C87094, 2008-005427-28

CLINICAL STUDY REPORT SYNOPSIS

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

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Sponsor:

UCB Pharma SA

Allée de la Recherche 60

1070 Anderlecht (Brussels)

Belgium

Official study title:

A Phase IIIb, multicenter study with a 12-week double-blind, placebo-controlled, randomized period followed by an open-label, extension phase to evaluate the safety and efficacy of certolizumab pegol administered to patients with active rheumatoid arthritis

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Name of finished product: Cimzia	**Volume:** Not applicable	
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Title of study: A Phase IIIb, multicenter study with a 12-week double-blind, placebo-controlled, randomized period followed by an open-label, extension phase to evaluate the safety and efficacy of certolizumab pegol administered to patients with active rheumatoid arthritis.

Investigator(s): This was a multicenter study; 179 Investigators enrolled subjects.

Study site(s): This was a multicenter study; 179 sites enrolled subjects.

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

Studied period: The total duration of subject participation was 44 weeks if CZP was commercially available at the time of the subject's Week 28 visit; otherwise, the subject's study duration was to be extended until CZP became commercially available. **First subject enrolled:** 23 Jul 2008 **Last subject completed:** 08 Mar 2011	**Phase of development:** Phase 3b

Objective(s): The primary objective of this study was to assess the clinical response rate as measured by American College of Rheumatology 20% response rate (ACR20; as defined by the 1987 classification criteria) at Week 12.

The secondary objectives of this study were as follows:

- To assess for all subjects at Week 12 the following:
  - The clinical response rate as measured by American College of Rheumatology 50% (ACR50) and 70% (ACR70) responses

    The reduction of disease activity by the Disease Activity Score–28 (DAS28[C-reactive protein, CRP]), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI)
  - The achievement of clinical remission (by DAS28[CRP], SDAI and CDAI)
  - The improvement in individual components of the ACR criteria, including tender joint count (TJC), swollen joint count (SJC), Health Assessment Questionnaire-Disability Index (HAQ–DI), CRP, Patient's Assessment of Arthritis Pain (PAAP), Patient's

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Global Assessment of Disease Activity (PtGADA), and Physician's Global Assessment of Disease Activity (PhGADA)
- Time to sustained ACR20 response
- European League Against Rheumatism (EULAR) response
- The tolerability and safety of CZP therapy in subjects with active rheumatoid arthritis (RA) over the first 12 weeks of treatment

- To assess every 8 weeks and at the Completion/Withdrawal Visit in the group remaining in the study after Week 12:
  - The clinical response rate as measured by ACR20/50/70 response criteria
  - The reduction of disease activity (by DAS28[CRP], SDAI and CDAI)
  - The achievement of clinical remission (by DAS28[CRP], SDAI and CDAI)
  - The change from Baseline in individual components of the ACR criteria, including TJC, SJC, HAQ–DI, CRP, PAAP, PtGADA, and PhGADA
- To evaluate the tolerability and safety of CZP therapy in subjects with active RA over the open-label treatment extension phase (OL Phase).
- To evaluate the influence of the following characteristics on ACR20 response rate at Week 12 and adverse events (AEs) with CZP therapy in subjects with active RA:
  - on methotrexate (MTX) versus RA treatment regimens without MTX
  - in anti-tumor necrosis factor alpha (TNFα)-naive subjects versus those with prior anti-TNFα use
  - in subjects with disease duration of less than 2 years from diagnosis versus greater than or equal to 2 years

The exploratory objectives of this study were as follows:

- To characterize the nature and time course of therapeutic response to CZP, as measured by messenger ribonucleic acid (mRNA) levels of genes relevant to the inflammatory and immune response process and genomic analysis, to explore candidate CZP response biomarkers using blood samples from consenting subjects in the [redacted] and [redacted]
- To collect at Baseline and Week 12 subject's willingness to self-inject the study drug
- To assess subject's sleep as measured by the Sleep Scale Medical Outcomes Study (MOS) at Baseline, Weeks 6, 12, every 8 weeks in the OL Phase, and at the

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Completion/Withdrawal Visit

- The resource utilization data using the UCB resource utilization data standards at Baseline, Weeks 2, 6, 12, every 8 weeks in the OL Phase, and at the Completion/Withdrawal Visit
- To assess subject's fatigue (tiredness) as measured by the Fatigue Assessment Scale at Baseline, Weeks 2, 6, 12, every 8 weeks in the OL Phase, and at the Completion/Withdrawal Visit
- To assess the disease activity as measured by the Rheumatoid Arthritis Disease Activity Index (RADAI) at Baseline, Weeks 2, 6, 12, every 8 weeks in the OL Phase, and at the Completion/Withdrawal Visit
- To assess subject's physical function as measured by the Functional Status Assessment (FSA) at Baseline, Weeks 2, 6, 12, every 8 weeks in the OL Phase, and at the Completion/Withdrawal Visit
- To assess the reduction of disease activity and achievement of clinical remission (by DAS28 (erythrocyte sedimentation rate; ESR)

Methodology: This was a Phase IIIb multicenter study with a 12-week, double-blind, placebo (PBO)-controlled, randomized phase (DB Phase) followed by an OL extension (OL Phase) to evaluate the safety and efficacy of CZP administered to subjects with moderate to severe RA.

Eligible subjects were randomized (4:1 ratio) to receive either CZP (400mg at Weeks 0, 2, and 4, followed by 200mg every 2 weeks [Q2W]) or PBO given Q2W, up to and including Week 10. The randomization was stratified according to the following three factors in order to ensure proper balance:

- Concomitant use of MTX: Yes versus No
- Prior anti-TNFα use: Yes versus No
- Disease duration category: <2 years versus ≥2 years

Subjects were allowed to enter the study without disease modifying antirheumatic drug (DMARD) therapy or to continue their current nonbiological treatment regimens for RA if the regimens could remain unmodified until Week 12.

Starting at Week 12, all subjects received treatment with OL CZP (200mg given Q2W) for a

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minimum of 16 additional weeks (through Week 28). If approval of the marketing application for CZP in RA and market availability occurred prior to a subject's Week 28 visit, the Week 28 visit was to be considered the Completion Visit. In this case, the maximum duration of subject participation was 44 weeks, which consisted of a Screening Phase of up to 4 weeks, the 12-week DB Phase, the 16-week OL Phase, and the 12-week Safety Follow-up (SFU) Phase. If CZP was not commercially available at the time a subject completed the Week 28 visit, the study duration was to be extended until CZP became commercially available.

Number of subjects (planned and analyzed): A total of 1048 subjects were planned for enrollment into this study and, ultimately, 1063 subjects were randomized (212 subjects to PBO and 851 subjects to CZP). A total of 955 subjects completed the DB Phase and entered the OL Phase (184 subjects in the PBO group and 771 subjects in the CZP group).

Diagnosis and main criteria for inclusion: Subjects had to be at least 18 years old, have a diagnosis of adult–onset RA of at least 3 months duration as defined by the 1987 American College of Rheumatology classification criteria, and have active RA disease as defined by: ≥5 tender joints (28 joint count) at Screening and Baseline; ≥4 swollen joints (28 joint count) at Screening and Baseline; and ≥10mg/L CRP and/or ≥28mm/hour ESR (Westergren) at Screening. Subjects must have had an unsatisfactory response or intolerance to at least one traditional DMARD.

Test product, dose(s) and mode of administration, batch number(s): Certolizumab pegol for injection was provided in 1mL prefilled syringes (PFS) with 25G needles, containing an injectable volume of 1mL of liquid CZP (acetate pH 4.7) for single subcutaneous use at a dosage strength of 200mg/mL. Batch numbers: [redacted].

Duration of treatment: During the 12-week DB Phase, subjects received either CZP (400mg at Weeks 0, 2, and 4, followed by 200mg Q2W) or PBO given Q2W through Week 10. Starting at Week 12, all subjects received treatment with OL CZP (200mg given Q2W) for a minimum of 16 additional weeks (through Week 28). If approval of the marketing application for CZP in RA and market availability occurred prior to a subject's Week 28 visit, the Week 28 visit was to be considered the Completion Visit. If CZP was not commercially available at the time a subject completed the Week 28 visit, the study duration was to be extended until CZP became commercially available.

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Reference therapy, dose(s) and mode of administration, batch number(s): Placebo for injection was provided in PFS of 0.9% saline (NaCl, preservative free) solution of pharmacopoeia (USP/Ph Eur) quality containing an injectable volume of 1mL of saline for single subcutaneous use. Batch numbers: [redacted].

Criteria for evaluation:

Efficacy: The primary efficacy variable was defined as the ACR20 responder rate at Week 12. The secondary efficacy variables included: ACR20/50/70 responder rates, DAS28(CRP), SDAI, and CDAI, improvement in individual components of the ACR criteria, including TJC, SJC, HAQ–DI, CRP, PAAP, PtGADA, and PhGADA, and EULAR response. The exploratory efficacy variables of this study included: Sleep Scale MOS, Fatigue Assessment Scale, RADAI, FSA, resource utilization data using the UCB resource utilization data standards, and DAS28(ESR).

Safety: Safety variables included AEs, clinical laboratory evaluations, vital signs, physical examinations, and TB testing.

Statistical methods: The primary efficacy variable, defined as the ACR20 responder rate at the Week 12 Visit, was analyzed on the Full Analysis Set (FAS), which included relevant data from all randomized subjects (Screening and Baseline data from the Pretreatment Period and all data from the DB Treatment Phase of the study). A logistic regression model was used including terms for:

- Treatment (CZP vs PBO)
- Concomitant use of MTX as defined at randomization (Yes vs No)
- Prior anti-TNFα use as defined at randomization (Yes vs No)
- Disease duration category as defined at randomization (<2 years vs ≥2 years)

The odds ratio (OR) comparing CZP to PBO was estimated from this logistic regression model and presented with 95% 2-sided confidence intervals (CIs). After unblinding the study, the goodness of fit of the logistic model was examined specifically by viewing the distribution of cell frequencies for the combination of all terms in the model along with the response. If one or more cells had zero observations, then the term disease duration was to be dropped from the model, and the analysis re-done with the remaining terms. The p-value was generated from the Wald test. Subjects who withdrew prematurely from the study prior to Week 12, or who had a missing ACR20 response at Week 12 were counted as non-

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responders.

The hypotheses of interest were stated as follows:

- Null (H_0): The OR for response (CZP/PBO) is equal to 1
- Alternative (H_1): The OR for response (CZP/PBO) is not equal to 1.

The primary efficacy variable was summarized and analyzed on the FAS separately for each stratification variable used in the primary logistic regression model. The percent of ACR20 responders was displayed by treatment group for each level of the stratification variable of interest. For each stratification variable, three unique models were constructed.

The first model included treatment and the respective stratification variable as factors. The OR comparing CZP to PBO and the corresponding 95% 2-sided CIs and p-values (from the Wald test) were displayed. In addition, the p-value for the stratification variable (covariate) term was displayed.

A second model with just treatment as a factor was constructed for each level of the stratification variable. The OR (CZP to PBO) and the corresponding 95% 2-sided CIs and p-values were displayed.

A third model included treatment, the respective stratification variable, and a treatment by stratification variable term as factors. The interaction (treatment by stratification variable) p-value was displayed from this model. Due to the relatively large sample size, interaction was tested at the 5% significance level.

Additional supportive and sensitivity analyses based on alternative statistical models and other nonstratification factors were also performed.

Summary and conclusions:

Subject disposition: A total of 1648 subjects were screened for the study; of these, 1063 subjects were subsequently randomized (212 to PBO and 851 to CZP). The majority of subjects (184 [86.8%] in the PBO group and 771 [90.6%] in the CZP group) completed the DB Phase; a slightly smaller percentage of subjects in the CZP group withdrew from the study prematurely (80 [9.4%]) compared to the PBO group (28 [13.2%]). Adverse event was the most common reason for discontinuation from the DB Phase in the CZP group (33 [3.9%] compared with 6 [2.8%] in the PBO group). Lack or loss of efficacy led to the discontinuation of 9 (1.1%) subjects in the CZP group compared with 6 (2.8%) subjects in the PBO group.

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All subjects who completed the DB Phase entered the OL Phase (184 in the PBO group and 771 in the CZP group). The majority of subjects (163 [88.6%] who previously received PBO and 646 [83.8%] who previously received CZP) completed the OL Phase. Lack of efficacy was the most common reason for discontinuation from the OL Phase in both subjects who were treated with PBO (8 [4.3%]) or CZP (30 [3.9%]) during the DB Phase.

Efficacy results: The primary efficacy endpoint of this study, the ACR20 response rate at Week 12, was achieved. The results of the primary efficacy analysis were robust and demonstrated that treatment with CZP at a dose of 400mg at Weeks 0, 2, and 4 followed by 200mg every 2 weeks resulted in a statistically significantly greater percentage of ACR20 responders at Week 12 compared with PBO (51.1% vs 25.9%; OR, 2.99; 95% CI: 2.14, 4.18; p<0.001). The results of the primary analysis were supported by the sensitivity analyses. The treatment effects observed for CZP compared with PBO on the primary efficacy variable were not confounded by Baseline key stratification factors (Baseline MTX status, prior anti-TNFα use, and disease duration category) or nonstratification factors (geographic region, gender, race, age, and Baseline DAS28[CRP]).

Secondary efficacy analyses also demonstrated that CZP was efficacious compared with PBO in improving signs and symptoms and physical function/health outcome measures through 12 weeks of treatment, and that these improvements were sustained through at least 28 weeks with OL treatment. Summaries of key secondary efficacy results were as follows.

- Significantly greater percentages of responders were observed at Week 12 in the CZP group compared with PBO for both ACR50 (CZP: 26.6%; PBO: 9.9%; OR: 3.29; 95% CI: 2.05, 5.31; p<0.001) and ACR70 (CZP: 12.9%; PBO: 2.8%; OR: 5.09; 95% CI: 2.20, 11.77; p<0.001). Responder rates observed at Week 12 continued to increase with CZP treatment during the OL Phase (ACR20: 59.4% at Week 20, 58.5% at Week 28; ACR50: 33.5% at Week 20, 35.0% at Week 28; ACR70: 15.6% at Week 20, 17.4% at Week 28).
- There was a statistically significantly greater mean decrease (improvement) from Baseline in DAS28(CRP) score for CZP compared with PBO at Week 12 (-1.64 vs -0.78; LS mean difference: -0.86; 95% CI: -1.04, -0.67; p<0.001). The DAS28(CRP) scores observed at Week 12 continued to decrease (improve) with CZP treatment during the OL Phase (-1.87 at Week 20 and -1.94 at Week 28).
- There was a statistically significantly greater mean decrease (improvement) from Baseline in both SDAI and CDAI scores for CZP compared with PBO at Week 12 (SDAI: LS mean difference: -8.67; 95% CI: -10.72, -6.61; p<0.001; CDAI: LS mean difference: -7.82; 95% CI: -9.82, -5.82; p<0.001). The scores observed at Week 12

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continued to decrease (improve) with CZP treatment during the OL Phase (SDAI: -21.92 at Week 20 and -22.35 at Week 28; CDAI: -21.26 at Week 20 and -21.66 at Week 28).

- A significantly greater percentage of subjects in the CZP group were DAS28(CRP), SDAI, and CDAI remitters at Week 12 (16.0%, 7.8%, and 8.3%, respectively) compared with subjects in the PBO group (5.7%, 1.9%, and 1.9%, respectively). The ORs for CZP vs PBO were: DAS28(CRP), 3.18 (95% CI: 1.72, 5.86; p<0.001); SDAI, 4.37 (95% CI: 1.58, 12.13; p=0.005); CDAI, 4.73 (95% CI: 1.71, 13.11; p=0.003). The remitter rates observed at Week 12 continued to increase with CZP treatment during the OL Phase (DAS28[CRP]: 19.6% at Week 20, 22.6% at Week 28; SDAI: 8.9% at Week 20, 11.4% at Week 28; CDAI: 9.4% at Week 20, 12.1% at Week 28).
- There were statistically significantly greater mean decreases (improvements) from Baseline in all ACR components for CZP compared with PBO at Week 12 (p<0.001 for all parameters). The decreases (improvements) in all the ACR components observed at Week 12 were maintained or continued to decrease with CZP treatment during the OL Phase.
- Larger proportions of subjects in the CZP group met the MCID for PAAP-VAS (59.1%), PtGADA-VAS (59.5%), and HAQ-DI (56.4%) at Week 12 compared with those in the PBO group (42.0%, 42.5%, and 37.7%, respectively). The proportions of subjects meeting the MCID for PAAP-VAS, PtGADA-VAS, and HAQ-DI at Week 12 continued to increase with CZP treatment during the OL Phase (Week 20: 68.2%, 68.8%, and 63.0%, respectively; Week 28: 68.0%, 68.9%, and 63.2%, respectively).
- The sustained ACR20 response rate (at 2 consecutive visits) at Week 12 during the DB Phase was significantly greater in the CZP group (53%) compared with the PBO group (22%) (p<0.001). The median time to achieve a sustained response was 47 days for the CZP group but was not estimable for the PBO group.
- A significantly greater percentage of subjects in the CZP group (73.4%) were good or moderate EULAR responders at Week 12 during the DB Phase compared with subjects in the PBO group (47.6%). The OR for CZP vs PBO was 3.04 (95% CI: 2.23, 4.14; p<0.001).
- For all secondary efficacy variables, the efficacy results observed during the OL Phase at Weeks 20 and 28 in subjects who previously received PBO closely approached those observed in subjects who previously received CZP.

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The exploratory efficacy analyses (MOS Sleep Scale, FASCA, RADAI, FSA, and DAS28[ESR]) also provided evidence of positive treatment effects for CZP compared with PBO during the 12-week DB Phase that were sustained at least through Week 28 with OL treatment.

Low medical resource utilizations were observed during the DB Phase, with the majority of subjects having no hospital stays, emergency room visits, concurrent medical procedures, or unforeseen healthcare provider consultations. Similar findings were reported between the 2 treatment groups during the DB Phase. A similar low rate of medical resource utilization was also observed during the OL Phase.

Safety results: Treatment with CZP at a dose of 400mg at Weeks 0, 2, and 4 followed by 200mg every 2 weeks in this study resulted in a safety profile that was consistent with that expected in subjects with RA receiving an anti-TNFα agent and with previous studies of CZP. No new important safety concerns were identified during this study.

- The mean number of study medication injections received during the DB Phase was 5.6 for the CZP group and 5.5 for PBO, and over 80% of subjects in both groups received all 6 doses of study medication. During the OL Phase, the mean number of study medication injections received was 9.6. Approximately 90% of subjects received ≥3 months of OL treatment with CZP, and 14% received ≥6 months of treatment.
- Overall, 571 subjects (67.5%) in the CZP group reported at least 1 TEAE during the DB Phase compared with 129 subjects (61.7%) in the PBO group. Adverse events in the following SOCs were reported at a higher incidence in the CZP group compared with PBO: Infections and Infestations (CZP: 29.0% vs PBO: 23.0%), Skin and Subcutaneous Tissue Disorders (CZP: 14.1% vs PBO: 7.2%), and General Disorders and Administration Site Conditions (CZP: 13.1% vs PBO: 10.0%). During the OL Phase, 663 subjects (69.5%) reported at least 1 TEAE, with a higher incidence in subjects who previously received PBO during the DB Phase (77.2%) compared with those who previously received CZP (67.7%); this pattern was also noted for the majority of the more common SOCs.
- Four TEAEs were reported at an incidence of ≥5% in any treatment group during the DB Phase: nausea, upper respiratory tract infection, rheumatoid arthritis, and headache. Of these, only upper respiratory tract infection was reported at a higher incidence in the CZP group compared with PBO (7.4% vs 5.3%). Seven TEAEs were reported at an incidence of ≥5% in any treatment group during the OL Phase, and all were reported at a higher incidence in subjects who previously received PBO during the DB Phase compared with

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those who received CZP: nasopharyngitis (7.1% vs 5.2%), sinusitis (6.0% vs 4.4%), upper respiratory tract infection (8.7% vs 7.8%), urinary tract infection (8.2% vs 6.6%), rheumatoid arthritis (9.8% vs 6.9%), headache (6.0% vs 3.1%), and rash (6.0% vs 3.1%).

- Four subjects experienced fatal TEAEs during or shortly after the study (CZP/CZP group: necrotizing pneumonia [possibly related to study drug], small cell lung cancer metastatic [unlikely related], and diverticulitis [possibly related]; PBO/CZP group: myocardial infarction [not related]).
- The majority of subjects with a TEAE during the DB Phase reported maximum intensities of mild or moderate. Severe TEAEs were reported by 7.8% of subjects in the CZP group and 7.2% of subjects in the PBO group. The most commonly reported severe TEAE was rheumatoid arthritis, occurring in 0.9% of CZP-treated subjects and 0.5% of PBO-treated subjects. The majority of subjects with a TEAE during the OL Phase reported maximum intensities of mild or moderate. Severe TEAEs were reported by 8.6% of subjects overall, with a similar incidence between subjects who previously received PBO and those who received CZP (9.2% and 8.4%, respectively). The most commonly reported severe TEAEs were arthralgia and rheumatoid arthritis, both occurring in 0.6% of subjects overall, and both of which had a higher incidence in subjects previously treated with PBO compared to those treated with CZP.
- The incidence of drug-related TEAEs during the DB Phase was higher in the CZP group (29.6%) compared with PBO (17.7%). The most commonly reported drug-related TEAEs were upper respiratory tract infection (CZP: 2.8%; PBO: 1.9%), headache (CZP: 2.1%; PBO: 3.8%), nausea (CZP: 1.8%; PBO: 0.5%), rash (CZP: 1.8%; PBO: 0.5%), and pruritus (CZP: 1.7%; PBO: 1.0%). The incidence of drug-related TEAEs during the OL Phase was 26.8% overall, with a similar incidence between subjects who previously received PBO and those who received CZP (28.3% and 26.5%, respectively). The most commonly reported drug-related TEAEs were upper respiratory tract infection (3.8%), urinary tract infection (3.0%), bronchitis (2.4%) and sinusitis (2.0%).
- Serious TEAEs were reported by 6.1% of subjects in the CZP group and 5.7% of subjects in the PBO group during the DB Phase. The incidence of serious TEAEs within each SOC was generally similar between the CZP and PBO groups, except for a slightly higher incidence of serious TEAEs in the Infections and Infestations SOC in the CZP group compared with PBO (2.6% vs 1.9%, respectively). The most commonly reported serious TEAEs were pneumonia (CZP: 0.5%; PBO: 0.5%), chest pain (CZP: 0.4%; PBO: 1.0%), and urinary tract infection (CZP: 0.4%; PBO: none). A total of 8.1% of subjects reported

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at least 1 serious TEAE during the OL Phase, with a higher incidence in subjects who previously received PBO (11.4%) compared with those who previously received CZP (7.3%). Of note, the incidence of serious TEAEs in the Infections and Infestations SOC (2.5%) was not higher than that reported with CZP treatment during the DB Phase (2.6%) despite the longer duration of exposure. The most commonly reported serious TEAEs were pneumonia (0.8%) and cellulitis (0.5%).

- The incidence of TEAEs leading to permanent discontinuation of study drug during the DB Phase was 4.7% in the CZP group and 3.8% in the PBO group. Rheumatoid arthritis was the most common TEAE leading to permanent discontinuation of study drug and occurred at a higher incidence in the PBO group compared with the CZP group (1.0% vs 0.5%). A total of 3.0% of subjects reported at least 1 TEAE leading to permanent discontinuation of study drug during the OL Phase, with a higher incidence in subjects who previously received CZP (3.4%) compared with those who previously received PBO (1.6%). The mostly commonly reported TEAEs leading to permanent discontinuation of study drug were pregnancy (0.3%), rheumatoid arthritis (0.2%), and small cell lung cancer metastatic (0.2%), each of which were reported only in subjects who previously received CZP during the DB Phase.
- There were few notable differences in the incidence of AEs by stratification factor during the DB Phase. In prior anti-TNFα users, the difference in the incidence of overall TEAEs between the CZP and PBO groups was greater (CZP: 71.0% vs PBO: 50.0%) when compared with nonusers (CZP: 65.4% vs PBO: 69.0%). In subjects with a disease duration of <2 years, the difference in the incidence of overall TEAEs between the CZP and PBO groups was greater in the direction of PBO (CZP: 68.9% vs PBO: 76.0%) when compared with those with a disease duration of ≥2 years (CZP: 67.0% vs PBO: 57.2%). These differences did not appear to be related to CZP treatment but, rather, were mostly due to differences in the incidence of TEAEs by stratum in PBO-treated subjects. Notably, prior anti TNFα users did not have a higher incidence of TEAEs in the Infections and Infestations SOC in either treatment group when compared with nonusers. The difference in the incidence of serious TEAEs between the CZP and PBO groups was also greater in prior anti-TNFα users when compared with nonusers (users: CZP 8.2% vs PBO 3.8%; nonusers: CZP 4.9% vs PBO 7.0%). Although a few differences were noted by stratification variables, these data should be interpreted with caution due to the differences in sample sizes across treatment groups and strata.
- The incidence of injection reactions during the DB Phase was higher in the CZP group (10.3%) compared with the PBO group (4.8%). The most commonly reported local

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injection site reactions were injection site erythema (CZP: 1.4%; PBO: 0), injection site reaction (CZP: 1.3%; PBO: 0.5%), and injection site pain (CZP: 0.9%; PBO: 0.5%). The most commonly reported systemic injection reactions were headache (CZP: 0.8%; PBO: 1.4%), pruritus (CZP: 0.8%; PBO: 0.5%), and rash (CZP: 0.7%; PBO: 0). There were 2 serious injection reactions reported during the DB Phase, both in the CZP group (angioneurotic edema and urticaria). A total of 3.9% of subjects reported at least 1 injection reaction during the OL Phase, with a higher incidence in subjects who previously received PBO (6.0%) compared with those who previously received CZP (3.4%). The most commonly reported local injection reactions were injection site discoloration and injection site reaction, each reported in 0.4% of subjects overall. The most commonly reported systemic injection reactions were rash (0.4%) and pruritus (0.3%). There were no serious injection reactions reported during the OL Phase.

- Serious infections were reported in 2.6% of subjects in the CZP group and 1.9% of subjects in the PBO group during the DB Phase. The most commonly reported serious infections were pneumonia (CZP: 0.5%; PBO: 0.5%) and urinary tract infection (CZP: 0.4%; PBO: 0). Herpes viral infections (by HLT) were reported in 2.4% of subjects in the CZP group compared with 0.5% of subjects in the PBO group and fungal infections (by HLT) in 1.5% of subjects in the CZP group compared with 0.5% of subjects in the PBO group. Serious infections were reported in 2.5% of subjects during the OL Phase, with a higher incidence in subjects who previously received PBO (3.3%) compared with those who previously received CZP (2.3%). The most commonly reported serious infections were pneumonia (0.8%), cellulitis (0.5%), bronchitis (0.3%), and urinary tract infection (0.3%). Herpes viral infections (by HLT) were reported in 1.5% of subjects overall and fungal infections (by HLT) in 0.9% of subjects. There was one report of TB during the study; a serious TEAE of disseminated tuberculosis in 1 subject in the CZP/CZP group.
- Four subjects (0.5%) in the CZP group and 2 subjects (0.9%) in the PBO group reported at least 1 malignancy during the DB Phase. With the exception of malignant melanoma, which was reported in 1 subject each in the CZP and PBO groups, all other reported malignancies occurred in 1 subject each and included carcinoid tumor, adenocarcinoma pancreas, and sarcoma uterus in the CZP group and breast cancer and hepatic neoplasm in the PBO group. Malignancies were reported in 7 subjects (0.7%) during the OL Phase, all of whom previously received CZP during the DB Phase. Small cell lung cancer metastatic was the only malignancy reported in 2 subjects. All other malignancies were each reported in 1 subject and included breast cancer, breast cancer metastatic, ovarian granulosa-theca cell tumor, mycosis fungoides, and malignant melanoma.

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- Cardiac AEs were reported at a lower incidence in the CZP group (1.7%) compared with the PBO group (2.4%) during the DB Phase. The most commonly reported cardiac AEs were tachycardia (CZP: 0.4%; PBO: 1.0%) and palpitations (CZP: 0.2%; PBO: 0.5%). One subject in the CZP group reported a TEAE of cardiac failure congestive during the DB Phase. Cardiac AEs were reported in 2.7% of subjects during the OL Phase, with a higher incidence in subjects who previously received PBO (3.3%) compared with those who previously received CZP (2.6%). The most commonly reported cardiac AEs were tachycardia (0.4%), cardiac failure congestive (0.3%), angina pectoris (0.3%), and myocardial infarction (0.3%). Three subjects (0.3%), all of whom were in the prior CZP group, reported a TEAE of cardiac failure congestive during the OL Phase.
- Vascular AEs were reported in 3.7% of subjects in the CZP group and 2.4% of subjects in the PBO group during the DB Phase. The most commonly reported vascular AE was hypertension occurring in 1.9% of subjects in both the CZP and PBO groups. Vascular AEs were reported in 3.7% of subjects during the OL Phase, with a similar incidence between subjects who previously received PBO and those who received CZP (3.8% and 3.6%, respectively). Similar to the DB Phase, the most commonly reported vascular AE was hypertension (2.1% overall; CZP/CZP: 1.8%; PBO/CZP: 3.3%).
- Five subjects became pregnant during the study, 4 in the CZP group and 1 in the PBO group. All 5 subjects were permanently withdrawn from the study due to their pregnancies. In 1 subject for whom follow-up information on the pregnancy was available at the time of this report, no complications, birth defects, or developmental impairments were reported.
- Two notable autoimmune events were identified based on sponsor medical review, both of which occurred following CZP treatment: lupus-like syndrome (CZP group during the DB Phase) and antiphospholipid antibodies positive (CZP/CZP group during the OL Phase).
- There were no cases of demyelinating disorders in this study. Three serious neurological AEs of syncope were identified based on sponsor medical review, all of which occurred following CZP treatment (3 subjects overall [1 subject in the CZP group during the DB Phase and 2 subjects in the CZP/CZP group during the OL Phase]).
- There were no TEAEs indicative of serious bleeding events during the DB Phase. One subject in the prior CZP group reported a serious TEAE of subdural hematoma during the OL Phase. There were no reported TEAEs suggestive of serious bone marrow aplasia or

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serious skin reactions during the study.

- Mean and median changes over time for hematology and biochemistry laboratory parameters were generally small, and not considered to be of clinical significance during the DB and OL Phases. No clinically significant patterns were observed with regard to shifts from Baseline in hematology or biochemistry parameters or markedly abnormal values during either the DB or OL Phases.
- Mean and median changes over time in vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate) during the DB and OL Phases were generally small and not considered to be of clinical significance. There were no notable treatment-related patterns in systolic or diastolic blood pressure increases during either the DB or OL Phases. The incidence of new onset post-Baseline hypertension was similar between the CZP and PBO groups during the DB Phase (23.1% and 25.4%, respectively) and no increase in incidence was observed during the OL Phase (24.6% overall).

Conclusions: Certolizumab pegol at a dose of 400mg at Weeks 0, 2, and 4 followed by 200mg every 2 weeks resulted in statistically significantly greater improvements in efficacy compared to PBO following 12 weeks of treatment regardless of concomitant MTX use, prior anti-TNFα use, or disease duration. A maintenance of clinical response was demonstrated with open-label CZP 200mg every 2 weeks through 28 weeks of treatment.

The safety profile, including the type and incidence of TEAEs, was consistent with that expected in subjects with RA receiving an anti-TNFα agent and with previous studies of CZP and no new important safety concerns were identified during this study. The AE profile of CZP did not appear to be consistently influenced by Baseline MTX status, prior anti-TNFα use, or disease duration category. However, due to sample size differences across treatment groups and strata, definitive conclusions regarding these treatment-by-subgroup interactions could not be made from this study.

The safety and efficacy of CZP was confirmed and showed a positive benefit/risk in this study population that more closely resembled patients treated in clinical practice.

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