C87028, CDP870-028, 2005-001350-24

CLINICAL STUDY REPORT SYNOPSIS

This synopsis is provided for informational purposes only and is not intended or recommended as a substitute for professional medical advice.

This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

———————————————————————————————————

Sponsor:

UCB, Inc.

1950 Lake Park Drive

Smyrna, GA 30080

UNITED STATES

Official study title:

A Phase III multi-centre, open-label, follow-on study to CDP870-027, to assess the efficacy and safety of lyophilised CDP870 an engineered human anti-TNF PEG conjugate, as additional medication to methotrexate, in the treatment of signs and symptoms and preventing structural damage in patients with active rheumatoid arthritis

CLINICAL STUDY REPORT SYNOPSIS: C87028

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 (CZP)	**Page:** Not applicable	

Title of study: *A Phase III multi-centre, open-label, follow-on study to CDP870-027, to assess the efficacy and safety of lyophilised CDP870 an engineered human anti-TNF PEG conjugate, as additional medication to methotrexate, in the treatment of signs and symptoms and preventing structural damage in patients with active rheumatoid arthritis

Investigators: This was a multicenter study; 121 Investigators enrolled subjects (Principal Investigator: Prof [redacted])

Study sites: This was a multicenter study; 121 centers in 22 countries enrolled subjects

Publications (references): Curtis JR, Chen L, Luijtens K, Navarro-Millan I, Goel N, Gervitz L, et al. Dose escalation of certolizumab pegol from 200 mg to 400 mg every other week provides no additional efficacy in rheumatoid arthritis: an analysis of individual patient-level data. Arthritis Rheum. 2011;63(8):2203-8.

Keystone EC, Combe B, Smolen J, Strand V, Goel N, van Vollenhoven R, et al. Sustained efficacy of certolizumab pegol added to methotrexate in the treatment of rheumatoid arthritis: 2-year results from the RAPID 1 trial. Rheumatology (Oxford). 2012;51(9):1628-38.

van der Heijde D, Keystone EC, Curtis JR, Landewe RB, Schiff MH, Khanna D, et al. Timing and magnitude of initial change in disease activity score 28 predicts the likelihood of achieving low disease activity at 1 year in rheumatoid arthritis patients treated with certolizumab pegol: A post-hoc analysis of the RAPID 1 trial. J Rheumatol. 2012; 39(7):1326-33.

Studied period: **First subject enrolled:** 21 Jun 2005 **Last subject completed:** 06 Feb 2012	**Phase of development:** Phase 3

Objective(s): The primary objective of this study was to continue to assess the safety of certolizumab pegol (CZP) 400mg subcutaneously (sc) every 2 weeks followed by CZP 200mg sc every 2 weeks in treating signs and symptoms and preventing structural damage in subjects with active rheumatoid arthritis (RA).

Secondary objectives included:

- Continued assessment of the tolerability of CZP sc every 2 weeks in combination with methotrexate (MTX) in subjects with active RA.
- Continued assessment of the efficacy of CZP sc every 2 weeks in combination with MTX in

* The study was registered on EudraCT with the following title: 'A Phase III multi-centre, open-label, follow-on study to CDP870-027, to assess the efficacy and safety of lyophilised CDP870 an engineered human anti-TNF PEG conjugate, dosed subcutaneously at 400 mg every two weeks as additional medication to methotrexate, in the treatment of signs and symptoms and preventing structural damage in patients with active rheumatoid arthritis.' (this note was added for clarification purposes afterwards)

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 (CZP)	**Page:** Not applicable	

subjects with active RA.

- Continued assessment of the effect of CZP sc every 2 weeks in combination with MTX on Physical Function in subjects with active RA.
- Continued assessment of the effect of CZP sc every 2 weeks in combination with MTX on Health Outcomes measures in subjects with active RA.
- Continued monitoring of the plasma concentration and immunogenicity profile of CZP sc every 2 weeks for the first 2 years of experience and then every 6 months between 2 and 3 years of experience in combination with MTX in subjects with active RA.

Methodology: This was an open-label extension (OLE) study with 2 different eligible populations:

Withdrawers: Those subjects who failed to achieve an American College of Rheumatology (ACR) 20 response at Week 12 and which was confirmed at Week 14 of the feeder study (C87027).

Completers: Those subjects who completed the Week 52 assessment of the feeder study (C87027).

The Entry Visit corresponded to Week 16 of the feeder study [C87027] for Withdrawers and Week 52 of the feeder study for Completers. Following the Entry Visit for each subject population, efficacy was assessed every 12 weeks until Last Visit (Completion/Withdrawal), and safety was assessed every 2 weeks until Last Visit (Completion/Withdrawal) and also at the Safety Follow-Up Visits 12 and 24 weeks after last dose of study medication.

Radiographic assessments (digitized with centralized reading) of the hands and feet were obtained at Entry. For subjects in the Completers population, the radiographic assessments at the C87027 Week 52 Visit may have served as the Entry assessments for C87028, while for subjects in the Withdrawers population, the radiographic assessments at the Week 16 Visit (ie, C87027 Withdrawal Visit) may have served as the Entry assessment for C87028. Radiographic assessments were also performed at Weeks 24, 48, 72, 96 or Early Withdrawal Visit if it occurred prior to Week 96. Radiographic assessments were made by a central reader.

All subjects (including those withdrawn from study treatment) had Safety Follow-Up Visits 12 and 24 weeks after last dose of study medication.

Protocol Amendment 1 reduced the study medication dose from CZP 400mg to CZP 200mg sc every 2 weeks, based on data from 2 pivotal Phase 3, double-blind studies (C87027 and C87050)

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 (CZP)	**Page:** Not applicable	

demonstrating no significant dose effect (ie, no significant difference between the CZP 400mg and CZP 200mg every 2 weeks dose regimens) with regard to safety and efficacy.
Number of subjects (planned and analyzed): It was estimated that approximately 800 subjects would be enrolled from C87027. A total of 846 subjects enrolled in the study, received study medication, and were included in the Safety Set (SS).
Diagnosis and main criteria for inclusion: To qualify for entry into the feeder study (C87027), subjects must have had a diagnosis of adult-onset RA (of at least 6 months duration, but not longer than 15 years prior to Screening) as defined by the 1987 ACR classification criteria. To be eligible to enroll in C87028: 1) subjects must have either failed to achieve an ACR20 response at Weeks 12 and 14 in C87027 or must have completed the entire Week 52 assessment of C87027 study; 2) female subjects must have been either postmenopausal for at least 1 year, surgically incapable of child bearing, or effectively practicing an acceptable method of contraception, and must have agreed to continue to use adequate contraception during the study and for 12 weeks after the last dose of study medication (or longer if required by local regulations); 3) subjects must have had a clear chest x-ray at Entry; and 4) subjects must not have had a history of chronic infection, recent serious or life-threatening infection, or a current sign or symptom that may have indicated an infection.
Test product, dose(s) and mode of administration, batch number(s): Certolizumab pegol was provided as a lyophilized product and reconstituted with water for injection (200mg/vial; 200mg/mL). All CZP injections were administered by authorized study personnel at the investigative sites. Subjects began treatment in C87028 with CZP 400mg sc every 2 weeks (given as 2 injections, volume of 1mL each). After a minimum of 6 months of treatment during C87028 with CZP 400mg sc every 2 weeks, the dose was reduced to CZP 200mg sc every 2 weeks (given as a single 1mL injection).
Duration of treatment: Treatment in C87028 was continued until approval of the marketing application for the indication of RA in the subject's country or region or until further notice from UCB. During C87028, the mean duration of exposure to CZP was 1278.7 days (3.5 years), and maximum duration of exposure to CZP per subject was 2143 days (5.9 years). Including the feeder study, the mean duration of exposure to CZP was 1518 days (4.2 years), and the maximum duration of exposure to CZP per subject was 2268 days (6.2 years).
Reference therapy, dose(s) and mode of administration, batch number(s): None

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 (CZP)	**Page:** Not applicable	

Criteria for evaluation:

Efficacy: As this was primarily a safety study, a primary efficacy variable was not defined.

Secondary efficacy variables included:

- Percentage of subjects achieving ACR20, ACR50, and ACR70 response, respectively, in relation to Baseline of the feeder study.
- Change from Baseline of the feeder study in the modified total Sharp score (mTSS), erosion score, and joint space narrowing (JSN) score based on x-rays of the hands and feet
- Change from Baseline of the feeder study in the Disease Activity Score for 28 joints using the erythrocyte sedimentation rate (DAS28[ESR])
- Percentage of subjects achieving the European League Against Rheumatism (EULAR) response criteria
- Change from Baseline of the feeder study in tender joint count (TJC), based on 68 joints
- Change from Baseline of the feeder study in swollen joint count (SJC), based on 66 joints
- Change from Baseline of the feeder study in the Health Assessment Questionnaire-Disability Index (HAQ-DI) score
- Change from Baseline of the feeder study in Patient's Assessment of Arthritis Pain (PtAAP) - Visual Analog Scale (VAS)
- Change from Baseline of the feeder study in Patient's Global Assessment of Disease Activity (PtGADA)-VAS (originally referred to as the Patient's Global Assessment of Arthritis)
- Change from Baseline of the feeder study in Physician's Global Assessment of Disease Activity (PhGADA)-VAS (originally referred to as the Physician's Global Assessment of Arthritis)
- Change from Baseline of the feeder study in duration of morning stiffness
- Ratio to Baseline of the feeder study in C-reactive protein (CRP) and ESR
- Percentage of subjects withdrawing due to lack of efficacy or adverse events (AEs)
- Time to withdrawal due to lack of efficacy or AEs
- Percentage of subjects in remission, based on DAS28(ESR), TJC, SJC, and HAQ-DI, respectively

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 (CZP)	**Page:** Not applicable	

Other efficacy variables included:

- Short-Form 36-item Health Survey (SF-36) - subscale and summary scores
- European Quality of Life-5 Dimensions (EQ-5D) Health State Evaluation (administered only in Europe)
- Work Productivity Survey (WPS)
- Fatigue Assessment Scale (FASCA)
- Healthcare Resource Utilization (HCRU) questionnaire

Pharmacokinetics: Plasma CZP concentrations were determined.

Immunology: Presence of anti-CZP antibodies, anti-double–stranded DNA (ds-DNA), and anti-nuclear antibodies (ANA) were determined.

Safety: The primary objective of the study was safety. Safety variables included extent of exposure, AEs, biochemistry, hematology, urinalysis, vital signs, chest x-ray, concomitant medication, physical examination, and urine pregnancy testing.

Statistical methods: All safety and efficacy analyses were performed on the SS. A subject was included in the SS if he/she was enrolled and took at least 1 dose of study medication in C87028. Baseline was defined as Baseline of the feeder study (C87027). Summaries were reported for the Withdrawer and Completer subpopulations separately, as well as combined, grouping by treatment in C87027 as well as total. Efficacy results were analyzed using observed case analysis; no missing data were imputed.

The percentage of subjects (and associated 95% confidence intervals [CIs]) achieving ACR20, ACR50, and ACR70 response (improvement was calculated from Baseline) were summarized by visit and anti-CZP antibody status.

Descriptive statistics of the actual values and change from Baseline values were provided for mTSS, erosion score, JSN score, and DAS28(ESR). Frequency counts and percentages of the EULAR response from Baseline were presented by visit. The frequency and percentage of subjects (and associated 95% CI) achieving DAS28(ESR) remission were presented by visit.

Descriptive statistics of the actual values, and change and percentage change from Baseline were provided for TJC, SJC, and HAQ-DI. The frequency and percentage of subjects (and associated 95% CIs) achieving remission in TJC (defined as TJC=0), SJC (defined as SJC=0), or HAQ-DI (defined as HAQ-DI=0) were presented by visit.

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 (CZP)	**Page:** Not applicable	

Descriptive statistics of the actual values, and change and percentage change from Baseline were provided for the assessments of disease activity (PtAAP-VAS, PtGADA-VAS, and PhGADA-VAS). Descriptive statistics of the actual values and change from Baseline were provided for the duration of morning stiffness by visit for all subjects. Summary statistics for the actual values and ratio to Baseline for CRP at each scheduled visit were presented.

Time to withdrawal (from Entry) was plotted using Kaplan–Meier product limit plots and also summarized in a table. Subjects who did not withdraw were censored at the last scheduled visit. Drop outs for reasons other than lack of efficacy and AEs were censored at the time of drop out.

For the SF-36, descriptive statistics of the actual values (including summaries at Baseline) and change from Baseline were presented for the 2 SF-36 summary scores (Mental Component Summary [MCS] and Physical Component Summary [PCS]), and the 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) by visit for all subjects. Descriptive statistics for actual values and change from Baseline in FASCA and EQ-5D VAS were presented by visit. Descriptive statistics were presented for each question of the WPS. For the HCRU questionnaire, the number and length of stay of hospitalizations, number of outpatient visits, number of medical procedures performed, and number of home healthcare visits with onset during treatment were summarized.

Descriptive statistics of CZP plasma concentrations were presented by visit and by anti-CZP antibody status.

Shift tables were produced for presence of ANA and anti-dsDNA antibodies. The percentage of subjects with and without antibodies to CZP was summarized at each scheduled visit in this study and overall.

Safety tables presented all subjects in the SS, without regard to subgroups. Adverse events from the feeder study C87027 were included if the event occurred under treatment with CZP in the feeder study. Only subjects from C87027 who entered this OLE study were included in the AE analyses. Summaries of all AEs, serious AEs (SAEs), AEs leading to death, and AEs leading to withdrawal included the incidence rate (per 100 patient-years [pt-yrs]) with associated 95% CI, and the exposure adjusted event rate (per 100 pt-yrs).

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 (CZP)	**Page:** Not applicable	

Summary and conclusions:

Subject disposition: A total of 846 subjects were enrolled in this study and received open-label CZP. A total of 349 subjects (41.3%) withdrew from the study; the most frequent reasons for withdrawal were subject decision (142 subjects [16.8%]) and AEs (137 subjects [16.2%]).

A higher percentage of C87027-Withdrawers withdrew from the study (51.0%) compared with C87027-Completers (35.9%). The incidence of reasons for withdrawal from the study was similar between C87027-Withdrawers and C87027-Completers, with the exceptions of lack of efficacy and subject decision, which were higher in C87027-Withdrawers (5.7% and 21.5%, respectively) compared with C87027-Completers (1.6% and 14.2%, respectively).

Subject demographics and other Baseline characteristics: For all subjects, the mean age was 51.5 years, and the majority of subjects (87.1%) were in the age category of 18 to 64 years. The majority of subjects were female (82.9%) and Caucasian (90.5%). Age, gender, ethnicity, RA disease characteristics at Baseline, and RA medication history at Baseline were comparable for Withdrawers and Completers.

Efficacy results:

Assessments of signs and symptoms:

The percentage of subjects achieving ACR20 response (approximately 80% to 90%) was maintained during this, long-term open-label extension study (overall duration 6.6 years). The percentage of subjects achieving ACR50 response (approximately 55% to 65%) and ACR70 response (approximately 35% to 45%) were also maintained during this long-term, open-label study. In general, the percentage of Withdrawers achieving ACR20, ACR50, and ACR70 responses were lower, compared with Completers.

In general, a lower percentage of subjects who were anti-CZP antibody positive, compared with subjects who were anti-CZP antibody negative, were ACR20 responders. There was a notable difference at the Last Visit (Completion/Withdrawal), 69.4% of subjects (95% CI: 59.3%, 78.3%) who were anti-CZP antibody positive were ACR20 responders, compared with 82.9% of subjects (95% CI: 80.0%, 85.5%) who were anti-CZP antibody negative; there was no overlap in the 95% CIs. The results for ACR50 and ACR70 responders were similar. These results are not unexpected since subjects who were anti-CZP antibody positive had lower mean CZP plasma concentrations.

For DAS28(ESR), the percentage of subjects meeting the remission criterion and the mean decreases (improvement) from Baseline in DAS28(ESR) values remained relatively constant for the duration of the study. At the Last Visit (Completion/Withdrawal), 25.1% of subjects achieved DAS28(ESR) remission and the mean change from Baseline in DAS28(ESR) value was -3.222.

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 (CZP)	**Page:** Not applicable	

In general, a lower percentage of Withdrawers, compared with Completers, met the DAS28(ESR) remission criterion, and the mean decreases from Baseline were smaller (indicating less improvement) for Withdrawers, compared with Completers, during the study.

For EULAR responses, the percentage of subjects meeting the criterion of a good response remained relatively constant for the duration of the study; at the Last Visit (Completion/Withdrawal), 42.4% of subjects had a good EULAR response. The percentage of Withdrawers with a good EULAR response was consistently smaller, compared with Completers.

For TJC, the percentage of subjects meeting the remission criterion and the mean decreases (improvement) from Baseline remained relatively constant for the duration of the study. At the Last Visit (Completion/Withdrawal), 28.6% of subjects achieved TJC remission, and the mean decrease from Baseline in TJC was -24.02. In general, a lower percentage of Withdrawers, compared with Completers, met the TJC remission criterion, and the mean decreases from Baseline were smaller (indicating less improvement) for Withdrawers, compared with Completers.

For SJC, the percentage of subjects meeting the remission criterion and the mean decreases (improvement) from Baseline remained relatively stable for the duration of the study. At the Last Visit (Completion/Withdrawal), 47.3% of subjects achieved SJC remission, and the mean decrease from Baseline in SJC was -18.56. In general, a lower percentage of Withdrawers, compared with Completers, met the SJC remission criterion, and the mean decreases from Baseline were smaller (indicating less improvement) for Withdrawers, compared with Completers.

For PtAAP-VAS, the mean decreases (improvement) from Baseline remained relatively stable for the duration of the study; at the Last Visit (Completion/Withdrawal), the mean decrease from Baseline in PtAAP-VAS was -34.2. Throughout the study, Withdrawers had smaller mean decreases from Baseline (less improvement), compared with Completers.

For PtGADA-VAS, the mean decreases (improvement) from Baseline remained relatively stable over the duration of the study; at the Last Visit (Completion/Withdrawal), the mean decrease from Baseline in PtGADA-VAS was -33.8. Throughout the study, Withdrawers had smaller mean decreases from Baseline (less improvement), compared with Completers.

For PhGADA-VAS, the mean decreases (improvement) from Baseline remained relatively stable for the duration of the study; at the Last Visit (Completion/Withdrawal), the mean decrease from Baseline in PhGADA-VAS was -42.7. In general, Withdrawers had smaller mean decreases from Baseline (less improvement) in PhGADA-VAS score, compared with Completers.

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 (CZP)	**Page:** Not applicable	

The geometric mean CRP ratio to Baseline was <1 (decrease indicates improvement) and remained relatively stable for the duration of the study; at the Last Visit (Completion/Withdrawal), the mean geometric CRP ratio to Baseline was 0.366. In general, Withdrawers showed larger geometric CRP ratio to Baseline (less improvement), compared with Completers.

The geometric mean ESR ratio to Baseline was <1 (decrease indicates improvement) and remained relatively stable for the duration of the study; at the Last Visit (Completion/Withdrawal), the mean geometric ESR ratio to Baseline was 0.511. At Entry into C87028, Withdrawers showed a larger geometric mean ESR ratio to Baseline (less improvement), compared with Completers; starting at Week 48, the geometric mean ESR ratios to Baseline were similar in Withdrawers and Completers.

For HAQ-DI, the mean decreases (improvement) from Baseline and the percentage of subjects achieving HAQ-DI remission remained relatively stable for the duration of the study. At the Last Visit (Completion/Withdrawal), the mean decrease from Baseline was -0.674 and 11.2% of subjects achieved HAQ-DI remission. Throughout the study, Withdrawers had smaller mean decreases from Baseline (less improvement) in HAQ-DI scores and a lower percentage of subjects achieved HAQ-DI remission, compared with Completers.

Decreases in duration of morning stiffness were relatively stable during the study; at the Last Visit (Completion/Withdrawal), the mean decrease from Baseline was -2.1 hours. In general, the duration of morning stiffness was similar for Withdrawers and Completers.

A total of 163 subjects (19.3%) withdrew from the study due to a lack of efficacy or AEs; a higher percentage of Withdrawers, compared with Completers, withdrew from the study due to lack of efficacy or AEs.

Assessments of structural damage:

The last assessment of structural damage was performed at Week 96, unless the subject withdrew from the study prior to the visit. For mTSS, there was little increase (worsening) from Baseline during the C87028 study. At Week 96, the mean increase from Baseline in mTSS was 0.95; the median change from Baseline was 0.00 at all time points during the study, indicating at least 50% of subjects had no radiographic progression from Baseline.

For JSN score, there was little increase (worsening) from Baseline during the C87028 study. At Week 96, the mean increase from Baseline in JSN score was 0.81; the median change from Baseline was 0.00 at all time points, indicating at least 50% of subjects had no radiographic progression from Baseline. Withdrawers tended to have slightly smaller increases from Baseline in JSN score, compared with Completers.

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 (CZP)	**Page:** Not applicable	

For erosion score, there was little increase (worsening) from Baseline during the C87028 study. At Week 96, the mean increase from Baseline in erosion score was 0.14; the median change from Baseline in erosion score was 0.00 at all time points, indicating at least 50% of subjects had no radiographic progression from Baseline. Throughout the study, Withdrawers and Completers had comparable mean changes from Baseline in erosion score.

Other efficacy variables - health outcomes assessments:

For SF-36 PCS and MCS scores, the mean increases (improvement) from Baseline remained relatively stable during the study. At the Last Visit (Completion/Withdrawal), the mean increase from Baseline for PCS and MCS scores was 8.813 and 4.612, respectively. For both PCS and MCS scores, Withdrawers had slightly smaller mean increases from Baseline (less improvement) compared with Completers.

All SF-36 subscore domains (bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning, and vitality) showed similar increases (improvement) from Baseline, as the PCS and MCS scores, that were maintained during C87028.

For the EQ-5D VAS (administered only to subjects enrolled at sites in [redacted]), the mean increase (improvement) from Baseline remained relatively stable for the duration of the study; at the Last Visit (Completion/Withdrawal), the mean increase from Baseline was 22.65. Withdrawers had smaller mean increases from Baseline (less improvement) in EQ-5D VAS compared with Completers.

In terms of work absenteeism, as assessed through the WPS (Question 2), the mean number of work days missed in the last 6 months because of arthritis remained relatively stable during the study. At the Last Visit (Completion/Withdrawal), the mean number of work days missed (absenteeism) over the previous 6 months was 1.5 days; the median was 0 days missed, indicating at least 50% of subjects did not miss any work days in the last 6 months because of arthritis. In terms of presenteeism at work outside home, household productivity, and daily activities, as assessed through the WPS full version, the results at the Last Visit (Completion/Withdrawal), indicated a low impact of RA on these outcomes over the previous 6 months.

For the FASCA, the mean decreases (improvement) from Baseline were maintained during the study; at the Last Visit (Completion/Withdrawal), the mean decrease from Baseline was -2.7. The mean decreases from Baseline were slightly smaller (less improvement) for Withdrawers, compared with Completers.

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 (CZP)	**Page:** Not applicable	

For the HCRU questionnaire, the majority of subjects reported no hospitalizations, no home care visits, and no medical procedures with onset during treatment, over the first 24 weeks of C87028. The mean number of reported outpatient visits and home care visits were low.

For all efficacy assessments, improvements were maintained after the CZP dose was reduced from 400mg every 2 weeks to 200mg every 2 weeks.

Pharmacokinetic results: Geometric mean CZP plasma concentrations remained relatively constant through Week 60 (when subjects were receiving CZP 400mg every 2 weeks) and gradually decreased starting at Week 72 (when subjects started receiving CZP 200mg every 2 weeks). At the Last Visit (Completion/Withdrawal), the geometric mean CZP plasma concentration was 10.1µg/mL.

Geometric mean CZP plasma concentrations were lower in subjects who were anti-CZP antibody positive, as expected due to the increased PK clearance of CZP in subjects with anti-CZP antibodies.

Immunologic results: Of the subjects with ANA results at Baseline and post-Baseline during C87028, 57.5% had normal ANA results at Baseline and ANA present at any post-Baseline visit, while 3.4% of subjects had ANA present at Baseline and normal ANA results at all post-Baseline assessments.

Of the subjects with anti-dsDNA antibody results at Baseline and post-Baseline during C87028, 5.9% were anti-dsDNA antibody negative at Baseline and anti-dsDNA positive at any post-Baseline visit, while 2 subjects who were anti-dsDNA antibody positive at Baseline remained anti-dsDNA antibody positive post-Baseline during C87028.

At some time during the study, 11.6% of subjects had anti-CZP antibodies, but the majority of subjects (88.4%) remained anti-CZP antibody negative throughout the study.

Safety results: The maximum duration of CZP treatment was 2268 days (6.2 years) including the feeder study (C87027) and 2143 days (5.9 years) during C87028. The safety profile of long-term CZP treatment was in line with the anti-tumor necrosis factor alpha (TNFα) class of drugs. No new safety concerns were identified during this study in relation to the safety profile observed in previous CZP studies of shorter duration (treatment duration ≤1 year) and another long-term OLE study (treatment duration up to 2737 days [7.5 years]) in subjects with RA. It does not appear that long-term treatment is associated with a change in the type or severity of AEs. There were no new safety concerns noted during the 12-week and 24-week Safety Follow-Up Visits.

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 (CZP)	**Page:** Not applicable	

Exposure:

- Overall, the mean total duration of exposure (including the feeder study) was 1518.0 days (approximately 4.2 years). The mean number of CZP injections from Baseline was 157.2.

Adverse events:

- Sixteen subjects (1.9%) died during the study. The events of neoplasm malignant and sudden death, reported in 2 subjects each (0.2%), were the only events reported in more than 1 subject. Adverse events leading to death were considered by the Investigator to be related to study medication in 5 subjects: pneumonia, neoplasm malignant, gastric cancer stage IV, disseminated tuberculosis (TB) (1 subject each), and 1 subject with pyrexia, colon cancer, metastases to liver, and metastases to lung.
- A total of 352 subjects (41.6%) reported SAEs. The most frequently reported SAEs were RA (4.0% of subjects) and pneumonia (3.4%).
- Overall, 803 subjects (94.9%) reported at least 1 AE during CZP treatment (including the feeder study).
- Adverse events were reported most frequently in the Infections and infestations system organ class (SOC) (78.6% of subjects) and the Musculoskeletal and connective tissue disorders SOC (46.6%).
- The most frequently reported AEs (>15% of subjects) were hypertension (18.9% of subjects), nasopharyngitis (18.7%), urinary tract infection (18.1%), RA (17.8%), and upper respiratory tract infection (16.3%).
- A total of 137 subjects (16.2%) reported at least 1 AE leading to withdrawal. The most frequently reported AEs leading to withdrawal were pneumonia (0.9% of subjects), pulmonary TB (0.7%), and disseminated TB and Herpes zoster (0.5% each).
- A total of 85.6% of subjects reported AEs of mild intensity, 76.6% reported AEs of moderate intensity, and 24.8% reported AEs of severe intensity. The most frequently reported severe AEs were RA (1.7% of subjects) and pneumonia (1.4%).
- A total of 62.4% of subjects reported at least 1 AE that was judged by the Investigator to be related to study medication. The most frequently reported related AEs were urinary tract infection (9.5% of subjects) and upper respiratory tract infection (5.2%).

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 (CZP)	**Page:** Not applicable	

- A total of 84 subjects (9.9%) reported at least 1 AE in the Injection and infusion site reactions high level term (HLT). The most frequently reported AEs were injection site reaction (2.1% of subjects) and injection site discoloration (2.0%).
- The most frequently reported AEs suggestive of systemic hypersensitivity reactions were headache (11.0% of subjects), rash (7.4%), and pyrexia (7.2%). Two subjects reported AEs related to anaphylactic responses (verbatim terms: anaphylactic reaction to bee sting and anaphylaxis to diclofenac); neither of the events was related to study medication.
- A total of 665 subjects (78.6%) had at least 1 AE in the Infections and infestations SOC; 16.4% of subjects reported an SAE. The most frequently reported SAEs in the Infections and infestations SOC were cellulitis (1.3% of subjects) and pulmonary TB (1.1%).
- A total of 19 subjects (2.2%) reported tuberculous infections: pulmonary TB (1.1% of subjects), disseminated TB and TB (0.5% each), and tuberculous pleurisy (0.2%). Of the 19 subjects with tuberculous infections, 15 were enrolled at sites in [redacted] and 4 were enrolled at sites in [redacted].
- A total of 44 subjects (5.2%) reported at least 1 malignancy. The most frequently reported malignancies were basal cell carcinoma (1.2% of subjects) and thyroid neoplasm (0.8%).
- A total of 109 subjects (12.9%) reported at least 1 AE in the Cardiac disorders SOC. The most frequently reported AEs were palpitations (2.0% of subjects), angina pectoris (1.8%), atrial fibrillation (1.8%), tachycardia (1.4%), and myocardial ischemia (1.1%).
- A total of 256 subjects (30.3%) reported at least 1 AE in the Vascular disorders SOC. The most frequently reported AE was hypertension (18.9% of subjects).
- The most frequently reported autoimmune AE was sarcoidosis (4 subjects [0.5%]).
- The following neurological AEs of interest were identified following Sponsor medical review: amnesia (0.6% of subjects), and confusional state, grand mal convulsion, and ischaemic stroke (0.1% each). In addition, 0.2% of subjects reported SAEs of headache.
- Serious AEs suggestive of bleeding that were reported in more than 1 subject were metrorrhagia (0.5% of subjects) and contusion (0.2%).
- Adverse events suggestive of bone marrow aplasia were neutropenia and leukopenia (2.6% of subjects each), thrombocytopenia (0.8%), lymphopenia (0.4%), and pancytopenia, granulocytopenia, and autoimmune thrombocytopenia (0.1% each).
- Serious AEs suggestive of serious skin reactions were dermatitis allergic, pityriasis rosea, pruritus generalised, purpura, rash, and urticaria (0.1%).

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 (CZP)	**Page:** Not applicable	

- The incidence of AEs, AEs leading to death, and related AEs were similar in subjects who were anti-CZP antibody negative and anti-CZP antibody positive. There were lower incidences of severe AEs, SAEs, and AEs leading to withdrawal in subjects who were anti-CZP antibody negative, compared with subjects who were anti-CZP antibody positive.
  - In subjects who were anti-CZP antibody positive, compared with subjects who were anti-CZP antibody negative, there was a higher incidence of AEs in the Investigations SOC, General disorders and administration site conditions SOC, and Skin and subcutaneous tissue disorders SOC.
  - There was also a higher incidence of the AE of RA (indicating worsening of RA) in subjects who were anti-CZP antibody positive (28.6%), compared with subjects who were anti-CZP antibody negative (16.4%). This is consistent with the reduced efficacy (ACR20, ACR50, and ACR70 response) seen in these subjects. Other AEs with a higher incidence in subjects who were anti-CZP antibody positive, compared with subjects who were anti-CZP antibody negative, were pyrexia, rhinitis, conjunctivitis, diarrhoea, dyspepsia, cough, ALT increased, and rash.
- The event rates for AEs, SAEs, and AEs leading to withdrawal were lower on or after the CZP dose change, compared with before the CZP dose change. The event rate for AEs leading to death was similar before the CZP dose change and on or after the CZP dose change.

Clinical laboratory results:

- None of the minimum or maximum mean and median changes from Baseline in hematology and biochemistry laboratory parameters were considered to be of clinical significance or clinical importance.

Vital signs:

- None of the minimum and maximum mean and median changes from Baseline in vital signs were considered to be of clinical significance or clinical importance.

Conclusions: The primary objective of this study was to assess the long-term safety of CZP 400mg sc every 2 weeks followed by CZP 200mg sc every 2 weeks in subjects with RA. The results of this study demonstrated treatment with CZP was in line with what would be expected with drugs of this type and mechanism of action and with placebo-controlled studies with CZP. No new safety concerns were identified during this study.

The secondary objectives of this study were to assess the continuing long-term efficacy of CZP in the treatment of the signs and symptoms and prevention of structural damage in subjects with

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 (CZP)	**Page:** Not applicable	

active RA. Long-term use of CZP 400mg sc every 2 weeks followed by CZP 200mg sc every 2 weeks resulted in maintenance of robust improvements in measures of the signs and symptoms of RA (ACR20, ACR50, ACR70, DAS28[ESR], EULAR response, TJC, SJC, PtAAP-VAS, PtGADA-VAS, PhGADA-VAS, CRP ratio, ESR ratio, HAQ-DI, and duration of morning stiffness) and health outcome measures (SF-36, EQ-5D, WPS, FASCA, and HCRU), with little or no worsening in assessments of structural damage (mTSS, JSN score, and erosion score) during this study (up to 6.2 years of treatment for those subjects who remained in the study). The improvements were maintained after the CZP dose was reduced from 400mg every 2 weeks to 200mg every 2 weeks.

Overall, considering both the safety and efficacy results, this study demonstrated a positive benefit-risk ratio of long-term treatment with CZP 400mg every 2 weeks initially. The dose reduction to CZP 200mg every 2 weeks did not change this assessment, confirming that CZP 200mg every 2 weeks is an appropriate dose regimen for long-term treatment of subjects with moderate to severe RA.

Report date: 31 Jan 2013