C87076, 2007-000828-40

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.

Sponsor:

UCB Pharma SA

Allée de la Recherche 60

1070 Anderlecht (Brussels)

Belgium

Official study title:

A Phase IIIB, multi-centre, double-blind randomized, placebocontrolled, parallel group, 52-week study to evaluate safety and efficacy of the PEGylated anti-TNFα Fab' fragment, certolizumab pegol, administered concomitantly with stable-dose DMARDs in patients with moderate to low disease activity rheumatoid arthritis

CLINICAL STUDY REPORT SYNOPSIS: C87076

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Cimzia	**Volume:** Not applicable	
Name of active ingredient: Certolizumab pegol	**Page:** Not applicable	

Title of study: A Phase IIIB, multi-centre, double-blind randomized, placebo-controlled, parallel group, 52-week study to evaluate safety and efficacy of the PEGylated anti-TNFα Fab′ fragment, certolizumab pegol, administered concomitantly with stable-dose DMARDs in patients with moderate to low disease activity rheumatoid arthritis.

Investigator(s): This was a multicenter study; Investigators at 36 centers enrolled at least 1 subject and Investigators at 30 centers randomized at least 1 subject.

Study site(s): This was a multicenter study; 53 centers were initiated, 36 centers enrolled at least 1 subject, and 30 centers randomized at least 1 subject

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

Studied period: The study consisted of a Screening Period (up to a maximum of 28 days), a Study Period which was a maximum of 24 weeks (for nonremitters at Week 24) or 52 weeks (for remitters at Week 24), and a Safety Follow-Up (SFU) Visit 12 weeks after final administration of study medication (only for those subjects who did not enter the Open-Label [OL], long-term follow-up [LTFU] study, C87080). **First subject enrolled:** 03 June 2008 **Last subject completed:** 10 December 2010	**Phase of development:** Phase 3b

Objective(s): The primary objective was to assess the clinical efficacy of certolizumab pegol (CZP) as an add-on therapy in demonstrating clinical remission at both Week 20 and Week 24 (defined as Clinical Disease Activity Index [CDAI] of ≤2.8).

The secondary objectives were to compare the efficacy of the 2 treatment arms in:

- Achievement of clinical remission at both Week 20 and Week 24 (defined as 28-joint count Disease Activity Score [erythrocyte sedimentation rate] [DAS28(ESR)] of <2.6)
- Achievement of clinical remission at both Week 20 and Week 24 (defined as Simplified Disease Activity Index [SDAI] of ≤3.3)

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- Maintenance of remission between Week 24 and Week 52 (based on CDAI, SDAI, and DAS28[ESR])
- Reduction of signs and symptoms of the disease at Week 24 as measured by American College of Rheumatology (ACR) criteria
- Improvement in subject's physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24
- Improvement in subject's HRQoL as measured by the Short Form 36-item Health Survey (SF-36) Physical and Mental Component Summary scores (PCS and MCS, respectively) and SF-36 domains at Week 24
- Relief in subject's pain, fatigue, and disease activity as measured by the Patient's Assessment of Arthritis Pain (PAAP)-visual analog scale (VAS), the Fatigue Assessment Scale (FASCA), and the Patient's Global Assessment of Disease Activity (PtGADA)-VAS at Week 24

The exploratory objectives were to compare the efficacy of the 2 treatment arms in:

- Reduction of signs and symptoms of the disease at Week 52 as measured by ACR criteria
- Improvement in subject's physical function as measured by HAQ-DI at Week 52
- Improvement in subject's HRQoL as measured by SF-36 PCS and MCS and SF-36 domains at Week 52
- Relief in subject's pain, fatigue, and disease activity as measured by PAAP-VAS, FASCA, and PtGADA-VAS at Week 52

In addition:

- To explore health status (Euro Quality of Life 5 Dimensions [EQ-5D] questionnaire) at Baseline and at Weeks 24 and 52
- To collect resource utilization data using the UCB resource utilization data standards at Baseline and at Weeks 24 and 52
- To assess productivity at Baseline and at Weeks 24 and 52 as measured by the Work Productivity and Activity Impairment Questionnaire specific for RA (WPAI-RA)
- To assess the PK profile and immunogenicity of CZP in combination with DMARD(s)

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Additional exploratory objectives as described in the final SAP and amendments:

- Achievement of clinical remission, Low Disease Activity (LDA), Moderate Disease Activity (MDA), and High Disease Activity (HDA) by visit (defined as CDAI ≤2.8, >2.8 to ≤10, >10 to ≤22, and >22, respectively)
- Achievement of clinical remission, LDA, MDA, HDA by visit (defined as DAS28[ESR] <2.6, ≥2.6 to ≤3.2, >3.2 to ≤5.1, and >5.1, respectively)
- Achievement of clinical remission, LDA, MDA, HDA by visit (defined as SDAI ≤3.3, >3.3 to ≤11, >11 to ≤26, and >26, respectively)
- Relief in disease activity as measured by Physician's Global Assessment of Disease Activity (PhGADA)-VAS at Week 52.
- Change from Baseline in CDAI score by visit
- Change from Baseline in DAS28(ESR) score by visit
- Change from Baseline in SDAI score by visit
- CDAI score by visit
- DAS28(ESR) score by visit
- SDAI score by visit
- HAQ-DI score by visit

The safety objectives were to evaluate the tolerability and safety of CZP therapy.

Methodology: The study was comprised of a Screening Period (up to a maximum of 28 days), a 52-week Study Period, and a SFU Visit, which occurred 12 weeks after the final administration of study medication (only for those subjects who did not enter the OL, LTFU study, C87080).

Subjects must have received combination or disease modifying antirheumatic drug (DMARD) monotherapy (ie, sulfasalazine ≤3g/day; leflunomide ≤20mg/day; hydroxychloroquine ≤400mg/day; methotrexate [MTX] ≤25mg/week) for at least 6 months prior to the Baseline Visit, with the dose and route of administration of the DMARD therapy remaining stable for at least 2 months prior to the Baseline Visit.

Eligible subjects were randomized at the Baseline Visit (V2, Week 0) to receive in a 1:1 ratio either CZP 400mg at Weeks 0, 2, and 4, followed by CZP 200mg every 2 weeks or

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placebo (PBO) every 2 weeks up to and including Week 22. All subjects continued to receive their DMARD therapy established before study entry until Week 52.

At Week 24, subjects did not receive any injection but were evaluated:

- Nonremitters (subjects who did not achieve remission as measured by CDAI at both Week 20 and Week 24) were discontinued from the study at Week 24 and were given the opportunity at this time to enter C87080 and continue receiving CZP treatment until it is commercially available for the indication of RA in the subject's country or region, or until further notice from UCB.
- Remitters (subjects who achieved remission as measured by CDAI at both Week 20 and Week 24) stopped their randomized treatment (PBO or CZP) and were followed until Week 52.
  - Remitters who flared between Week 24 and Week 52 were re-treated with the same dosing regimen of CZP as above (3 administrations of CZP 400mg every 2 weeks, followed by CZP 200mg every 2 weeks) up to and including Week 50. A flare was defined as CDAI ≥11 which had to be confirmed at 2 consecutive visits 4 weeks apart.
    - The earliest initial re-treatment drug administration for subjects who flared could have been at Week 32 (eg, flared at Week 28 and confirmed at Week 32).
    - Subjects who flared after Week 44 could not complete their loading regimen of 3 administrations of CZP 400mg every 2 weeks in this study, but if they decided to enter C87080, they could complete their loading regimen as part of C87080. Remitters who flared were allowed to enter C87080 at Week 52.
  - Remitters who did not flare between Week 24 and Week 52 had their study visits every 4 weeks without the administration of study medication. These subjects remained in the study until Week 52 and were not allowed to enter C87080.

The final administration of study medication in C87076 was at Week 50. All subjects (except those who entered C87080) were to have a SFU Visit 12 weeks after their final dose of study medication.

Number of subjects (planned and analyzed): A total of 170 subjects were planned to be enrolled (85 subjects per treatment group); ultimately, 271 subjects were screened and 194 subjects were randomized (96 subjects in the CZP+DMARD(s) group and 98 subjects in the placebo+DMARD(s) group).

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Diagnosis and main criteria for inclusion: Subjects enrolled were male or female, at least 18 years of age, with a diagnosis of adult-onset rheumatoid arthritis (RA) of at least 6 months duration but not longer than 10 years as defined by the 1987 ACR classification criteria. Subjects had to have moderate to low disease activity as defined by all of the following: CDAI >6 and ≤16 at Screening and Baseline; ≥2 tender joints (28-joint count) at Screening and Baseline; ≥2 swollen joints (28-joint count) at Screening and Baseline; and fulfilling 1 of the following 2 criteria at Screening: ≥28mm/hour ESR (Westergren), or CRP >10mg/L. Subjects had to be receiving combination or DMARD monotherapy (ie, sulfasalazine ≤3g/day; leflunomide ≤20mg/day; hydroxychloroquine ≤400mg/day; MTX ≤25mg/week) for at least 6 months prior to the Baseline Visit, with the dose and route of administration being stable for at least 2 months prior to the Baseline Visit.

Subjects were excluded if they had a diagnosis of any other inflammatory arthritis or had a secondary, noninflammatory type of arthritis that in the Investigator's opinion was symptomatic enough to interfere with evaluation of the effect of study drug on the subject's primary diagnosis of RA. Subjects were not allowed to have a history of an infected joint prosthesis at any time with that prosthesis still *in situ*. Subjects had to be free of analgesics for 24 hours prior to Baseline, NSAIDs/COX-2 inhibitor regimens could not be changed within 14 days prior to Baseline, oral corticosteroid doses could not be changed within 28 days prior to Baseline, DMARDs (azathioprine, cyclosporine, penicillamine, gold, cyclophosphamide, minocycline, and micophenolic acid) could not be used within 6 months prior to Baseline, intra-articular (IA)/intramuscular (IM)/intravenous (iv) corticosteroids and IA hyaluronic acid could not be used within 28 days prior to Baseline, and subjects were not allowed to have received any previous biological therapy for RA or any experimental nonbiological therapy, within or outside a clinical study, in the 3 months prior to the Baseline Visit.

Subjects were not allowed to have active tuberculosis (TB) (or history of active TB), or a positive chest x-ray for TB, or a positive (defined as induration of ≥5mm) purified protein derivatives (PPD) skin test, or had close contact with an individual with active TB. Subjects who had a PPD skin test ≥5mm could enter the study, provided that active TB was excluded and provided that they were adequately treated for latent TB (eg, isonicotinic acid hydrazide [INH] therapy for 9 months [with vitamin B6]), and provided that treatment was initiated at at least 1 month prior to first administration of CZP.

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Test product, dose(s) and mode of administration, batch number(s): CZP for subcutaneous (sc) injection, 200mg/mL containing the active ingredient (anti-TNF, humanized antibody Fab' fragment - polyethylene glycol conjugate [CZP Fab' - PEG]) in prefilled, individually packaged, 1mL syringes with 25 gauge needles, containing an injectable volume of 1mL of CZP solution for injection (acetate pH 4.7) for single use.

Batch numbers: [redacted]

Duration of treatment: During the Double-Blind (DB) Treatment Phase subjects received either CZP 400mg at Weeks 0, 2, and 4, followed by CZP 200mg every 2 weeks or PBO every 2 weeks until Week 22. At Week 24, subjects who were CDAI remitters at Week 20 and Week 24 entered the OL Treatment Phase of the study. During the OL Treatment Phase, subjects only received treatment if they experienced a disease flare. Remitters who flared between Week 24 and Week 52 were re-treated with the same dosing regimen of CZP (3 administrations of CZP 400mg every 2 weeks, followed by CZP 200mg every 2 weeks) until Week 50.

Reference therapy, dose(s) and mode of administration, batch number(s): Placebo for sc injection was provided in prefilled syringe of 0.9% saline (preservative free) solution of pharmacopoeia (USP /Phr. Eur.) quality.

Batch numbers: [redacted].

Criteria for evaluation:

Efficacy: The primary efficacy variable was the proportion of subjects in CDAI remission (CDAI ≤2.8) at both the Week 20 and Week 24 Visits.

The secondary efficacy variables were as follows:

- Proportion of subjects in DAS28(ESR) remission (DAS28[ESR] <2.6) at both the Week 20 and Week 24 Visits
- Proportion of subjects in SDAI remission (SDAI ≤3.3) at both the Week 20 and Week 24 Visits
- Time from stopping treatment (Week 24 Visit) to loss of remission. This analysis was done defining loss of remission as CDAI >2.8 at 2 consecutive visits. The same analysis was repeated twice: once based on the definition of loss of remission as SDAI >3.3 at 2 consecutive visits, and once on DAS28[ESR] ≥2.6 at 2 consecutive visits

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- ACR20, ACR50 (American College of Rhematology 50% response criteria), and ACR70 (American College of Rhematology 70% response criteria) responder rate at the Week 24 Visit
- Change from Baseline in HAQ-DI at Week 24
- Change from Baseline in SF-36 PCS and MCS and SF-36 domains at Week 24
- Change from Baseline in PAAP-VAS, FASCA, and PtGADA-VAS at Week 24

The exploratory efficacy variables were as follows:

- ACR20, ACR50, and ACR70 responder rate at Week 52 Visit
- Change from Baseline in HAQ-DI and domain scores at Week 52
- EQ-5D assessment at Baseline, Week 24, and Week 52
- Resource utilization at Baseline, Week 24, and Week 52
- WPAI-RA at Baseline, Week 24, and Week 52
- Change from Baseline in SF-36 PCS and MCS scores and SF-36 domains at Week 52
- Change from Baseline in PAAP-VAS, FASCA, and PtGADA-VAS at Week 52

Additional other efficacy variables as described in the final SAP and amendments

- ACR20, ACR50, and ACR70 responder rate by visit
- Proportion of subjects in CDAI remission (CDAI ≤2.8) by visit
- Proportion of subjects in DAS28(ESR) remission (DAS28[ESR] <2.6) by visit
- Proportion of subjects in SDAI remission (SDAI ≤3.3) by visit
- Change from Baseline in CDAI score by visit
- Change from Baseline in SDAI score by visit
- Change from Baseline in DAS28(ESR) score by visit
- Proportion of subjects reaching acceptable state (score ≤1.04) and physical function norm threshold (score ≤0.50) for HAQ-DI by visit
- Change from Baseline in TJC by visit

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- Change from Baseline in SJC by visit
- Change from Baseline in HAQ-DI and domain scores by visit
- Change from Baseline in PhGADA-VAS at Week 52
- Change from Baseline in PAAP-VAS, FASCA, PtGADA-VAS and PhGADA-VAS by visit
- Proportion of subjects reaching acceptable state (score ≤37) for PtGADA by visit
- Proportion of subjects reaching acceptable state (score ≤35) for PAAP-VAS by visit
- Proportion of subjects reaching acceptable state (score ≤5) for FASCA by visit
- Proportion of subjects reaching a HRQOL within half-standard deviation (SD) of population norms for SF-36 PCS and MCS (defined as score ≥45) at Week 24 and Week 52
- The number and percentage of subjects reaching population norms in HRQOL for SF-36 PCS and MCS (defined as score ≥50) at Week 24 and Week 52
- Change from Baseline in CRP level by visit
- Change from Baseline in ESR level by visit
- Change from Baseline in EQ-5D at Week 24 and Week 52
- Change from Baseline in WPAI-RA at Week 24 and Week 52
- Proportion of subjects in LDA, MDA, HDA by visit (defined as CDAI >2.8 to ≤10, >10 to ≤22, and >22, respectively).
- Proportion of subjects in LDA, MDA, HDA by visit (defined as DAS28[ESR] ≥2.6 to ≤3.2, >3.2 to ≤5.1, and >5.1, respectively).
- Proportion of subjects in LDA, MDA, HDA by visit (defined as SDAI >3.3 to ≤11, >11 to ≤26, and >26, respectively).
- Time to flare
- Association between CDAI, DAS28(ESR), and SDAI activity states
- Association between CDAI, DAS28(ESR), and SDAI remissions

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Pharmacokinetics/Immunologic measurements: Plasma samples for the measurement of CZP concentrations and anti-CZP antibodies were collected at Baseline (Week 0), Week 4, Week 12, and at Week 24 or the Withdrawal Visit.

Safety: The following safety variables were assessed:

- Adverse events (AEs). Injection reactions were assessed as a special group of AEs. These were classified as injection site reactions or systemic injection reactions. The latter was further classified as "acute" and "delayed" based on the timing and the presentation of the typical symptoms.
- Vital signs
- Physical examinations (including TB testing)
- Clinical laboratory values (hematology, serum biochemistry, and urinalysis)

Statistical methods:

The Full Analysis Set (FAS), which included all relevant data for all randomized subjects, was used for the primary, supportive primary, secondary, and other efficacy analyses conducted for the DB Treatment Phase. The Week 24 Remitter Set (W24RS) was used for all secondary and other efficacy analyses conducted for the OL Treatment Phase. The Safety Set (SS) was used for all safety summaries and analyses conducted for the DB Treatment Phase of the study. The Open-label Set (OLS), Open-label Set – Re-treated (OLS-RT), and the Open-label Set Non-Re-treated (OLS-NRT) were used for all safety summaries and analyses conducted for the OL Treatment, Untreated Phase and Re-treated Phase of the study. All Baseline values were obtained from the Pretreatment Period.

The primary efficacy variable, defined as the proportion of subjects in CDAI remission (CDAI ≤2.8) at both the Week 20 and Week 24 Visits, was analyzed on the FAS using a logistic regression model, which included terms for treatment and country/region. The odds ratio (OR) measuring the treatment effect (CZP vs PBO) was estimated from this logistic regression model and presented with 95% 2-sided confidence intervals. The p-value was generated from the Wald test.

If more than 15% of subjects in the FAS had at least 1 major protocol deviation during the DB Treatment Phase, the primary efficacy variable was also analyzed on the Per-Protocol Set (PPS) using the same methods. The primary efficacy variable was further examined by Baseline characteristics (geographic region/country, gender, race, age, Baseline CDAI score, Baseline CRP, Baseline ESR, Baseline DAS28[ESR] score, past TNF-inhibitor use,

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duration of disease, steroid use, concomitant use of MTX, rheumatoid factor, concomitant use of DMARDs, concomitant MTX dose, and anti-CCP).

For all analyses of SDAI, CDAI, and DAS28(ESR) remission rates and ACR20, ACR50, and ACR70 response rates, non-response (remission) imputation (NRI) was performed, such that a subject having missing data for the time point assessed was conservatively counted for that particular visit as a nonremitter or nonresponder depending on the variable considered. This was done whether the data was just missing, after a rescue medication intake, or the subject discontinued from the study early prior to the time point assessed.

The primary efficacy variable was also analyzed at both the Week 20 and Week 24 Visits using a different imputation strategy as was planned for the primary analysis. This sensitivity analysis was conducted using the same logistic model previously specified but on last observation carried forward (LOCF) data.

In general, for secondary and exploratory efficacy variables, continuous variables were summarized by treatment group and visit (where applicable) with the statistics mean, standard deviation (SD), median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. Continuous variables, in general, were imputed using LOCF and for dichotomous variables, subjects with missing data were conservatively considered as nonresponders/nonremitters/not having reached the target threshold.

Categorical variables were summarized by treatment group with frequency counts and percentages. A missing category was included as applicable or the sample size (subjects with nonmissing results) is displayed.

Unless stated otherwise, all statistical tests were 2-sided and conducted at the 0.05 alpha level. P-values are presented to 3 decimal places. No inferential analyses were conducted for the OL Treatment Phase.

Summary and conclusions:

Subject disposition: A total of 271 subjects were screened and 194 subjects were randomized into the DB Treatment Phase (96 subjects into the CZP+DMARD[s] group and 98 subjects into the placebo+DMARD[s] group). All 194 randomized subjects were included in both the SS and the FAS. A total of 155 subjects (73 [76.0%] subjects in the CZP+DMARD[s] group and 82 [83.7%] subjects in the placebo+DMARD[s] group) were included in the PPS. The majority of subjects (164 [84.5%]) completed the DB Treatment Phase of the study. A total of 12.5% of subjects in the CZP+DMARD(s) group and 18.4% of subjects from the placebo+DMARD(s) group discontinued from the DB Treatment

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Phase. The most common reason for discontinuation in the CZP+DMARD(s) group was adverse event (6 [6.3%] subjects). The most common reasons for discontinuation in the placebo+DMARD(s) group were adverse event and lack of efficacy (6 [6.1%] subjects each). Lack of efficacy was reported by 2 (2.1%) subjects in the CZP+DMARD(s) group. Additional reasons for discontinuation included loss of efficacy (1 [1.0%] subject in the placebo+DMARD[s] group), withdrawal of consent (4 [4.2%] subjects in the CZP+DMARD[s] group and 3 [3.1%] subjects in the placebo+DMARD[s] group), and "other" (2 [2.0%] subjects in the placebo+DMARD[s] group).

A total of 27 subjects entered the OL Treatment Phase of the study (20 subjects from the CZP+DMARD[s] group and 7 subjects from the placebo+DMARD[s] group). All of these subjects completed the OL Treatment Phase except for 1 subject from the CZP+DMARD(s) group who discontinued due to an adverse event (3.7% of subjects overall). In addition, 1 subject [redacted] from the CZP+DMARD(s) group (3.7% of subjects overall) completed the Week 28 Visit and as a result was counted in the OL Treatment Phase, even though this subject was not considered a remitter at Week 24. Subsequently, this subject entered the OL, long-term follow-up study C87080 and is neither counted as completing or discontinuing the OL Treatment Phase.

Of the 27 subjects who entered the OL Treatment Phase of the study, 24 (88.9%) were included in the W24RS (18 subjects from the CZP+DMARD[s] group and 6 subjects from the placebo+DMARD[s] group), which included all subjects from the FAS who were in remission at Week 24 and had at least 1 visit in the OL Treatment Phase. Three subjects from the OLS were excluded from the W24RS (the previously mentioned subject who was not a remitter at Week 24 [redacted], and 2 additional subjects who were remitters at Week 20 and Week 24, but who used rescue medications at Baseline [redacted]).

Fourteen of the 24 subjects in the W24RS flared during the OL Treatment Phase and required re-treatment (10 subjects from the CZP+DMARD[s] group and 4 subjects from the placebo+DMARD[s] group), while 10 subjects did not require re-treatment during the OL Treatment Phase (8 subjects from the CZP+DMARD[s] group and 2 subjects from the placebo+DMARD[s] group).

Efficacy results: The primary objective of this study was to assess the clinical efficacy of CZP as an add-on therapy in demonstrating clinical remission at both Week 20 and Week 24 (defined as CDAI of ≤2.8) in patients with moderate to low disease activity rheumatoid arthritis. For the primary efficacy variable of clinical remission at both

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Week 20 and Week 24 in the FAS, treatment with 200mg CZP, after an initial dose of 400mg at Weeks 0, 2, and 4, led to a significantly greater proportion of subjects in CDAI remission at both Week 20 and Week 24 compared with placebo (18.8% vs 6.1%, OR: 3.82; p=0.013).

Due to the fact that >15% of subjects in the FAS had at least 1 major protocol deviation, the primary efficacy variable was also analyzed for the PPS. Using the PPS, a greater proportion of subjects in the CZP+DMARD(s) group were also in CDAI remission at both Week 20 and Week 24 compared with the placebo+DMARD(s) group (17.8% vs 7.3%); however, the likelihood of increased CDAI remission was not significant (p=0.071).

On the other hand, the results of the primary analysis using the FAS are supported by a sensitivity analysis using LOCF data (p=0.026). Additionally, secondary and supportive analyses by Baseline factors all supported increased clinical remission with CZP treatment, with the exception of age, where older subjects (≥65 years) had no increased likelihood of remission when treated with CZP+DMARD(s) compared with placebo+DMARD(s).

Secondary efficacy variables also support the use of the CZP 200mg regimen compared with placebo:

- The proportion of subjects in DAS28(ESR) and SDAI remission at both Week 20 and Week 24 using NRI were significantly greater for subjects in the CZP+DMARD(s) group compared with the placebo+DMARD(s) group (19.8% vs. 3.1%, OR: 7.67; p=0.002 and 14.6% vs. 4.1%, OR: 4.12; p=0.023, respectively). Similar results were obtained using observed values; however, results for SDAI were not significant.
- During the OL Treatment Phase, the majority of subjects in the W24RS lost CDAI remission, and never achieved or lost SDAI and DAS28(ESR) remission. The median number of days until loss of CDAI and SDAI remission was similar for subjects who were in the CZP+DMARD(s) group during the DB Treatment Phase (43.5 days and 29.0 days, respectively) compared with those subjects in the placebo+DMARD(s) group during the DB Treatment Phase (41.5 days and 25.5 days, respectively); however, the median number of days until loss of DAS28(ESR) remission was greater in subjects treated with CZP+DMARD(s) during the DB Treatment Phase (29.0 days) compared with subjects treated with placebo+DMARD(s) during the DB Treatment Phase (1.0 day).
- A significantly greater proportion of subjects in the CZP+DMARD(s) group were ACR20 and ACR50 responders at Week 24 compared with the placebo+DMARD(s)

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group (ACR20: 36.5% vs. 15.3%, OR: 3.25, p=0.001; ACR50: 20.8% vs. 7.1%, OR: 3.58, p=0.011). Similar results were reported using the observed data for ACR20 and ACR50 responder rates; however, the difference in ACR50 response rates between CZP+DMARD(s) and placebo+DMARD(s) was not significant, likely due to the small number of subjects available for analysis.

- A greater proportion of subjects in the CZP+DMARD(s) group were also ACR70 responders at both Week 20 and Week 24 compared with the placebo+DMARD(s) group (9.4% vs. 3.1%); however, this difference was not significant (OR: 3.08; p=0.111), likely due to the small number of subjects available for analysis. Similar results were reported using the observed data for ACR70 responder rates.
- At Week 24, subjects in the CZP+DMARD(s) group had a significantly greater LS mean decrease in the HAQ-DI score compared with subjects in the placebo+DMARD(s) group (Diff: CZP/PBO: -0.19; p=0.005). Similar results were obtained using observed data.
- Subjects treated with CZP+DMARD(s) had a significantly greater improvement at Week 24 in SF-36 PCS and MCS compared with subjects treated with placebo+DMARD(s) (PCS: p=0.002; MCS: p=0.050). Subjects treated with CZP+DMARD(s) also had a significantly greater improvement from Baseline at Week 24 in the following SF-36 domains: physical functioning (p<0.001), bodily pain (p=0.002), general health (p=0.006), vitality (p=0.001), and mental health (p=0.005). For the remaining 3 SF-36 domains (role physical, social functioning, and role emotional), subjects treated with CZP+DMARD(s) had a numerically, but not significantly, greater improvement from Baseline.
- Subjects treated with CZP+DMARD(s) had a significantly greater improvement at Week 24 in PAAP-VAS, PtGADA-VAS, and FASCA compared with subjects treated with placebo+DMARD(s) (PAAP-VAS: p<0.001; PtGADA-VAS: p=0.009; FASCA: p=0.002). Similar results were found using observed data.
- A greater proportion of subjects in the CZP+DMARD(s) group compared with the placebo+DMARD(s) group had MCID improvements in PAAP-VAS (45.8% vs. 24.5%), PtGADA-VAS (44.8% vs. 27.6%), HAQ-DI (43.8% vs. 29.6%), and FASCA (49.0% vs. 27.6%).

The exploratory efficacy analyses were designed to evaluate the effect of CZP by visit during the DB and OL Treatment Phase, to evaluate quality of life related outcomes and resource utilization, and to further evaluate a possible maintence of CZP effect through

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Week 52. Unfortunately, due to the small number of subjects in the W24RS (n=24) and the fact that 14/24 of these subjects required re-treatment during the OL Treatment Phase (4/6 subjects in the placebo+DMARD[s] group and 10/18 subjects in the CZP+DMARD[s] group), it is difficult to make any meaningful comparisons between treatment groups or draw any firm conclusions based upon the data for the OL Treatment Phase of the study. Data are summarized below, but no conclusions are being drawn from the OL Treatment Phase data.

- For every post-Baseline visit through the Week 24 Visit of the DB Treatment Phase, the CZP+DMARD(s) group had a higher percentage of subjects in CDAI, DAS28(ESR), and SDAI remission and LDA based on the CDAI, DAS28(ESR), and SDAI compared with the placebo+DMARD(s) group. Similarly, at every post-Baseline visit through Week 24 of the DB Treatment Phase, the CZP+DMARD(s) group had a lower percentage of subjects with MDA or HDA based on the CDAI, DAS28(ESR), and SDAI compared with the placebo+DMARD(s) group.
- During the DB Treatment Phase, subjects in the CZP+DMARD(s) group reported a decrease from Baseline in CDAI, SDAI, and DAS28(ESR) scores as early as Week 4, which continued to decrease through Week 12, and these decreases were maintained through Week 24. During the DB Treatment Phase, the placebo+DMARD(s) group reported a steady increase in CDAI and SDAI scores and minimal decreases at all visits in DAS28(ESR).
- In the W24RS, a total of 14 (58.3%) subjects experienced a disease flare during the OL Treatment Phase, with a lower incidence in subjects previously treated with CZP+DMARD(s) during the DB Treatment Phase (10/18 subjects [55.6%]) compared with subjects previously treated with placebo+DMARD(s) during the DB Treatment Phase (4/6 subjects [66.7%]). Additionally, the median number of days before experiencing a disease flare was greater in subjects treated with CZP+DMARD(s) during the DB Treatment Phase (128.0 days [95% CI: 56.0, NC]) compared with subjects treated with placebo+DMARD(s) during the DB Treatment Phase (55.5 days [95%CI: 26.0, NC]).
- During the DB Treatment Phase, subjects in the CZP+DMARD(s) group reported a higher percentage of ACR20, ACR50, and ACR70 responders compared with the placebo+DMARD(s) as early as Week 4. Continued increases in responder rates were observed for the CZP+DMARD(s) group through Week 12 (ACR20 and ACR50) and Week 20 (ACR70), which were maintained through Week 24. Subjects in the

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placebo+DMARD(s) group reported only minimal increases in ACR20, ACR50, and ACR70 responder rates over the 24-week period.

- During the OL Treatment Phase, at Week 28, 54.2%, 37.5%, and 29.2% of subjects were ACR20, ACR50, and ACR70 responders, respectively. At Week 52, 33.3%, 20.8%, and 12.5% of subjects were ACR20, ACR50 and ACR70 responders, respectively. The percentage of subjects who were ACR20, ACR50, and ACR70 responders at Week 52 were similar regardless of the treatment regiment the subject received during the DB Treatment Phase.
- For the HAQ-DI score, subjects in the CZP+DMARD(s) group reported a decrease from Baseline as early as Week 4, with further decreases out to Week 16 that were subsequently maintained to Week 24. Subjects in the placebo+DMARD(s) group reported minimal decreases at all visits.
- For the W24RS during the OL Treatment Phase using LOCF, the mean change from Baseline in HAQ-DI overall was -0.26 at the Week 28 Visit and this decrease was maintained at the Week 52 Visit (-0.18).
- Improvements, as measured by mean change from Baseline, were maintained at Week 52 for those subjects in the W24RS group for SF-36 PCS and MCS, and all of the SF-36 domains.
- During the DB Treatment Phase, for the FAS using LOCF, subjects in the CZP+DMARD(s) group reported decreases in PAAP-VAS, PtGADA-VAS, PhGADA-VAS, and FASCA was as early as Week 4, which continued to decrease through Weeks 8 to 20, and then were subsequently maintained through Week 24. Subjects in the placebo+DMARD(s) group reported minimal changes in the PAAP-VAS, PtGADA-VAS, PhGADA-VAS, and FASCA at all visits.
- For the W24RS during the OL Treatment Phase using LOCF, the mean changes from Baseline at Week 28 for subjects overall in the PAAP-VAS, PtGADA-VAS, PhGADA, and FASCA were -10.00, -11.55, -13.50, and -0.76, respectively. At Week 52 for subjects overall in the W24RS, the changes in PAAP-VAS, PtGADA-VAS, PhGADA, and FASCA were -7.74, -7.40, -19.67, and -0.86, respectively.
- During the DB and OL Treatment Phases, the majority of subjects did not have additional consultations not foreseen by the protocol, did not require any hospital stays, did not require an emergency room visit, and did not have any concurrent medical procedures.

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- The mean change from Baseline in EQ-5D VAS score for the FAS at Week 24 was 10.8 for the CZP+DMARD(s) group and -1.1 for the placebo+DMARD(s) group. The mean change from Baseline in EQ-5D VAS score for the W24RS at Week 52 was 25.5.
- Improvements in WPAI-RA scores were observed for subjects in the CZP+DMARD(s) group at Week 24 compared with Baseline in all 4 assessments. For the placebo+DMARD(s) group, scores on the WPAI-RA either worsened or remained similar at Week 24 compared with Baseline. At Week 52, subjects in the W24RS reported improvements in absenteeism, presenteeism, overall work impairment due to RA, and daily activity impairment due to RA.

Pharmacokinetics/Immunologic results:

Pharmacokinetics: For subjects overall and by antibody status, the highest geometric mean plasma CZP concentrations were reported at Week 4; however, the CZP levels observed in the negative anti-CZP antibody group were substantially higher than those observed in the positive anti-CZP antibody group (38.571µg/mL versus 20.405µg/mL, respectively), and the levels tended to remain higher in the negative anti-CZP antibody group compared with the positive anti-CZP antibody group at Week 12 (25.875µg/mL vs. 6.230µg/mL) and at Week 24 (21.286µg/mL vs. 1.428µg/mL, respectively).

Immunologic: A positive anti-CZP antibody level was defined as >2.4units/mL (with negative ≤2.4units/mL) measured on at least 1 visit. The percentage of subjects who were anti-CZP antibody positive increased over time throughout the DB Treatment Phase. At Baseline (Week 0) and Week 4, no subjects were positive for anti-CZP antibodies. At Week 12, 3 (3.1%) subjects were positive for anti-CZP antibodies, and at Week 24, 5 (5.2%) subjects were positive for anti-CZP antibodies. Cumulatively during the DB Treatment Phase, a total of 7 (7.3%) subjects developed anti-CZP antibodies.

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Safety results:

- Subjects in both treatment groups received an average of approximately 11 study medication injections, and >80% of subjects in both treatment groups had a mean duration of exposure ≥20 weeks during the DB Treatment Phase. During the OL Treatment Phase, the 14 subjects who were re-treated received an average of 8.0 study medication injections, and the mean duration of exposure during the OL Treatment Phase was ≥8 weeks for >90% of subjects.
- Overall, 66 (68.8%) subjects in the CZP+DMARD(s) group and 66 (67.3%) subjects in the placebo+DMARD(s) group reported at least 1 TEAE during the DB Treatment Phase of the study. The overall incidence rate for TEAEs per 100 patient-years was similar between treatment groups (CZP+DMARD[s]: 210.26 events/100PY [95% CI: 162.62, 267.50]; placebo+DMARD[s]: 222.75 events/100PY [95% CI: 172.28, 283.40]). Treatment-emergent AEs were most commonly reported in the SOC of infections and infestations and were similar in both groups (CZP+DMARD[s] group: 36.5% and placebo+DMARD[s] group: 37.8%).
- The most commonly reported TEAEs were tachycardia, vertigo, diarrhea, abdominal pain, abdominal pain upper, nausea, gastroenteritis, herpes simplex, influenza, bronchitis, nasopharyngitis, rhinitis, upper respiratory tract infection, urinary tract infection, transaminases increased, rheumatoid arthritis, headache, and hypertension. Of these TEAEs, all were reported at a similar incidence and occurred at similar incidence rates in the CZP+DMARD(s) and placebo+DMARD(s) groups, with the exception of tachycardia and transaminases increased which were reported at a slightly higher incidence and incidence rate in the CZP+DMARD(s) group compared with the placebo+DMARD(s) group, and vertigo and headache which were reported at a slightly higher incidence and incidence rate in the placebo+DMARD(s) group compared with the CZP+DMARD(s) group.
- Overall, 7 (25.9%) subjects reported at least 1 TEAE during the OL Treatment Phase of the study (all in subjects who received CZP+DMARD[s] during the DB Treatment Phase). Treatment-emergent AEs were most commonly reported in the SOC of infections and infestations (14.8% of subjects overall). The most commonly reported TEAEs were nausea and bronchitis (both reported by 2 [10%] subject who received CZP+DMARD[s] during the DB Treatment Phase).
- The majority of subjects with a TEAE during the DB Treatment Phase reported maximum intensities of mild or moderate. At least 1 severe TEAE was reported by

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3.1% of subjects in the CZP+DMARD(s) group and 6.1% of subjects in the placebo+DMARD(s) group. No severe TEAE (PT) was reported by more than 1 subject.

- The majority of subjects with a TEAE during the OL Treatment Phase reported maximum intensities of mild or moderate. Only 1 subject, in the OLS-NRT group during the OL Treatment Phase, reported a severe TEAE (cerebrovascular accident).
- The incidence and incidence rate of drug-related TEAEs during the DB Treatment Phase was similar for the CZP+DMARD(s) group (30.2% and 57.06 events/100PY) and the placebo+DMARD(s) group (26.5% and 53.14 events/100PY). The most commonly reported drug-related TEAE was upper respiratory tract infection, which occurred at a similar incidence and incidence rate in both treatment groups. All of the other most commonly reported drug-related TEAEs were reported in a small percentage of subjects in either treatment group.
- During the OL Treatment Phase, 1 subject in the OLS-RT group reported 3 drug-related TEAEs during the Re-treated Phase: rhinitis, cough, and hyperhidrosis. No other drug-related TEAEs were reported by any subjects during the OL Treatment Phase.
- No subjects died during the study.
- Serious TEAEs were reported by 5.2% of subjects (7.85 events/100PY) in the CZP+DMARD(s) group and 7.1% of subjects (11.82 events/100PY) in the placebo+DMARD(s) group. There were no SAEs that were reported by more than 1 subject.
- One subject who received CZP+DMARD(s) during the DB Treatment Phase reported an SAE of cerebrovascular accident during the Untreated Phase of the OL Treatment Phase. No other SAEs were reported during the OL Treatment Phase.
- During the DB Treatment Phase, the incidence and incidence rate of TEAEs leading to permanent discontinuation of study drug was similar between treatment groups (6.3% [9.41 events/100PY] for the CZP+DMARD[s] group and 6.1% [9.99 events/100PY] for the placebo+DMARD[s] group). Rheumatoid arthritis was the only TEAE leading to permanent discontinuation of study drug reported in more than 1 subject. One subject who received CZP+DMARD(s) during the DB Treatment Phase reported a TEAE leading to permanent study drug discontinuation (cerebrovascular accident) during the Untretaed Phase of the OL Treatment Phase.

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- During the DB Treatment Phase, the incidence and incidence rate of TEAEs leading to temporary discontinuation of study drug was similar between treatment groups (17.7% [29.39 events/100PY] for the CZP+DMARD[s] group and 15.3% [27.24 events/100PY] for the placebo+DMARD[s] group). The 7 TEAEs leading to temporary study drug discontinuation in more than 1 subject were all reported in the SOC of infections and infestations. During the OL Treatment Phase, 2 subjects, both of whom were randomized to the CZP+DMARD(s) group during the DB Treatment Phase, reported TEAEs leading to temporary study drug discontinuation. Both TEAEs were in the SOC of infections and infestations.
- During the DB Treatment Phase, 2 subjects in the CZP+DMARD(s) group and 1 subject in the placebo+DMARD(s) group reported a serious TEAE in the SOC of infections and infestations (otitis media, hemophilus sepsis with polyarthralgia, and pneumonia, respectively). No serious TEAEs were reported in the SOC of infections and infestations during the OL Treatment Phase. There were no reports of tuberculosis during the DB or OL Treatment Phases.
- During the DB Treatment Phase, 2 subjects in the placebo+DMARD(s) group reported a malignancy (breast cancer and basal cell carcinoma); no subjects in the CZP+DMARD(s) group reported a malignancy. No malignancies were reported during the OL Treatment Phase.
- During the DB Treatment Phase, cardiac AEs were reported at a higher incidence and incidence rate in the CZP+DMARD(s) group (6.3%; 9.55 events/100 PY) compared with the placebo+DMARD(s) group (1.0%; 1.65 events/100PY). The only cardiac AEs reported by more than 1 subject was tachycardia (reported by 3 [3.1%] subjects in the CZP+DMARD[s] group). None of the cardiac AEs were considered serious, or led to permanent discontinuation of study drug. No cardiac AEs were reported during the OL Treatment Phase.
- During the DB Treatment Phase, vascular AEs were reported at a slightly lower incidence and incidence rate in the CZP+DMARD(s) group (3.1% [4.68 events/100PY]) compared with the placebo+DMARD(s) group (4.1% [6.74 events/100PY]). The most commonly reported vascular AE was hypertension, which occurred in 3.1% of subjects in the CZP+DMARD(s) group and 2.0% of subjects in the placebo+DMARD(s) group. None of the vascular AEs were considered serious or led to permanent or temporary study drug discontinuation. No vascular AEs were reported during the OL Treatment Phase.

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- There were no cases of demyelinating disorders in this study and no notable neurological SAEs.
- One notable autoimmune event was reported (Wegener's granulomatosis) by a subject in the placebo+DMARD(s) group. The AE was considered serious, severe, led to study drug discontinuation, and was reported resolved.
- The incidence of injection site reaction TEAEs during the DB Treatment Phase was higher in the CZP+DMARD(s) group (8.3%) compared with the placebo+DMARD(s) group (2.0%). Only 2 injection site reactions were reported by more than 1 subject: injection site rash and erythema. The incidence of acute systemic injection reactions was low (1.0% in the CZP+DMARD[s] group and 0% in the placebo+DMARD[s] group), as was the incidence of delayed systemic injection reactions (4.2% in the CZP+DMARD[s] group and 3.1% in the placebo+DMARD[s] group). The only systemic injection reaction reported more than once was angioneurotic edema, which was reported twice by Subject [redacted] in the CZP+DMARD(s) group, once as an acute systemic injection reaction and once as a delayed systemic injection reaction. There were no injection reactions reported during the OL Treatment Phase.
- No clinically important or unexpected findings were observed for hematology variables, biochemistry variables, or vital signs. The number of subjects with physical examination abnormalities was low and similar between treatment groups.
- During the DB Treatment Phase, post-Baseline hypertension in subjects who were non-hypertensive at Baseline was reported by 4/13 subjects in the CZP+DMARD(s) group compared with 8/17 subjects in the placebo+DMARD(s) group.

Conclusions: Certolizumab pegol 200mg, after an initial dose of 400mg at Weeks 0, 2, and 4, along with concomitant DMARD therapy resulted in significantly higher rates of clinical remission at both Week 20 and Week 24 compared with placebo and concomitant DMARD therapy.

Treatment with CZP 200mg, after an initial dose of 400mg at Weeks 0, 2, and 4, was well tolerated. The AE profile was consistent with use of an anti-TNFα therapy in subjects with RA. No new safety signals were detected.

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