SYNOPTIC CLINICAL STUDY REPORT: UP0019

Name of company: UCB Pharma	**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: An Observational Follow-Up Study of Women who Become Pregnant While Participating in a Certolizumab Pegol (CZP) Clinical Study or Whose Pregnancies Have Otherwise Been Reported to UCB Due to Potential CZP Exposure During Pregnancy

Investigator: One Investigator enrolled 1 subject and the resulting 1 live-born infant.

Study site: One site enrolled 1 subject and the resulting 1 live-born infant.

Publications (references): None

Study period: The total duration of individual subject participation in this study was variable depending on when the pregnancy was identified and the gestational age at which the woman enrolled into the observational study. The pregnancy was to be followed through outcome, and the subject and any live offspring were to be followed up to 18 months duration. Maximum duration for a prospectively enrolled subject was 27 months (9 months of pregnancy + 18 months after pregnancy outcome). **First subject enrolled:** 16 Nov 2016 **Last subject completed:** 18 Dec 2017 UP0019 was terminated due to insufficient enrollment. No new safety signals were noted in the single subject and the resulting 1 live-born infant enrolled in the study.	**Phase of development:** Postauthorization Safety Study (PASS)

Principal Investigator and administrative structure:

Principal Investigator: [redacted], PhD, INC Research

Administration: INC Research, 3201 Beechleaf Ct, Suite #600, Raleigh, NC 27604, USA; PAREXEL International Corporation, 195 West St, Waltham, MA 02451, USA

Clinical Project Manager and Program Delivery Lead: [redacted], UCB

Lead Clinical Development Representative: [redacted], UCB

Clinical Trial Statistician: [redacted], UCB

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Study Physician: [redacted], UCB		

Objectives:

The primary objectives for this observational follow-up study were to estimate the risks of major congenital malformations (MCMs) and to evaluate pregnancy outcomes among women who became pregnant while enrolled in a CZP study or whose pregnancies had otherwise been reported to UCB due to potential CZP exposure during pregnancy.

The secondary objectives of the study were to characterize reported pregnancies, including pregnancy complications, and to monitor infant health, growth, and development during the first 18 months of life.

Other study objectives were to summarize disease-related treatments and disease activity among participating women during pregnancy and in the first 18 months after pregnancy outcome.

Methodology: This follow-up study was a multi-country, noninterventional, cohort study of women who became pregnant while enrolled in a CZP study conducted by UCB or 1 of its development partners, or whose pregnancies had otherwise been reported to UCB due to potential CZP exposure during pregnancy. Any CZP clinical study participant who became pregnant while in the study, regardless of treatment arm (CZP, placebo, or comparator), was eligible for this observational follow-up study. Upon enrollment into this study, all subjects were followed as per current clinical practice and healthcare provider (HCP) discretion for their specific condition under treatment, and no additional laboratory procedures were required. The choice of medical treatment was made independently by the treating physician during the regular course of practice and was not assigned or supplied by the UP0019 study. For each participating woman or infant, there would have been multiple potential reporters: the treating HCP, the obstetric HCP, the pediatric HCP, and the subject. The study collected data that are routinely documented in the subject's medical record as part of routine care, with the possible exception of the disease activity assessments. Disease activity is often assessed in routine care, and collection of this information was critical to evaluating disease severity during pregnancy and after pregnancy outcome. This study followed the internationally recognized Guidelines for Good Pharmacoepidemiology Practice.

The intent of this observational follow-up study was to collect and summarize data systematically on pregnancy and pregnancy outcomes, regardless of treatment decisions, with an emphasis on the presence or absence of MCMs, along with potential confounding factors prior to conception and during pregnancy (such as maternal age, concomitant medications, medical history, and disease severity), as well as the first 18 months after pregnancy outcome, and 18-month follow up of live-born infants. Both prospectively (ie, before pregnancy outcome was

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known) and retrospectively (ie, pregnancy outcome was already known) reported pregnancies were eligible for enrollment in the observational study; however, only prospective pregnancies were to be included in the primary analysis.

Data were to be collected from reporting physicians at time of enrollment; during pregnancy at 28±4 gestation weeks; around the time of pregnancy outcome (delivery or end of pregnancy); for obstetric HCP during 3 to 8 weeks postpartum; for other physicians at 4, 12, and 18 months after pregnancy outcome. From subjects, data were collected at the time of enrollment; during the second trimester (21±3 weeks); during the 3rd trimester (32±3 weeks); and at 4, 12, and 18 months after pregnancy outcome. Infant data were to be collected at birth and at 4, 12, and 18 months of age. Targeted follow-up was also to have taken place for specific cases to gather additional information to assist in data interpretation if required.

For women whose pregnancies did not end in a live-born infant, the pregnancy follow-up schedule was to have proceeded directly to the collection of pregnancy outcome data with the exception of infant data. The end of pregnancy, postpartum, and 4-, 12-, and 18-month maternal postpartum assessments were to have involved the subject and treating HCP only, were not to have collected any infant data, and were not to have involved the pediatric HCP.

Retrospective cases enrolled in the study had data collected and entered into the study database using the same procedures as for prospective cases where possible; however, these retrospective cases were summarized separately and were not included in the primary analysis. Retrospective reports were reviewed and reported separately as a listing.

For full text of the study description, refer to the UP0019 protocol, dated 11 Dec 2015.

Number of subjects (planned and analyzed): Based on the number of cases reported in the United States, Canada, Germany, and France, it was estimated that approximately 36 prospectively reported CZP-exposed pregnant women would enroll annually. Due to the early termination of the study and lack of recruitment over 26 months, 1 retrospectively reported CZP-exposed pregnant woman resulting in 1 live-born infant was enrolled in the study.

Diagnosis and main criteria for inclusion: Minimum criteria for enrollment were the following:

1. Pregnancy was identified while the subject was participating in an interventional or noninterventional CZP study conducted by UCB, or a development partner, regardless of phase or treatment arm (ie, commercial or investigational, placebo or comparator treatment), or whose pregnancies were spontaneously reported to UCB due to potential CZP exposure during pregnancy.
2. Sufficient information to classify the pregnancy as prospective or retrospective was available.

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3. Full initial reporter (ie, woman or HCP) contact information reported to allow for follow-up (name, address, telephone number/email address) and contact information for at least 1 applicable HCP if initial contact was the woman.
4. Consent to participate was provided.

Reported cases that did not meet the minimum criteria for enrollment were not eligible for inclusion in the study and were not entered into the study database. UCB Drug Safety handled these cases using routine pharmacovigilance measures.

Eligible subjects' pregnancies were classified as either prospectively or retrospectively reported based on whether the outcome of pregnancy was unknown (prospective) or known (retrospective) at the time of consent.

For this study, a known pregnancy outcome was defined as:

- A prenatal diagnosis of a fetus with a congenital defect at the time of consent, or
- A pregnancy that had already been completed at the time of consent.

Collection of exposure and outcome information followed the same time schedule for both the prospective and retrospective cohort to the extent possible.

For a pregnancy to be enrolled in the prospective cohort, the subject must have met minimum enrollment criteria and her pregnancy outcome could not have been known (ie, no prenatal diagnosis of a fetus with a congenital defect and the pregnancy was still ongoing at the time of consent).

For a pregnancy to be enrolled in the retrospective cohort, the subject must have met minimum enrollment criteria and her pregnancy outcome must already have been known (ie, a congenital defect had already been identified at the time of consent into the pregnancy follow-up study, or the pregnancy had been completed at the time of consent). Reported pregnancies in which the resulting infant was over 1 year of age at the time of informed consent were not eligible to participate in the study.

Retrospective reports may have been biased toward the reporting of more unusual and severe cases and were less likely to be representative of the general population experience than reports made prior to the knowledge of the pregnancy outcome. Therefore, they were not to be included in the primary analyses for this study. Data were collected on retrospective pregnancy reports, however, to maximize the data available on reported pregnancies and to assist in characterizing any identified patterns of congenital defects.

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Study treatments: The choice of continued medical treatment was made independently by the treating physician in the regular course of practice and was not to have been influenced by participation in the study. No additional laboratory procedures, clinical visits, or tests were applied.

Neither CZP nor other medications were provided or paid for by the Sponsor in this observational follow-up study.

Duration of treatment: Not applicable.

Reference therapy: None

Criteria for evaluation:

Due to the early termination of the study and enrollment of only 1 retrospectively reported CZP-exposed pregnant woman resulting in 1 live-born infant, the planned statistical analyses were not conducted. Refer to Section 8 of the Statistical Analysis Plan (SAP) for details regarding the planned analyses.

The primary variables were:

- Major congenital malformations
- Pregnancy outcome (live birth, spontaneous abortion, stillbirth, induced abortion)

The secondary variables were:

- Maternal pregnancy-related events
- Type of delivery
- Gestational age at birth
- Birth weight
- Size for gestational age
- Adverse events in infants within the first 18 months of life
- Pediatric anthropometric measurements and select developmental milestones at 4, 12, and 18 months

Other variables were:

- Events occurring during pregnancy and within 18 months after pregnancy outcome indicating increased disease activity or disease progression
- Maternal disease-related treatments during pregnancy and within 18 months after pregnancy outcome

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- Physician's Global Assessment (PGA) score at time of consent, at 28±4 weeks gestation, around the time of pregnancy outcome, and at 4, 12, and 18 months after pregnancy outcome for all diseases
- Patient's Global Assessment (PtGA) score at time of consent, at 21±3 weeks gestation, at 32±3 weeks gestation, around the time of pregnancy outcome, and at 4, 12, and 18 months after pregnancy outcome for all diseases
- Routine Assessment of Patient Index Data 3 (RAPID3) score at time of consent, at 21±3 weeks gestation, at 32±3 weeks gestation, around the time of pregnancy outcome, and at 4, 12, and 18 months after pregnancy outcome for women with rheumatoid arthritis
- Health Assessment Questionnaire-Disability Index (HAQ-DI) score at time of consent, at 21±3 weeks gestation, at 32±3 weeks gestation, around the time of pregnancy outcome, and at 4, 12, and 18 months after pregnancy outcome for women with psoriatic arthritis
- Harvey-Bradshaw Index (HBI) score at time of consent, at 21±3 weeks gestation, at 32±3 weeks gestation, around the time of pregnancy outcome, and at 4, 12, and 18 months after pregnancy outcome for women with Crohn's disease (CD)
- Bath Ankylosing Spondylitis Functional Index (BASFI) score at time of consent, at 21±3 weeks gestation, at 32±3 weeks gestation, around the time of pregnancy outcome, and at 4, 12, and 18 months after pregnancy outcome for women with ankylosing spondylitis or axial spondyloarthritis
- Dermatology Life Quality Index (DLQI) score at time of consent, at 21±3 weeks gestation, at 32±3 weeks gestation, around the time of pregnancy outcome, and at 4, 12, and 18 months after pregnancy outcome for subjects with psoriasis

Pharmacokinetics/pharmacodynamics: Not applicable.

Safety: The safety variables were:

- Exposure to CZP
- Adverse events (AEs) were classified by System Organ Class (SOC), high level term (HLT), and preferred term (PT) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA)® coding at the time of first data transfer
- AEs of interest for this study were captured using a check-box in the case report form (CRF) and included the following:
  - Serious infections
  - Malignancies

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  - Congestive heart disorders captured in the CRF under the term Cardiac Failure
  - Demyelinating disorders
  - Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia captured in the CRF under the term Other
  - Serious bleeding events
  - Lupus and lupus-like symptoms
  - Serious skin reactions
- Pediatric laboratory values
- Neonatal/pediatric hospital admissions
- Prenatal testing information
- Infant nutrition status (receiving breast milk, formula milk, and/or solids)

Statistical methods: Listings were generated using SAS® Version 9.3 or higher. For a full description of the planned statistical analyses, refer to the SAP, dated 15 Dec 2016.

For this synoptic clinical study report, the planned analyses were not conducted since only 1 retrospectively reported CZP-exposed pregnant woman resulting in 1 live-born infant was enrolled in this study. Additionally, size for gestational age was not calculated. Results for the variables listed above are presented in listings for the subject enrolled and for the Enrolled Set, which consisted of the pregnancy and offspring that met minimum eligibility criteria and consented to the study.

For the purposes of this study, a MCM:

1. Followed the Centers for Disease Control and Prevention guidelines and was defined as any major structural malformation or chromosomal defect diagnosed or with signs/symptoms
2. On a case-by-case basis, was subject to independent review, any structural or chromosomal defect detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus or deceased infant

Safety results for the variables listed above are presented in listings, with the exception of exposure to CZP. Medical history, AEs, and illnesses were coded using MedDRA Version 21.0. All medications were coded using the most current version of the World Health Organization Drug Dictionary. Medical procedures were not coded.

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Study population results:

Subject disposition: One subject ([redacted]) participated in UP0019. This subject was considered retrospective because she provided consent after delivery and therefore birth outcome was known at the time of enrollment (Listing 1.3 and Listing 1.5). The subject met study eligibility criteria (Listing 1.1), and subject visit dates are provided in Listing 1.5. The subject continued treatment with CZP 200mg every 2 weeks throughout pregnancy and at least until she was lost to follow-up ([redacted]). The subject discontinued participation in UP0019 during the postpregnancy period (Listing 1.4) and was lost to follow-up (Listing 1.3), and the subject had no important protocol deviations (Listing 1.6). No other subject provided consent or failed to meet eligibility criteria (Listing 1.2).

Study demographics: The subject was [redacted] years of age at the beginning of pregnancy and was [redacted] and [redacted] or [redacted] (Listing 2.1.1). The subject's prepregnancy weight and BMI were [redacted] kg and [redacted] kg/m^2, respectively. The infant's gestational age at birth was 37 weeks and 2 days, which was considered early term. The infant was female and weighed [redacted] g at birth, with a length of [redacted] cm and head circumference of [redacted] cm. The infant's APGAR Scores were [redacted] (Listing 2.1.2). All prenatal testing for the subject and infant was normal (Listing 5.6).

Enrollment characteristics, weight, and lifestyle data are provided in Listing 2.2, Listing 2.3, and Listing 2.4, respectively. The subject's primary condition for treatment with CZP was CD (Listing 2.2).

Medical history: The subject had history of [redacted] and a previous [redacted] that required an emergency [redacted] as a result of [redacted] (Listing 2.5.1); the subject was not exposed to CZP during this previous [redacted]. During the pregnancy in this study while on CZP, the mother experienced [redacted] and [redacted], reported as medical conditions of interest (Listing 2.9.1).

The subject had a concomitant medical procedure of Cesarean section, which is described below (Listing 2.7.1). The infant had no concomitant medical procedures (Listing 2.7.2). Concomitant vaccinations for the infant were given per routine vaccination calendar (Listing 2.8). There were no paternal risk factors for birth defects (Listing 2.5.2).

Concomitant medications for the subject are provided in Listing 2.6.1 and for the infant in Listing 2.6.2. No AEs of interest for CZP were reported for the subject (Listing 2.9.2).

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Results: Due to the early termination of the study and enrollment of only 1 retrospectively reported CZP-exposed pregnant woman resulting in 1 live-born infant, no analyses were conducted. There were no birth defects reported for the infant (Listing 3.1.1 and Listing 3.1.2).

The subject had induced labor, recommended due to [redacted] and history of [redacted]. The subject delivered via Cesarean section that was considered medically necessary due to a prior [redacted] (Listing 3.2).

The results for the following assessments were listed for the subject: PGA score (Listing 6.1), PtGA score (Listing 6.2), and HBI score (Listing 6.5).

Additional listings are provided for the following: RAPID3 questions (Listing 6.3.1) and RAPID3 responses (Listing 6.3.2); HAQ-DI questions (Listing 6.4.1), HAQ-DI responses (Listing 6.4.2), and HAQ-DI score (Listing 6.4.3); BASFI questions (Listing 6.6.1) and BASFI score (Listing 6.6.2); and DLQI questions (Listing 6.7.1) and DLQI responses (Listing 6.7.2). Because the subject had CD, there are no responses for these assessments.

Safety results: The subject was exposed to CZP 200mg every 2 weeks during all 3 trimesters of pregnancy and during the postpartum period until she was lost to follow-up (Listing 2.6.1). No illnesses or AEs were reported for the infant (Listing 5.1); however, 1 pediatric laboratory value was listed as abnormal during the early postnatal period: bilirubin (high) (Listing 5.4). On postnatal Day 3, the infant developed high bilirubin values ([redacted] mg/dL, transient). The bilirubin elevation was considered to be resolving at the time of reporting, and its relationship to CZP was unknown. No postpartum complications were reported for the subject (Listing 5.2).

Pediatric anthropometric measurements at 4, 12, and 18 months are presented in Table 1. The infant was fed breast milk exclusively for approximately 2 months and then received formula milk along with breast milk for approximately 2 months (Listing 5.5). At 4 months postpregnancy, the infant was fed formula milk due to insufficient milk production and convenience. Solid foods were fed beginning approximately 4 months postpregnancy. At the time of data cut-off, the infant was continuing to be fed with formula milk and solid food.

Table 1: Pediatric Anthropometric Measurements at 4, 12, and 18 months

Time point	Weight (g)	Length (cm)	Head circumference (cm)
4 months postpregnancy outcome	[redacted]		
12 months postpregnancy outcome			
18 months postpregnancy outcome			

Data source: Listing 5.3

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There were no abnormal findings reported for the neuromotor development of the infant (Listing 5.3), and no birth defects were reported for the infant (Listing 3.1.1 and Listing 3.1.2). There were no abnormal findings reported for any prenatal tests (Listing 5.6), and there were no neonatal or pediatric intensive care unit admissions reported (Listing 6.8).

Conclusions: UP0019 was terminated due to insufficient enrollment and included an observation of 1 reported pregnancy in a woman with CD treated with CZP throughout all trimesters and during the postpartum period, reported retrospectively. In this pregnant subject presenting with [redacted] and with a history of [redacted], labor was induced, and the subject delivered via Cesarean section that was considered medically necessary due to a prior [redacted]. The subject delivered 1 live child at gestational week 37. No postpartum complications were noted. The infant had no reported birth defects or disorders other than a transitory bilirubin elevation on postnatal Day 3 and was breastfed and developing normally.

No new safety concerns or AEs of interest for CZP were noted based on the data of 1 mother-infant pair reported in this study.

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Approval Signatures

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Document Approvals	
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