C87051, 2005-002629-30

CLINICAL STUDY REPORT SYNOPSIS

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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.

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Sponsor:

UCB, Inc.

1950 Lake Park Drive

Smyrna, GA 30080

USA

Official study title:

A Phase III multi-center, open-label, follow-up study, to assess the safety and efficacy of liquid certolizumab pegol as additional medication to methotrexate, in the treatment of signs and symptoms and in the prevention of joint damage in patients with active rheumatoid arthritis who participated in Study CDP870-050

CLINICAL STUDY REPORT SYNOPSIS: C87051

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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-center, open-label, follow-up study, to assess the safety and efficacy of liquid certolizumab pegol as additional medication to methotrexate, in the treatment of signs and symptoms and in the prevention of joint damage in patients with active rheumatoid arthritis who participated in Study CDP870-050

Investigator(s): This was a multicenter study: 68 Investigators enrolled subjects (Principal Investigator: Prof [redacted])

Study site(s): This was a multicenter study; 68 centers in 13 countries enrolled subjects

Publication(s) (reference[s]): None

Studied period: **First subject enrolled:** 10 Nov 2005 **Last subject completed:** 08 Feb 2012	**Phase of development:** Phase 3

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

The secondary objectives were:

- Continued assessment of the tolerability of liquid CZP sc every 2 weeks in subjects with active RA
- Continued assessment of the efficacy of liquid CZP sc every 2 weeks in subjects with active RA
- Continued assessment of the effect of liquid CZP sc every 2 weeks on physical function in subjects with active RA
- Continued assessment of the effect of liquid CZP sc every 2 weeks on health outcome measures in subjects with active RA
- Continued monitoring of the plasma concentration and immunogenicity profile of liquid CZP sc every 2 weeks in subjects with active RA.

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Methodology: This was a multicenter, open-label, follow-up study to C87050 with 2 different eligible populations:

Withdrawers: Those subjects who failed to achieve an American College of Rheumatology (ACR) 20 response at Week 12 which was confirmed at Week 14 of the feeder study (C87050).

Completers: Those subjects who completed the Week 24 assessment of the feeder study (C87050).

The Entry Visit corresponded to Week 16 of the feeder study for Withdrawers and Week 24 of the feeder study for Completers. All visit weeks are from Entry into C87051. Following the Entry Visit (Week 0), eligible subjects were assessed for efficacy at Weeks 12, 24, 40, and 52 and then every 12 weeks following Week 52, through the Last Visit (Completion/Withdrawal). Safety was assessed at all visits beginning at Entry and included the Safety Follow-Up Visits that occurred 12 and 24 weeks after the last dose of study medication.

Radiographic assessments (digitized with centralized reading) of the hands and feet were obtained at Entry, Weeks 24, 76, and 104 or at the early Withdrawal Visit if it occurred prior to Week 104. Radiographic assessments were performed by a central reader. Subjects who were defined as "Withdrawers" in C87050 were expected to complete an x-ray of their hands and feet at 24 weeks after randomization in C87050; however, this x-ray may have been completed during participation in C87051.

All subjects, including those withdrawn from study treatment, were to have Safety Follow-Up Visits 12 and 24 weeks after their last dose of study medication.

Protocol Amendment 3 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) 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.

Three substudies evaluated self-injection of CZP in a subset of subjects in C87051.

Number of subjects (planned and analyzed): It was estimated that approximately 450 subjects would be enrolled from C87050. A total of 567 subjects enrolled in the study, received study medication, and were included in the Safety Set (SS).

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Diagnosis and main criteria for inclusion: To quality for entry into the feeder study (C87050), 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 C87051: 1) subjects must have either failed to achieve an ACR20 response at Weeks 12 and 14 in C87050 or must have completed the entire Week 24 assessment of C87050 study; 2) subjects must have had a clear chest x-ray at Entry; 3) female subjects must have been either postmenopausal for at least 2 years, surgically incapable of childbearing, 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); 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 liquid formulation was supplied as 3mL vials, containing an extractable volume of 1mL of liquid CZP for single use at a dosage strength of 200mg/mL. In addition, CZP for injection was supplied in prefilled, individually packaged, 1mL syringes with 25G needles (prefilled syringes [PFS]), containing an injectable volume of 1mL of liquid CZP for single use at a dose strength of 200mg/mL.

For the self-injection substudies, CZP for injection was supplied as:

- Prefilled, individually packaged 1mL syringes with 25G needles (PFS) containing an injectable volume of 1mL of liquid CZP for single use at a dosage strength of 200mg/mL.
- Ergonomically-improved, prefilled, 1mL syringes with 25G needles (PFS) containing an injectable volume of 1ml of liquid CZP for single use at a dosage strength of 200mg/mL.
- An individual package for auto-injection, containing one 1mL auto injector (AI) device with a 25G needle containing an injectable volume of 1mL of liquid CZP for single use at a dosage strength of 200mg/mL. This formulation was used at a limited number of sites only by subjects participating in the AI substudy.

Duration of treatment: Treatment in C87051 was continued until after marketing approval or until further notice by UCB. During C87051, the mean duration of exposure to CZP was 1301.6 days (3.6 years), and maximum duration of exposure to CZP per subject was 1945 days (5.3 years). Including the feeder study, the mean duration of exposure to CZP was 1423.3 days (3.9 years), and the maximum duration of exposure to CZP per subject was 2085 days (5.7 years).

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Reference therapy, dose(s) and mode of administration, batch number(s): None

Criteria for evaluation:

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

Secondary efficacy variables were:

- Percentage of subjects achieving ACR20, ACR50, and ACR70 response in relation to Baseline of the feeder study (C87050)
- Change from Baseline of the feeder study in 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 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
- Change from Baseline of the feeder study in Physician's Global Assessment of Disease Activity (PhGADA)-VAS
- Change from Baseline of the feeder study in duration of morning stiffness
- Change from Baseline of the feeder study in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)

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- 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

Other efficacy variables were:

- 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) antibodies, and antinuclear antibodies (ANA) were determined.

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

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 during C87051. Baseline was defined as Baseline of the feeder study (C87050). Summaries were reported for the Withdrawer and Completer subpopulations separately, as well as combined, grouping by treatment in C87050 as well as total. Efficacy results were analyzed using observed case analysis; no missing data were imputed.

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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.

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 values for CRP and ESR 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.

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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 (C87050) were included if the event occurred under treatment with CZP in the feeder study. Only subjects from C87050 who entered this open-label 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).

Summary and conclusions:

Subject disposition: A total of 567 subjects were enrolled in this study and received open-label CZP. A total of 221 subjects (39.0%) withdrew from the study; the most frequent reasons for withdrawal were AEs (102 subjects [18.0%]) and subject decision (87 subjects [15.3%]).

A similar percentage of C87050-Withdrawers (39.9%) and C87050-Completers (38.3%) withdrew from the study. A lower percentage of C87050-Withdrawers (15.9%) withdrew due to AEs, compared with C87050-Completers (19.2%), and a higher percentage of C87050-Withdrawers withdrew due to subject decision and lack of efficacy (17.8% and 4.3%, respectively), compared with C87050-Completers (13.9% and 0.8%, respectively).

Subject demographics and other Baseline characteristics: For all subjects, the mean age was 51.6 years, and the majority of subjects (85.7%) were in the age category of 18 to 64 years. The majority of subjects were female (81.7%) and Caucasian (98.6%). Age, gender, ethnicity, RA disease characteristics at Baseline, and RA medication history at Baseline were comparable for Withdrawers and Completers; there were no meaningful differences.

Efficacy results:

Assessments of signs and symptoms:

The percentage of subjects achieving ACR20 response (approximately 75% to 85%) was maintained during this long-term, open-label extension study (overall duration approximately 6.3 years). The percentage of subjects achieving ACR50 response (approximately 45% to 55%) and ACR70 response (approximately 20% to 30%) 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.

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Throughout the study, a lower percentage of subjects who were anti-CZP antibody positive were ACR20, ACR50, and ACR70 responders, compared with subjects who were anti-CZP antibody negative. The difference was notable for ACR50 responders at the Last Visit (Completion/Withdrawal); 31.4% of subjects (95% CI: 21.8%, 42.3%) who were anti-CZP antibody positive were ACR50 responders, compared with 50.3% of subjects (95% CI: 45.7%, 54.9%) who were anti CZP antibody negative; there is no overlap in the 95% CIs. 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 the feeder study (C87050) remained relatively stable for the duration of the study. At the Last Visit (Completion/Withdrawal), 17.5% of subjects achieved DAS28(ESR) remission and the mean change from Baseline in DAS28(ESR) value was -2.990. 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 increased from Entry into C87051 through Week 40, and after Week 40 remained relatively stable for the duration of the study; at the Last Visit (Completion/Withdrawal), 36.0% of subjects had a good EULAR response. The percentage of subjects with a good EULAR response was, in general, smaller for Withdrawers, compared with Completers.

For TJC, the percentage of subjects meeting the remission criterion increased from Entry into C87051 through Week 52, and remained relatively stable for the duration of the study. For mean decreases (improvement) from Baseline of the feeder study in TJC, there were decreases from Entry into C87051 through Week 12 and the decreases remained relatively stable for the duration of the study. At the Last Visit (Completion/Withdrawal), 21.8% of subjects achieved TJC remission, and the mean decrease from Baseline in TJC was -23.24 (decrease indicates improvement). 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 of the feeder study remained relatively stable for the duration of the study. At the Last Visit (Completion/Withdrawal), 42.4% of subjects achieved SJC remission, and the mean decrease from Baseline in SJC was -17.71. In general, a lower percentages of Withdrawers, compared with Completers, achieved SJC remission during the study, and throughout the study, the mean decreases from Baseline were smaller (indicating less

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improvement) for Withdrawers, compared with Completers.

For PtAAP-VAS, the mean decreases (improvement) from Baseline of the feeder study remained relatively stable for the duration of the study; at the Last Visit (Completion/Withdrawal), the mean decrease from Baseline in PtAAP-VAS was -26.6 (decrease indicates improvement). Throughout the study, in general, 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 -26.2. Throughout the study, in general, Withdrawers had smaller mean decreases from Baseline (less improvement), compared with Completers.

For PhGADA-VAS, the mean decreases (improvement) from Baseline of the feeder study remained relatively stable for the duration of the study; at the Last Visit (Completion/Withdrawal), the mean decrease from Baseline in PhGADA-VAS was -41.9. In general, Withdrawers had smaller mean decreases from Baseline (less improvement) in PhGADA-VAS score, compared with Completers.

The geometric mean CRP ratio to Baseline of the feeder study 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 0.363. In general, Withdrawers showed larger geometric CRP ratio to Baseline (less improvement), compared with Completers.

The geometric mean ESR ratio to Baseline of the feeder study 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 0.520. At Entry into C87051 through Week 40, Withdrawers showed larger geometric mean ESR ratio to Baseline of the feeder study (less improvement), compared with Completers; starting at Week 52, the results were similar for Withdrawers and Completers.

For HAQ-DI, the mean decreases (improvement) from Baseline of the feeder study 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 -0.567 and 9.4% of subjects achieved HAQ-DI remission. Throughout the study, Withdrawers had smaller mean decreases from Baseline (less improvement) in HAQ-DI scores and, in general, a lower percentage of subjects achieved HAQ-DI remission, compared with Completers.

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Decreases in duration of morning stiffness were relatively stable during the study; at the Last Visit (Completion/Withdrawal), the mean decrease from Baseline was -2.3 hours. In general, the duration of morning stiffness was similar for Withdrawers and Completers, with the exception of Entry into C87051.

A total of 97 subjects (17.1%) withdrew from the study due to a lack of efficacy or AEs; a similar percentage of C87050-Withdrawers (18.3% of subjects) and C87050-Completers (16.4%) withdrew from the study due to lack of efficacy or AEs.

For all signs and symptoms assessments, Withdrawers had rapid improvement (from Baseline of the feeder study) during the first 24 weeks after Entry into C87051 and the improvements were maintained throughout the study.

Assessments of structural damage:

The last assessment of structural damage was performed at Week 104, unless the subject had withdrawn from the study prior to the visit. For mTSS, there was little increase (worsening) from Baseline of the feeder study during the C87051 study. At Week 104, the mean increase from Baseline in mTSS was 0.99; 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 of the feeder study. Withdrawers had larger mean increases from Baseline (indicating worsening) in mTSS, compared with Completers, except at Entry into C87051. Withdrawers had a higher mean mTSS at Baseline of the feeder study, compared with Completers (40.26 and 33.51, respectively).

For JSN score, there was little increase (worsening) from Baseline of the feeder study during the C87051 study. At Week 104, the mean increase from Baseline in JSN score was 0.70; the median change from Baseline was 0.00 at all time points, indicating at least 50% of subjects had no radiographic progression from Baseline of the feeder study. Withdrawers had larger mean increases from Baseline (increase indicates worsening) in JSN score, compared with Completers, except at Entry into C87051.

For erosion score, there was little increase (worsening) from Baseline of the feeder study during the C87051 study. At Week 104, the mean increase from Baseline in erosion score was 0.29; 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 of the feeder study. Throughout the study, Withdrawers had larger mean increases from Baseline (increase indicates worsening) in erosion score, compared with Completers.

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Other efficacy variables - health outcomes assessments:

For SF-36 PCS and MCS scores, the mean increases (improvement) from Baseline of the feeder study remained relatively stable during the study. At the Last Visit (Completion/Withdrawal), the mean increase from Baseline for PCS and MCS scores was 6.628 and 4.325, respectively. For both PCS and MCS scores, in general, Withdrawers had 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 of the feeder study, as the PCS and MCS scores, that were maintained during C87051.

For the EQ-5D VAS, the mean increase (improvement) from Baseline of the feeder study remained relatively stable for the duration of the study; at the Last Visit (Completion/Withdrawal), the mean increase from Baseline was 22.1. 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, few work days were missed because of arthritis over the previous 6 months; at the Last Visit (Completion Withdrawal), the mean was 1.3 work days missed. The results also indicated maintained improvements in terms of both workplace and household productivity, and daily activities, as assessed through the WPS full version over the first 24 weeks of C87051.

For the FASCA, the mean decreases (improvement) from Baseline of the feeder study were maintained during the study; at the Last Visit (Completion/Withdrawal), the mean decrease from Baseline was -3.1. The mean decreases from Baseline were smaller (less improvement) for Withdrawers, compared with Completers.

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 C87051. The mean number of reported outpatient visits and home care visits were low.

Pharmacokinetics results: Geometric mean plasma CZP concentrations ranged from 26.9µg/mL to 43.6µg/mL from Week 12 to Week 64 (when subjects were receiving CZP 400mg every 2 weeks) and gradually decreased after Week 64 (when subjects started receiving CZP 200mg every 2 weeks). At the Last Visit (Completion/Withdrawal), the geometric mean plasma CZP concentration was 10.8µg/mL.

Geometric mean plasma CZP 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.

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Immunologic results: Of the subjects with ANA results at Baseline and post-Baseline during C87051, 53.4% had normal ANA results (corresponding to dilutions of <1:40) at Baseline and ANA present (corresponding to dilutions of ≥1:40) at any post-Baseline visit, while 2.6% of subjects had ANA present at Baseline and normal ANA levels at all post-Baseline assessments.

Of the subjects with anti-dsDNA antibody results at Baseline and post-Baseline during C87051, 15.6% were anti-dsDNA antibody negative (corresponding to dilutions of <30 IU/mL) at Baseline and anti-dsDNA antibody positive (corresponding to dilutions of ≥30 IU/mL) at any post-Baseline visit, while 4 subjects (0.7%) who were anti-dsDNA antibody positive at Baseline were anti-dsDNA antibody negative at all post-Baseline assessments.

At some point during the study, 15.2% of subjects had anti-CZP antibodies (defined as having a value >2.4U/mL), but the majority of subjects (84.8%) remained anti-CZP antibody negative (defined as having no values >2.4U/mL) throughout the study

Safety results: The maximum duration of CZP treatment was 2085 days (5.7 years) including the feeder study (C87050) and 1945 days (5.3 years) during C87051. The safety profile of long-term CZP treatment was in line with the anti-tumor necrosis factor alpha (anti-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 other long-term open-label extension (OLE) studies (treatment duration ≤2737 days [7.5 years]) in subjects with RA. There were no new safety concerns noted during the 12-Week and 24-Week Safety Follow-Up Visits.

Exposure:

- Overall, the mean total duration of exposure (including the feeder study) was 1423.3 days (3.9 years). The mean number of CZP injections (subjects received CZP 200mg per injection) from Baseline was 141.6.

Adverse events:

- Seventeen subjects (3.0%) died during C87051. The events of myocardial ischaemia and cerebrovascular accident, reported in 2 subjects each (0.4%), 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 6 subjects: colon cancer, gastric cancer, gastrointestinal cancer metastatic, hepatic cirrhosis, toxic shock syndrome streptococcal, and tuberculosis (TB) of central nervous system.

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- A total of 200 subjects (35.3%) reported SAEs during CZP treatment (including the feeder study). The most frequently reported SAE was RA (3.4% of subjects).
- Overall, 505 subjects (89.1%) 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) (69.7% of subjects) and the Musculoskeletal and connective tissue disorders SOC (34.2%).
- The most frequently reported AEs (>15% of subjects) were upper respiratory tract infection (16.0% of subjects) and RA (15.2%).
- A total of 100 subjects (17.6%) reported at least 1 AE leading to withdrawal. The most frequently reported AEs leading to withdrawal were pulmonary TB (1.4% of subjects) and TB (0.7%).
- A total of 76.7% of subjects reported AEs of mild intensity, 65.8% reported AEs of moderate intensity, and 22.9% reported AEs of severe intensity. The most frequently reported severe AEs were RA (1.6% of subjects) and pulmonary TB (1.1%).
- A total of 47.1% of subjects reported at least 1 AE that was judged by the Investigator to be related to study medication. The most frequently reported related AE was activated partial thromboplastin time prolonged (8.5% of subjects).
- A total of 17 subjects (3.0%) reported at least 1 AE in the Injection and infusion site reactions high level term (HLT). The most frequently reported AE was injection site erythema (1.1% of subjects).
- The most frequently reported AEs suggestive of systemic hypersensitivity reactions were headache (7.8% of subjects), pyrexia (3.9%), and rash (3.4%).
- A total of 395 subjects (69.7%) had at least 1 AE in the Infections and infestations SOC; 13.8% of subjects reported an SAE. The most frequently reported SAEs in the Infections and infestations SOC were pneumonia and pulmonary TB (1.6% of subjects each).

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- A total of 17 subjects (3.0%) reported tuberculous infections: pulmonary TB (1.6% of subjects), TB (0.7% of subjects), and disseminated TB, lymph node TB, meningitis tuberculous, TB of central nervous system, and TB of intrathoracic lymph nodes (0.2% of subjects each). All 17 subjects who reported tuberculous infections were enrolled at sites in [redacted]. No other serious opportunistic infections were identified.
- A total of 24 subjects (4.2%) reported at least 1 malignancy. The most frequently reported malignancies were lung neoplasm and lung neoplasm malignant (3 subjects each [0.5%]).
- A total of 51 subjects (9.0%) reported at least 1 AE in the Cardiac disorders SOC. The most frequently reported AEs were myocardial ischaemia (8 subjects [1.4%]), angina pectoris and tachycardia (7 subjects each [1.2%]), and cardiomegaly (6 subjects [1.1%]).
- A total of 107 subjects (18.9%) reported at least 1 AE in the Vascular disorders SOC. The most frequently reported AE was hypertension (77 subjects [13.6%]).
- The most frequently reported autoimmune AE was autoimmune thyroiditis (3 subjects [0.5%]).
- The following neurological AEs of interest were identified following Sponsor medical review: transient ischaemic attack (7 subjects [1.2%]), cerebrovascular accident (2 subjects [0.4%]), and cerebral haemorrhage and cerebral ischaemia (1 subject each [0.2%]).
- Serious AEs suggestive of bleeding were reported in 9 subjects (1.6%); events reported in more than 1 subject were metrorrhagia (3 subjects [0.5%]) and haematuria (2 subjects [0.4%]).
- Adverse events suggestive of bone marrow aplasia were leukopenia (11 subjects [1.9%]), thrombocytopenia (5 subjects [0.9%]), lymphopenia (4 subjects [0.7%]), neutropenia (2 subjects [0.4%]), and pancytopenia (1 subject [0.2%]).
- One SAE was suggestive of a serious skin reaction: leukocytoclastic vasculitis (1 subject [0.2%]).

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- The incidence of AEs, AEs leading to death, SAEs, AEs leading to withdrawal, severe AEs and related AEs were higher in subjects who were anti-CZP antibody positive, compared with subjects who were anti-CZP antibody negative.
  - 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 following SOCs: General disorders and administration site conditions, Musculoskeletal and connective tissue disorders, and Renal and urinary disorders
  - There was a higher incidence of the AE of RA in subjects who were anti-CZP antibody positive (26.7%), compared with subjects who were anti-CZP antibody negative (13.1%).
- The event rates for AEs, SAEs, and AEs leading to withdrawal were higher before the CZP dose change, compared with on or after the CZP dose change. The event rate for AEs leading to death was slightly lower before the CZP dose change, compared with on or after the CZP dose change.

Clinical laboratory results:

- None of the minimum or maximum mean and median changes from Baseline of the feeder study 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 of the feeder study 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 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

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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 5.7 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.

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