# C87077, 2007-005288-86

# CLINICAL STUDY REPORT SYNOPSIS



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**Sponsor:**

UCB Pharma SA

Chemin du Foriest

1420 Braine-l'Alleud

BELGIUM

**Official study title:**

A Phase IIIb, Open-Label, Run-In and Double-Blind, Placebo-Controlled, Randomized Study to evaluate the Safety and Efficacy of Certolizumab Pegol administered concomitantly with stable-dose Methotrexate in patients with Active Rheumatoid Arthritis

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| **Name of finished product:** Cimzia | **Volume:** Not applicable | |
| **Name of active ingredient:** Certolizumab pegol | **Page:** Not applicable | |

**Title of study:** A Phase IIIb, open-label, run-in and double-blind, placebo-controlled, randomized study to evaluate the safety and efficacy of certolizumab pegol administered concomitantly with stable-dose methotrexate in patients with active rheumatoid arthritis

**Investigator(s):** This was a multicenter study. Investigators at 63 sites screened subjects (52 sites enrolled subjects).

**Study site(s):** This study was conducted at centers in the [redacted]
63 sites screened subjects; 52 sites enrolled subjects.

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

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| **Studied period**: The total duration of study was a maximum of 34 weeks (nonresponders at Week 16) or 50 weeks (responders at Week 16).<br><br>**First subject enrolled:** 02 Jan 2008<br>**Last subject completed:** 01 Mar 2011 | **Phase of development:** Phase 3b |

**Objective(s):** The primary objective of this study was to assess the clinical efficacy of 2 dose regimens of certolizumab pegol (CZP) (200mg administered every 2 weeks [Q2W] and 400mg administered every 4 weeks [Q4W]) in combination with methotrexate (MTX) as compared to MTX alone for maintenance of clinical response over an additional 16 weeks in subjects who have responded (ie, achieved American College of Rheumatology 20% classification criteria [ACR20]) to the initial 18 weeks of treatment (CZP 400mg at Weeks 0, 2, and 4 followed by CZP 200mg and placebo at Weeks 6, 8, 10, 12, 14, and 16 plus MTX).

The following secondary objectives were assessed in all subjects:

- To assess the clinical response rates by ACR20, ACR50, and ACR70 at Week 16
- To assess the reduction of disease activity at Week 16 by Disease Activity Score – 28 joint count (erythrocyte sedimentation rate) [DAS28(ESR)], Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI)
- To assess the achievement of clinical remission at Week 16 by DAS28(ESR), SDAI,

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and CDAI

- To assess the improvement in physical function at Week 16 as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI)
- To evaluate the tolerability and safety of CZP therapy in subjects with active RA on a stable dose of concomitant MTX therapy

Additional objectives designed to provide information for submission and/or publication purposes (not planned in the protocol) were added prior to finalization of the SAP and prior to database lock:

- To assess the clinical response rates (by ACR20, ACR50 and ACR70) at Week 4, Week 8, Week 12, and Week 18
- To assess the improvement of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels at Week 16

The following secondary objectives were assessed in the subjects randomized at Week 18:

- To assess the clinical response rates (ACR50 and ACR70) at Week 34
- To assess the reduction of disease activity at Week 34 by DAS28(ESR), SDAI, and CDAI
- To assess the achievement of clinical remission at Week 34 (by DAS28[ESR], SDAI, and CDAI)
- To assess the improvement in individual components of the ACR criteria at Week 34, ie, HAQ–DI, Patient's Assessment of Arthritis Pain (PAAP) visual analog scale (VAS), and Patient's Global Assessment of Disease Activity (PtGADA) VAS (note that this objective was presented as 3 separate bullet points in the original protocol)
- To assess the reduction in fatigue as measured by the Fatigue Assessment Scale (FASCA) at Week 34
- To assess the improvement in subject's Health-Related Quality of Life as measured by the Short Form 36-item Health Survey (SF-36) at Week 34
- To assess the time to loss of ACR20 response (at 2 consecutive visits) after Week 18 (added with Protocol Amendment 5, dated 11 Jul 2008)

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Additional secondary objectives designed to provide information for submission and/or publication purposes (not planned in the protocol) were added prior to finalization of the SAP and prior to database lock for all subjects randomized at Week 18:

- To assess the clinical response rates (by ACR20, ACR50, and ACR70) at Week 4, Week 8, Week 12, Week 16, Week 18, Week 20, and every 4 weeks until Week 34 (described separately)
- To assess the improvement in individual components of the ACR criteria at Week 34, such as tender joint count (TJC), swollen joint count (SJC), CRP, ESR, and Physician's Global Assessment of Disease Activity (PhGADA) VAS
- To assess the European League against Rheumatism (EULAR) response at Week 34

**Methodology:** This was a multicenter study with an 18-week open-label Run-In (RI) Period followed by a 16-week double-blind (DB), placebo-controlled, randomized period for the evaluation of the safety and efficacy of CZP in subjects with active rheumatoid arthritis (RA) and an incomplete response to MTX.

During the RI Period, CZP was administered at a dose of 400mg (2 injections) at Weeks 0, 2, and 4 and at a dose of 200mg with placebo (1 injection of placebo, 1 injection of CZP) at Weeks 6, 8, 10, 12, 14, and 16. All subjects were required to continue MTX at the same dosage they were taking at study entry. The dose of MTX should have remained stable throughout the study, unless there was a need to reduce the dose for reasons of toxicity. At Week 18, all subjects were grouped as responders (achieved ACR20) or nonresponders based on the results of the ACR20 at Week 16. Nonresponders were withdrawn from the study at Week 18. Responders were randomized in a 1:1:1 ratio to receive CZP 200mg Q2W+MTX, or CZP 400mg Q4W+MTX, or placebo+MTX for 16 weeks (DB Period). Randomized subjects who experienced flares (an equal to or worse than Baseline swollen and tender joints count at 2 consecutive visits between Week 18 and Week 34 inclusive) were withdrawn from the study.

Subjects who were nonresponders and those who completed the DB Period (Week 34 assessment) or had flares were given the opportunity to receive treatment with CZP in open-label safety study C87084. A 12-Week Safety Follow-Up (SFU) was conducted for subject who did not enroll in C87084.

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**Number of subjects (planned and analyzed):** A total of 335 subjects were planned to be enrolled; ultimately, 333 subjects were enrolled; 209 subjects completed the RI Period and were randomized to receive CZP 200mg Q2W+MTX (n=70), CZP 400mg Q4W+MTX (n=70), or placebo+MTX (n=69). A subject randomized to the CZP 400mg Q4W+MTX group was withdrawn before receiving blinded study medication.

**Diagnosis and main criteria for inclusion:** Subjects enrolled were male or females, at least 18 years of age, with moderately to severely active adult-onset RA of at least 6 months duration but not longer than 15 years as defined by the 1987 ACR classification criteria. Active disease was defined as ≥6 tender joints (28 joint count) and ≥4 swollen joints (28 joint count) at Screening and Baseline and ≥10 mg/L [>1mg/dL] c-reactive protein (CRP) AND/OR > 28mm/hour erythrocyte sedimentation rate (ESR [Westergren]). Subjects had to be rheumatoid factor positive and/or anti-cyclic citrullinated peptide (anti-CCP) antibody positive.

Subjects had to have received treatment with MTX (10 to 25mg/week, with or without folic acid) for ≥3 months prior to Baseline with a stable dosage (≥10mg weekly) for ≥2 months prior to Baseline.

Subjects were excluded if they had any inflammatory arthritis other than RA or a noninflammatory type of arthritis that may have interfered with the efficacy assessments in this study. Subjects at a high risk for infection, with a history of infected joint prosthesis while the prosthesis was in situ, with current signs or symptoms of any infection, or a history of chronic or recent serious infection were not enrolled. Subjects were also excluded based on chest x-ray findings suggestive of malignancy or infection (including tuberculosis [TB]). Subjects were not allowed to have active TB (or history of active TB), positive chest x-ray for TB, or positive purified protein derivatives (PPD) skin test (defined as induration of ≥5mm) or have 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 least 1 month prior to first administration of CZP.

Subjects must have been free of medications that may have interfered with the assessment of efficacy or safety. Subjects who failed to respond to previous treatment with an anti-tumor necrosis factor-alpha (TNFα) agent were excluded. Subjects were excluded if they had received any biological agent for RA within 3 months before enrolment (1 month for etanercept and anakinra), had received previous treatment with a biological agent resulting in a severe hypersensitivity or anaphylactic reaction, or had not initially responded to

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previous anti-TNF therapy. Oral corticosteroids (10mg/day prednisone equivalent) and non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors were permitted provided that the doses were stable within 28 and 14 days of Baseline, respectively and remained stable during the study. Other medications (analgesics, corticosteroids, or disease modifying antirheumatic drugs [DMARDs]) were prohibited for specified times prior to Baseline arthritis assessments.

**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 RI Period, all subjects received sc CZP at a dose of 400mg at Weeks 0, 2, and 4, followed by CZP 200mg and placebo at Weeks 6, 8, 10, 12, 14, and 16. At Week 18, subjects who were ACR20 responders at Week 16 were randomized to receive either sc CZP 200mg Q2W+MTX, CZP 400mg Q4W+MTX, or placebo+MTX (DB Period):

- CZP 200mg Q2W: 1 injection of CZP and 1 injection of placebo at Weeks 18, 20, 22, 24, 26, 28, 30, and 32.
- CZP 400mg Q4W (two 200mg injections): 2 injections of CZP 200mg at Weeks 18, 22, 26, 30; and 2 injections of placebo at Weeks 20, 24, 28, and 32.
- placebo Q2W: 2 injections of placebo at Weeks 18, 20, 22, 24, 26, 28, 30, and 32.

**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 ACR20 responder rate at Week 34 (Visit 19) in the subjects randomized at Week 18. ACR20 responder rate was defined as a decrease of >20% from Baseline in the number of tender joints (28 joints) and swollen joints (28 joints) plus a 20% improvement in any 3 of the following 5 core measurements: Patient's or Physician's Global Assessment of Disease Activity (PtGADA and PhGADA,

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respectively), Patient's Assessment of Arthritic Pain (PAAP), Health Assessment Questionnaire-Disability Index (HAQ-DI) and serum CRP.

The following secondary efficacy variables were assessed in all subjects:

- ACR20, ACR50, and ACR70 responder rates at Week 16
- Disease Activity Score – 28 joint count (erythrocyte sedimentation rate) [DAS28(ESR)] remission (<2.6) rate, Simplified Disease Activity Index (SDAI) remission (≤3.3) rate, and Clinical Disease Activity Index (CDAI) remission (≤2.8) rate at Week 16
- Change from Baseline in DAS28(ESR), SDAI, and CDAI scores at Week 16
- Change from Baseline in HAQ–DI at Week 16

Additional variables not planned in the protocol (added in the Statistical Analysis Plan [SAP]):

- ACR20, ACR50 and ACR70 responder rates at Week 4, Week 8, Week 12 and Week 18
- Ratio to Baseline at Week 16 in CRP and ESR levels

Additional variables not planned in the protocol or SAP:

- Change from Baseline in tender joint count (TJC) and swollen joint count (SJC) at Week 16

The following secondary efficacy variables were assessed in the subjects randomized at Week 18:

- ACR50 and ACR70 responder rates at Week 34
- DAS28(ESR) remission (<2.6) rate, SDAI remission (≤3.3) rate, and CDAI remission (≤2.8) rate at Week 34
- Change from Baseline in DAS28(ESR), SDAI and CDAI scores at Week 34
- Change from Baseline at Week 34 in individual components of the ACR including HAQ-DI, PAAP- visual analog scale (VAS), and PtGADA-VAS
- Change from Baseline in Short Form 36-item Health Survey (SF-36) domains as well

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as Mental Component Summary (MCS) and Physical Component Summary (PCS) at Week 34

- Change from Baseline in the Fatigue Assessment Scale (FASCA) at Week 34
- The time to loss of ACR20 response (at 2 consecutive visits) after Week 18

Additional variables not planned in the protocol (added in the SAP):

- ACR20, ACR50, and ACR70 at Week 4, Week 8, Week 12, Week 16, Week 18, Week 20, and every 4 weeks until Week 34 (exclusive)
- Change from Baseline at Week 34 in individual components of the ACR including TJC, SJC, CRP (ratio to Baseline), ESR (ratio to Baseline), and PhGADA–VAS
- European League Against Rheumatism (EULAR) response criteria (improvement in DAS28[ESR] from Baseline and DAS28[ESR] disease activity at Week 34)

**Pharmacokinetic/Immunologic measurements:** Plasma samples for the measurement of CZP concentrations and anti-CZP antibodies were collected at Baseline and at Week 16, Week 28, and Week 34.

**Safety:** The safety variables were:

- Adverse events (AEs)
- Clinical laboratory evaluations (hematology, biochemistry, and urinalysis parameters)
- Lipid profiles
- Vital signs
- Physical examinations and TB testing

**Statistical methods:** The primary efficacy variable (ACR20 responder rate at Week 34) was analyzed on the Full Analysis Set (FAS). The FAS was defined as all randomized subjects irrespective of any protocol deviations who received at least 1 injection of study medication.

The following logistic regression model was used:

$Y = \alpha + \beta_0\ CZP\ 200mg + \beta_1\ CZP\ 400mg$ with

- Y defined as ACR20 responder status
- CZP 200mg defined as a dichotomous variable, taking as value 1 if the subject was

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randomized in the CZP 200mg+MTX arm in the DB Period, and 0 otherwise.

- CZP 400mg defined as a dichotomous variable, taking as value 1 if the subject was randomized in the CZP 400mg+MTX arm in the DB Period, and 0 otherwise

The 2 odds ratios comparing CZP 200mg Q2W+MTX to placebo+MTX and CZP 400mg Q4W+MTX to placebo+MTX were obtained from this model by estimating $\exp(\beta_0)$ and $\exp(\beta_1)$, respectively, and presented with 95% 2-sided confidence intervals. The p-values from the associated Wald tests (for $\beta_0$ and $\beta_1$ respectively) were also provided. The Hochberg approach was used in order to account for multiplicity.

The primary efficacy analysis utilized the nonresponder imputation (NRI) method for handling missing data. Subjects who withdrew prematurely from the DB Period for any reason, who took a rescue medication during the study, or who had a missing ACR20 response at Week 34 were counted as nonresponders.

Secondary, supportive, and sensitivity analyses were also conducted for the primary efficacy variable:

- Secondary analysis by Baseline factors using the FAS and the NRI method for handling missing data.
- Supportive analysis using the Per Protocol Set (PPS), defined as all subjects eligible for the FAS who did not have any major protocol deviations affecting the primary efficacy variable, and the NRI method for handling missing data. Note that subjects who took a rescue medication during the study were excluded from the PPS from the time of the rescue medication intake.
- Sensitivity analyses using the FAS and partial last observation carried forward (LOCF) and LOCF methods for handling missing data.
- Partial LOCF: Subjects who prematurely withdrew due to an AE, lack of efficacy, or loss of efficacy were considered nonresponders at Week 34, regardless of their previous status. Subjects who withdrew for any other reason or with a missing assessment at Week 34 had their previous (including early termination) visit responder status carried forward (across both periods if applicable) for Week 34. ACR20 responder status at Week 34 for subjects who took a rescue medication during the study was imputed by the last status available before the time of intake.
- LOCF: Missing values because of subject withdrawal, a missing assessment at Week 34, or because of data exclusion after the use of rescue medication were imputed by

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carrying forward the last available efficacy measurement (across both periods if applicable).

**Subject disposition:** A total of 620 subjects were screened for the study, and 333 entered the RI Period. All 333 subjects were included in the Modified Enrolled Set (ES). The majority of subjects (209 [62.8%]) completed the RI Period. Lack of efficacy was the most common reason for discontinuation (93 subjects [27.9%]). Adverse event led to discontinuation of 17 subjects (5.1%). Most subjects who did not complete the RI Period were discontinued at Week 16 or Week 18 (58 and 31 subjects, respectively). The most common reason at these visits was lack of efficacy, which is largely attributable to study design, whereby "lack of efficacy" (not achieving ACR20) resulted in subjects not being eligible for randomization to the DB Period. Ninety-three of the 124 (75.0%) subjects who were discontinued early from the RI Period completed the 12-Week SFU Visit.

All 209 subjects who completed the RI Period were randomized in the DB Period. The majority of randomized subjects across all treatment groups completed the DB Period (78.3% to 90.0%) with more subjects (88.6%) in the Total CZP+MTX group completing compared with the placebo+MTX group (78.3%). The most common reason for early discontinuation among subjects who received CZP+MTX was AE (7 subjects [5.0%]). The most common reason among subjects who received placebo+MTX was loss of efficacy (10 subjects [14.5%]). There was no particular pattern with respect to timing of early discontinuations. Only 8 subjects in each treatment group completed the 12-Week SFU visit.

**Efficacy results:** The results of the primary efficacy analysis, maintenance of clinical response (ie, ACR20) in subjects who responded to an initial 18 weeks of treatment, were robust and demonstrated that either continued treatment with CZP 200mg Q2W+MTX or switching to the CZP 400mg Q4W+MTX dose regimen resulted in statistically significantly superior efficacy compared with placebo+MTX in maintaining the ACR20 response over an additional 16 weeks of treatment. The ACR20 response rates for the primary endpoint were numerically similar for the 2 CZP+MTX dose regimens. The results of the primary analysis were supported by the sensitivity analyses.

Secondary efficacy analyses also demonstrated that both the CZP 200mg Q2W+MTX and the CZP 400mg Q4W+MTX maintenance dose regimen were efficacious compared with placebo+MTX after 34 weeks of treatment and that improvements in signs and symptoms and physical function/health outcome measures achieved after 18 weeks of open-label treatment were sustained for up to 16 additional weeks during the DB Period. Comparable maintenance of response was demonstrated among subjects who continued treatment with

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CZP 200mg Q2W+MTX and subjects who switched to the CZP 400mg Q4W+MTX dose regimen. Furthermore, exploratory analyses of secondary efficacy endpoints provided evidence of positive treatment effects for both CZP+MTX maintenance dose regimens compared with placebo+MTX. Summaries of key results follow.

Greater percentages of subjects in both CZP+MTX groups achieved an ACR50 and ACR70 response at Week 34 compared with subjects in the placebo+MTX group. The response rates at Week 34 were numerically similar for the 2 CZP+MTX groups.

Favorable profiles for both CZP+MTX groups were observed over time for ACR20, ACR50, and ACR70 response rates compared with the placebo+MTX group. Although fewer subjects across all 3 treatment group achieved an ACR20 response at Week 34 compared with the start of the DB Period (Week 18), the CZP+MTX groups displayed increasing separation from the placebo+MTX group over time, with greater response rates compared to placebo+MTX at each assessment during the DB Period. The percentage of responders was sustained to a similar degree for subjects in the CZP 200mg Q2W+MTX and the CZP 400mg Q4W+MTX groups. The application of the conservative NRI rule and self-selection bias may have contributed to the apparent loss of ACR20 response rates over time observed for the CZP+MTX treatment groups during the DB Period. It is noteworthy that the apparent slight decline in ACR20 response rates over time based on the NRI rule were not observed with other efficacy analyses which applied LOCF imputation for missing data.

The results of ACR50 and ACR70 response rates over time were supportive of the ACR20 response rates over time. The ACR50 response rate for the CZP 400mg Q4W+MTX group was the same at Week 34 as at the start of the DB Period. A small decrease was noted in the CZP 200mg Q2W+MTX group at Week 34 compared with the start of the DB Period. A substantially larger decrease was seen in the placebo+MTX group at Week 34 compared with the start of the DB Period. The ACR70 response rate was similar at Week 34 and the start of the DB Period for the CZP 200mg Q2W+MTX. The response rate increased at Week 34 compared to the start of the DB Period in the CZP 400mg Q4W+MTX group. A decline in the ACR70 response rate was observed in the placebo+MTX group at Week 34 compared with the start of the DB Period. Taken together, these results suggest that "good" responders at Week 16 (ie, subjects who achieved an ACR70 response) in contrast to moderate or mild responders (ie, subjects who achieved an ACR50 and ACR20 response) not only maintained but showed continued improvement of clinical response with longer treatment exposure.

Overall, the pattern of ACR response over time for both dose regimens demonstrated

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continued clinical benefit, supporting the use of CZP 400mg Q4W+MTX as an alternative maintenance dose regimen to CZP 200mg Q2W+MTX once clinical response is achieved.

Individual ACR component results demonstrated improvements in the signs and symptoms of RA for both CZP+MTX maintenance dose regimens. Subjects in both active groups had significantly greater improvements relative to Baseline in all ACR component scores at Week 34 compared with subjects in the placebo+MTX group. Improvements in individual ACR components achieved during the RI Period were maintained to the end of the DB Period for both CZP+MTX regimens. The ACR component results were comparable for the 2 CZP+MTX maintenance dose regimens.

Improvements in disease activity based on the results of DAS28(ESR), CDAI, and SDAI were demonstrated for both CZP+MTX dose regimens compared with placebo+MTX. Greater percentages of subjects in both CZP+MTX groups were in DAS28(ESR), SDAI, and CDAI remission at Week 34 compared with the placebo+MTX group. Subjects in both CZP+MTX maintenance dose regimens had significantly greater improvements in DAS28(ESR), SDAI, and CDAI scores at Week 34 compared with subjects in the placebo+MTX group. Improved response compared to the start of the DB Period was observed over time for both CZP+MTX groups with a greater percentage of subjects who were DAS28(ESR), SDAI, and CDAI remitters at Week 34 compared with the start of the DB Period. In contrast, a loss of response was observed for the placebo+MTX group with fewer subjects classified as DAS28(ESR), SDAI, and CDAI remitters over time during the DB Period.

Similarly, the percentages of subjects with a EULAR response of "good" (defined as a responder) at Week 34 were significantly greater for subjects in both CZP+MTX groups compared with subjects in the placebo+MTX group. Improved response was observed over time for the CZP+MTX groups with greater percentages of subjects reporting a EULAR response of "good" at Week 34 compared with the start of the DB Period. A loss of response was apparent for the placebo+MTX group with a smaller percentage of subjects with EULAR response of "good" at Week 34 compared with the start of the DB Period.

Irrespective of the dose regimen, subjects treated with CZP+MTX reported significant improvements in physical function and disability (HAQ-DI, SF-36 PCS and physical functioning domain) and reduction in fatigue (FASCA) compared with placebo+MTX. Comparable results were observed for the 2 CZP+MTX dose regimens. The improvements at Week 34 were similar to the start of the DB Period.

Improvements in the CZP+MTX groups over placebo+MTX were clinically relevant with substantially fewer subjects withdrawing because of loss of efficacy in either CZP+MTX

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group compared with placebo+MTX.

For the ACR20 response, none of the treatment-by-subpopulation interactions (at the 15% level) were statistically significant except for Baseline ESR ≥30mm/hour. Therefore, regardless of age, gender, race, weight, BMI, duration of RA, Baseline DAS(ESR), Baseline CDAI, concomitant DMARD use, MTX dose, Baseline steroid use, past anti-TNF use, RF at Screening, Baseline CRP, anti-CCP status at Screening, or antibodies to CZP at Week 18, CZP+MTX showed a robust clinical response for maintenance of ACR20 at Week 34.

The interaction for ESR ≥30mm/hour is most likely driven by the higher percentage of responders in both CZP+MTX groups (74.5% in the CZP 200mg Q2W+MTX group and 70.8% in the CZP 400mg Q4W+MTX group) compared to placebo+MTX (39.1%) in the ESR ≥30mm/hour category, but may also be influenced by the slightly higher response in the placebo+MTX group with ESR <30mm/hour (56.5%) (less severely ill subjects) compared to the CZP 200mg Q2W+MTX (50.0%) and CZP 400mg Q4W+MTX (52.4%) groups. The Baseline factor by treatment interaction for Baseline ESR ≥28mm/hour was not significant (p=0.156).

In summary, once clinical response is achieved, CZP 400mg Q4W+MTX was demonstrated to be effective as an alternative to the CZP 200mg Q2W+MTX maintenance dose regimen for sustaining clinical benefit in subjects with moderate to severe RA and an incomplete response to MTX. Robust clinical efficacy was demonstrated based on the primary efficacy endpoint (ACR20) and multiple measures of signs and symptoms as well as physical functioning and health outcome measures. There were no clinically relevant differences between the previously demonstrated efficacious maintenance dose regimen (CZP 200mg Q2W+MTX) and the CZP 400mg Q4W+MTX dose regimen.

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**Pharmacokinetic results:** The CZP plasma concentrations at Week 16 were similar for all groups, irrespective of the treatment group to which they were randomized at Week 18.

In subjects treated with CZP 200mg Q2W+MTX, only trough concentration ($C_{trough}$) samples were taken, with the highest observed mean (geometric) plasma CZP concentrations for anti-CZP antibody negative subjects at Week 16 (21.5µg/mL), which decreased slightly at Week 28 (17.6µg/mL) and Week 34 (16.1µg/mL).

The highest CZP plasma concentrations were observed in subjects treated with CZP 400mg Q4W+MTX with the highest observed mean (geometric) plasma CZP concentration for anti-CZP antibody negative subjects occurring mid-way through the dose interval at Week 28 (29.4µg/mL) and the lowest concentrations ($C_{trough}$) occurring at Week 34 (<10.1µg/mL).

**Immunologic results:** The incidence of antibodies against CZP were highest in the PBO+MTX group after discontinuation of CZP treatment (ie, beyond Week 16). The incidence of anti-CZP antibodies varied across the treatment groups even at Week 16, at which point all subjects had received the same treatment. Of note, the analysis of percentage of antibodies at any visit was potentially confounded by the fact that the Week 28 visit was not a trough sample for the CZP 400mg Q4W dose group.

Overall, anti-CZP antibody status showed no observable trends between responders and nonresponders throughout the study.

**Safety results:** The study population was representative of patients with moderate to severe RA and an incomplete response to MTX.

A total of 333 subjects entered the RI Period and received sc CZP at a dose of 400mg at Weeks 0, 2, and 4, followed by CZP 200mg at Weeks 6, 8, 10, 12, 14, and 16. The mean number of study medication injections received was approximately 8 (range: 1 to 9). The duration of exposure during the RI Period was 16 weeks for 91% of subjects.

A total of 208 subjects (CZP 200mg Q2W+MTX: 70; CZP 400mg Q4W+MTX: 69; placebo+MTX: 69) who completed the RI Period received treatment in the DB Period for up to an additional 16 weeks beginning at Week 18. Subjects across treatment groups received an average of approximately 7 study medication injections (range: 1 to 8). The duration of exposure during the DB Period was at least 8 weeks for more than 95% of subjects across treatment groups and the duration of exposure was up to 16 weeks for more than half of subjects across treatment groups.

Treatment with CZP was generally well tolerated during both the RI and DB Periods. No

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new important safety concerns were identified. The safety profile, including the type and incidence of treatment-emergent AEs (TEAEs), was consistent with that expected in subjects with RA receiving an anti-TNFα agent and with previous studies of CZP. Overall, most TEAEs were mild or moderate in intensity and were not described by the Investigator as drug-related. No deaths and no pregnancies were reported during the study through the SFU period.

RI Period TEAEs:

During the RI Period, at least one TEAE was reported for 76.0% of subjects. The majority of subjects had TEAEs with a maximum intensity of mild or moderate (68.2%) and TEAEs classified by the Investigator as not or unlikely related to study medication (71.2%).

Upper respiratory tract infection (12.6%) and urinary tract infection (8.1%) were the only TEAEs reported in greater than 5% of subjects. Rheumatoid arthritis (4 subjects [1.2%]), cellulitis (2 subjects [0.6%]), and pneumonia (2 subjects [0.6%]) were the only severe TEAEs (by preferred term) reported in more than 1 subject.

Treatment-emergent SAEs were reported in 5.4% of subjects (27 SAEs among 18 subjects). The only SAEs reported by more than 1 subject were cellulitis (3 subjects [0.9%]) and pneumonia (2 subjects [0.6%]). Treatment-emergent AEs leading to permanent study drug discontinuation were reported in 6.6% of subjects. The only TEAEs leading to permanent study drug discontinuation reported by more than 1 subject were cellulitis (3 subjects [0.9%]) and rash (2 subjects [0.6%]).

DB Period TEAEs:

The overall incidence of TEAEs was similar across treatment groups (CZP 200mg Q2W+MTX: 62.9%; CZP 400mg Q4W+MTX: 60.9%; placebo+MTX: 62.3%) during the DB Period. The majority of subjects reported TEAEs with maximum intensities of mild or moderate across treatment groups. There were more subjects with severe AEs in the CZP+MTX groups than in the placebo+MTX group (5.0% vs 1.4%, mostly in the CZP 200mg Q2W+MTX group) and there were slightly more TEAEs that were attributed to study medication by the Investigator in the CZP+MTX groups compared with the placebo+MTX group (20.1% vs 15.9%); the differences between CZP 200mg Q2W and CZP 400mg Q4W must be interpreted with caution given the rather small sample sizes.

Adverse events were most commonly reported in the system organ class (SOC) categories of Infections and infestations (CZP 200mg Q2W+MTX: 28.6%; CZP 400mg Q4W+MTX: 36.2%; placebo+MTX: 34.8%) and Musculoskeletal and connective tissues disorders (CZP 200mg Q2W+MTX: 11.4%; CZP 400mg Q4W+MTX: 15.9%; placebo+MTX: 18.8%). The

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most commonly reported individual TEAEs were pyrexia, upper respiratory tract infection, urinary tract infection, nasopharyngitis, arthralgia, and rheumatoid arthritis. The only TEAEs reported at a greater incidence with CZP treatment compared with placebo treatment were pyrexia (CZP 200mg Q2W+MTX: 5.7% vs placebo+MTX: 1.4%) and arthralgia (CZP 400mg Q2W+MTX: 7.2% vs placebo+MTX: 2.9%).

Eleven serious AEs (SAEs) were reported among 5 subjects (7.1%) in the CZP 200mg Q2W+MTX group and single SAEs were reported for 2 subjects (2.9%) in the CZP 400mg Q4W+MTX group. No individual SAE (by preferred term) was reported by more than 1 subject in either CZP+MTX group. No SAEs were reported by subjects in the placebo+MTX group.

The incidence of TEAEs leading to permanent discontinuation of study drug was low (4 subjects [5.7%] in the CZP 200mg Q2W+MTX group and 1 subject [1.4%] in the CZP 400mg Q4W+MTX group). No subjects in the placebo+MTX group discontinued the study due to a TEAE.

Events of Special Interest:

No new safety concerns were identified based on review of events in the categories of infections, malignancies, injection reactions, cardiac, hepatic, vascular, immune system, and neurologic events of interest.

There was no indication of increased risk of malignancies, although the duration of exposure in this study precludes firm conclusions regarding this risk.

Other safety evaluations:

No clinically important deleterious effects or unexpected findings of CZP+MTX were observed for hematology variables, biochemistry variables, or vital signs. Events of elevated blood pressure (BP) during the study (systolic BP value ≥140mmHg and/or a diastolic BP value ≥90mmHg at 2 or more post-Baseline visits) were low and generally occurred in subjects with a history of hypertension/high blood pressure. Hypertension resulted in permanent discontinuation of study drug for 1 subject during the RI Period. There were no reports of SAEs of hypertension.

Changes observed in the lipid profile of RA subjects in this study are consistent with findings reported in the literature (van Sijl et al, 2011). Mean and median changes over time in lipid parameters (cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides) were generally small and not considered to be of clinical significance for any treatment group in either the RI Period or DB Period. A greater percentage of CZP+MTX-treated subjects experienced shifts in lipid

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parameters from Baseline to post-Baseline compared with the placebo+MTX group, although the incidence of markedly abnormal values was rare (<1%).

- Geometric mean and median ratio from Baseline values for cholesterol, LDL, HDL, and triglycerides were 1.0. Minimum and maximum ratio from Baseline values were 1 and 2, respectively, for cholesterol and HDL cholesterol. The ranges for LDL cholesterol and triglycerides were 0 to 3 and 0 to 6, respectively.

**Conclusions:** Treatment with CZP 200mg Q2W+MTX or CZP 400mg Q4W+MTX as the maintenance dose regimen is well tolerated and no new safety signals were identified. The potential modest effects on lipid parameters based on the exploratory analyses in this study are consistent with those described in the literature.

Both the CZP 200mg Q2W+MTX and the CZP 400mg Q4W+MTX dose regimens are superior to placebo+MTX for maintenance of clinical response over at least 16 weeks in subjects with active RA and an incomplete response to MTX. In addition, both the CZP 200mg Q2W+MTX and the CZP 400mg Q4W+MTX dose regimens were efficacious compared with placebo+MTX in reducing signs and symptoms of RA and improving physical function and health outcomes, including fatigue.

This study demonstrated that both efficacy and safety were maintained after switching from a CZP dose regimen of 200 mg Q2W to that of 400 mg Q4W. This would suggest that subjects who respond (ACR 20 response) to an initial 18 weeks of CZP 200 mg Q2W+MTX can expect to maintain their clinical response after switching to CZP 400 mg Q4W+MTX, as well as experience a comparable safety profile.

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