any time point was 0.0758µg/mL (at Day 6).
  - Only 3 mothers had breast milk concentrations above the LLOQ (0.032µg/mL) at all time points during the study.
  - 56% of all samples were BLQ.
- The estimated average daily infant dose of CZP potentially ingested over the dosing interval was minimal (median: 0.003503mg/kg/day; range: 0 to 0.0104mg/kg/day).
- The calculated daily amount of CZP potentially ingested by the infant was low or 0 at all time points during the study; the highest calculated amount in any infant was 0.0114mg/kg/day (at Day 6).
- There was no difference in the PK parameters by subgroup analysis (mother's indication or supplemental nutrition [yes/no]).
- [redacted]

Safety results: The safety results in the mothers were in line with the known safety profile of CZP and there were no concerning AEs reported in the infants during this study.

- Treatment-emergent AEs were reported in 10 mothers (55.6%) and were most commonly reported in the SOC of Infections and infestations (6 mothers [33.3%]). The most commonly reported TEAEs (by PT) were upper respiratory tract infection and headache (2 mothers [11.1%] each).
- Treatment-emergent AEs were reported in 8 infants (47.1%) and were most commonly reported in the SOC of Infections and infestations (7 infants [41.2%]). The most commonly reported TEAEs (by PT) were nasopharyngitis (4 infants [23.5%]) and upper respiratory tract infection (3 infants [17.6%]).
- In the mothers, most TEAEs reported were mild or moderate in intensity. One mother reported a severe TEAE of breast abscess that was also an SAE; in the infants, all TEAEs reported were mild or moderate in intensity and no TEAEs were reported that were severe in

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intensity.

- Four mothers (22.2%) reported drug-related TEAEs and the most commonly reported drug-related TEAE (by PT) was upper respiratory tract infection (2 mothers [11.1%]). In the infants, 1 TEAE of nasopharyngitis (mild in intensity) was considered drug related per the Investigator.
- One mother (5.6%) reported an SAE of breast abscess during the study, and no SAEs were reported in the infants during the study.
- One mother (5.6%) discontinued due to a TEAE (herpes zoster) during the Screening Period.
- No deaths and no TEAEs of interest were reported during this study.
- There were no clinically relevant concerns identified for vital sign parameters.
- There were no abnormalities and complications reported for any of the pregnancies.

Conclusions:

- No to minimal transfer of CZP from the plasma to breast milk was observed. In addition, due to the low bioavailability of monoclonal antibodies after oral administration (related to the proteolytic activity and acidic environment in the infant's stomach), the estimated amount of CZP ingested by the infant via breast milk is not expected to be of clinical relevance.
- [redacted]
- The safety profile of the mothers was consistent with the known safety profile of CZP; the infants of mothers exposed to CZP had a safety profile consisting of clinical events similar to those occurring in an untreated population of similar age.

Report date: 17 May 2016