# CLINICAL STUDY REPORT SYNOPSIS: RA0096

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| **Name of company:** UCB Japan | **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 Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Efficacy and Safety of CDP870 in Patients with Early-stage Rheumatoid Arthritis Who Are Naïve to Methotrexate and Have Poor Prognostic Factors

**Investigator(s):** 70 sites in Japan enrolled subjects.

**Study site(s):** This study was initiated at 73 study centers in Japan with a total of 378 subjects screened at 70 sites.

**Publication(s) (reference[s]):** Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, et al. The first double-blind, randomised, parallel-group Certolizumab pegol study in methotrexate-naïve early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. Ann Rheum Dis. 2015;0:1–9.

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| **Study period:** This Clinical Study Report (CSR) provides results of all study periods through the end of the study. The total possible duration was approximately 104 weeks with a subsequent 10-week Safety Follow-Up Period.<br><br>**First subject enrolled:** 11 Oct 2011<br>**Last subject completed date:** 20 Oct 2014 | **Phase of development:** Phase 3 |

**Objective(s):** The objective of this study was to compare the efficacy of certolizumab pegol (CZP) in combination with methotrexate (MTX) in subjects with early rheumatoid arthritis (RA), who were MTX-naïve and had poor prognostic factors, to that of MTX monotherapy with inhibition of joint damage progression after 1 year of treatment as the primary endpoint. In addition, maintenance of the efficacy of CZP is being investigated exploratively in a Follow-Up Observation Period for 1 year with MTX monotherapy after CZP withdrawal. The safety, pharmacokinetics, and immunogenicity were also investigated.

**Methodology:** RA0096 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study in adult subjects with early RA who were MTX-naïve and had poor prognostic factors. After an up to 4-week Screening Period subjects received CZP+MTX or placebo (PBO)+MTX during a 52-week, double-blind, placebo-controlled Treatment Period. Subjects completing the Double-Blind Period were eligible to enroll in the 52-week Post-Treatment Period providing MTX monotherapy. Rescue treatment

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was available to subjects meeting predefined criteria.

Subjects meeting the eligibility criteria were allocated to 1 of the following treatment groups:

- Certolizumab pegol administered subcutaneously (sc) at a loading dose of CZP 400mg every second week (Q2W) at Weeks 0, 2, and 4; followed by a dose of CZP 200mg Q2W sc from Week 6 to Week 50 and an oral dose of MTX administered from Week 0 onwards
- Placebo administered sc Q2W at Weeks 0, 2, and 4; followed by placebo Q2W sc from Week 6 to Week 50 and an oral dose of MTX administered from Week 0 onwards

Rescue treatment was available to subjects who did not achieve an improvement of symptoms at and after Week 24 (Visit 16). The Rescue Treatment Period started after the subject's dropout from the original study schedule and lasted up to Week 104.

A Safety Follow-up Visit was performed at 10 weeks after the final study drug administration for subjects who withdrew from the study during the Double-Blind Period, discontinued or terminated rescue treatment, withdrew during the early phase (up to Week 8) of the Post-Treatment Period, or continued the Post-Treatment Period for more than 8 weeks. In this case, the examination performed at Visit 32 (Week 8 of the Post-Treatment Period, ie, 10 weeks after the final study drug administration during the Double-Blind Period) was regarded as a follow up examination.

This CSR presents a complete analysis through the end of the study for each individual subject.

**Number of subjects (planned and analyzed):** A total of 150 subjects per treatment group was planned to be included. The actual number of subjects randomized was 161 subjects in the CZP+MTX group and 158 subjects in the PBO+MTX group.

**Diagnosis and main criteria for inclusion:** RA0096 included adult male and female subjects ≥20 years and <65 years of age who were within their first year of RA since onset (defined as the time when continuous symptoms of arthritis started). Subjects were to be naïve to MTX and were required to have active disease in a moderate or higher degree of their Disease Activity Score-28 (erythrocyte sedimentation rate) (DAS28[ESR]) ≥3.2. Subjects were to have the following high anti-cyclic citrullinated peptide (CCP) antibody titer and must have met at least 1 of the other 2 criteria for poor prognostic factors.

- High anti-CCP antibody titer: ≥13.5U/mL (3 times the standard range)
- Positive rheumatoid factor: >20IU/mL (standard range)
- Presence of bone erosion (evidenced by the x-ray examination of hands and feet)

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**Test product, dose(s) and mode of administration, batch number(s):** Certolizumab pegol was supplied as a modified prefilled syringe with an injection solution containing 200mg of CZP in 1mL.

Batch numbers: [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted])

**Duration of treatment:** 52 weeks during the Double-Blind Period, 52 weeks during the Post-Treatment Period, and during the Rescue Treatment Period up to Week 104.

**Reference therapy, dose(s) and mode of administration, batch number(s):** Placebo was supplied as modified prefilled syringe containing 1mL of saline.

Batch numbers: [redacted] ([redacted]), [redacted] ([redacted]), [redacted] ([redacted])

**Criteria for evaluation:**

**Efficacy:**

The primary efficacy variable was:

- Inhibition of joint damage progression (modified total Sharp score [mTSS] at Week 52)

The secondary efficacy variables were:

- Inhibition of joint damage progression (mTSS at Week 24)
- DAS28(ESR) remission rate and American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) remission rate (Weeks 24 and 52)

The other efficacy variables were:

- DAS28(ESR) remission rate and ACR/EULAR remission rate
- DAS28(ESR) and Simplified Disease Activity Index (SDAI)
- ACR20, ACR50, and ACR70 responder rate
- Disease activity markers: number of tender joint count (TJC), number of swollen joint count (SJC), Health Assessment Questionnaire (HAQ), Patient's assessment of arthritis pain (PtAAP), Patient's Global Assessment of Disease Activity (PtGADA), Physician's Global Assessment of Disease Activity (PhGADA), C-reactive protein (CRP), ESR, matrix metalloproteinase-3 (MMP-3)
- Labor productivity

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**Pharmacokinetics/pharmacodynamics:** The pharmacokinetic (PK) variables were the plasma CZP concentration and the plasma anti-CZP antibody concentration.

**Safety:** The safety variables were adverse events (AEs), laboratory tests, autoantibodies, body weight and vital signs, electrocardiography, and chest x-ray examination.

**Statistical methods:**

Primary analysis of the primary efficacy variable (mTSS at Week 52)

The primary efficacy variable was the mTSS. The analysis was performed in the Full Analysis Set (FAS) and Per-Protocol Set (PPS). The mTSS was analyzed using LINEAR at Week 52.

The primary Week 52 analysis assessed whether treatment up to Week 52 with the CZP group was superior to the placebo group in mTSS at Week 52. The 2-sided null and alternative hypotheses were:

- H0: $\pi C = \pi M$
- Ha: $\pi C \neq \pi M$

where $\pi C$ represented subjects in the CZP group at Week 52 and $\pi M$ represented subjects in the placebo group at Week 52.

An analysis of covariance (ANCOVA) model was performed for the change from Baseline by converting the measured values to rank scores and using the treatment group as a factor and the Baseline rank score as a covariate. The mean of the corresponding rank was assigned for tied values. The p-value for the treatment effect was also presented.

The Hodges-Lehman point estimates and corresponding 95% confidence interval (CI) was calculated for the difference between the CZP group and the placebo group as primary of summary statistics.

In addition, for the measured values, an ANCOVA model was performed for the change from Baseline using the treatment group as factor and Baseline value as a covariate. The least square means (LSMeans) with a 95% CI for each group and the difference in LSMeans with a 95% CI were calculated.

Supportive and sensitivity analyses of the primary efficacy variable

An ANCOVA model on the rank scores and the Hodges-Lehmann point estimates was performed in the FAS using last observation carried forward (LOCF) and observed case (OC).

A mixed model for repeated measures with subject as a random effect and the treatment group and visit as a fixed effect was performed for the change from Baseline in the FAS using OC. The

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covariance structure of residual errors was a completely general (unstructured) covariance matrix parameterized directly in terms of variances and covariance.

For erosion score and joint space narrowing score, the following analysis was performed in the FAS using LINEAR, LOCF and OC, as with mTSS:

- An ANCOVA model on the rank scores
- An ANCOVA model on the measured values
- The Hodges-Lehmann point estimates and corresponding 95% CI
- Descriptive statistics

In the PPS using LINEAR, an ANCOVA model on the rank scores, Hodges-Lehmann point estimates and corresponding 95% CI and descriptive statistics were performed for erosion score and joint space narrowing score.

For the erosion score and joint space narrowing score, a cumulative probability plot of the change from Baseline was presented graphically in the FAS using LINEAR. For the mTSS, erosion score, and joint space narrowing score, descriptive statistics for the change from Baseline were presented graphically in the FAS using LINEAR. Also subgroup analyses for the change from Baseline in the mTSS at Week 52 were performed.

Nonprogression rate Proportion of subjects for the change from Baseline

The following analysis was performed in the FAS using LINEAR, LOCF and OC. For the mTSS, erosion score, and joint space narrowing score at Week 52, the nonprogression as defined by the change from Baseline ≤0.5 and 95% CI by the Clopper Pearson method, was presented. Fisher's exact test was used for the comparison between the CZP and the placebo group.

Subgroup analyses were performed. In the PPS, the same analyses were performed for the mTSS, erosion score, and joint space narrowing score using LINEAR.

**Summary and conclusions:**

**Subject disposition:** At Week 0, a total of 161 subjects was randomized to receive CZP+MTX and 158 subjects were randomized to receive PBO+MTX. Two subjects in the CZP+MTX group and 1 subject in the PBO+MTX group were randomized, but did not receive the study drug due to violation of inclusion/exclusion criteria (1 subject per treatment group) or investigator decision (1 subject in the CZP+MTX group).

During the Double-Blind Period, subject disposition was well balanced across both treatment groups; however, the percentage of subjects who completed the Double-Blind Period was higher in the CZP+MTX group (68.9%) as compared with the PBO+MTX group (46.2%). Lack of

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efficacy was the major reason for discontinuation accounting for 22.4% of subjects in the CZP+MTX group and 44.9% of subjects in the PBO+MTX group. The percentage of subjects discontinuing due to AEs was comparable in both treatments groups.

Overall, 108 subjects in the CZP+MTX to MTX group and 71 subjects in the PBO+MTX to MTX group entered the Post-Treatment Period. The percentage of completers was 68.5% of subjects in the CZP+MTX to MTX group and 80.3% of subjects in the PBO+MTX to MTX group, respectively.

The All Subjects group evaluated in the Rescue Treatment Period included 151 subjects who switched to rescue treatment during the Double-Blind Period or the Post-Treatment Period regardless of the treatment in the Double-Blind Period. The Re-treated Subjects group included 28 subjects who initially were in low disease activity (LDA) after 52 weeks of treatment with CZP in the Double-Blind Period, but who flared during the Post-Treatment Period. The majority of subjects in both groups (approximately 90%) completed the Rescue Treatment Period.

**Efficacy results: Double-Blind Period (Week 0 to 52)**

The results of this study demonstrated that CZP in combination with MTX is effective in the inhibition of structural damage progression and the treatment of signs and symptoms of RA in MTX-naïve subjects with early RA onset and poor prognostic factors.

The results of the primary variable (inhibition of joint damage progression at Week 52) with CZP+MTX treatment were robust and statistically significant as compared to PBO+MTX. Similarly, the results of the secondary variables related to joint damage progression inhibition as well as variables evaluating signs and symptoms demonstrated a robust and significant efficacy of CZP+MTX treatment compared to PBO+MTX in this population.

***Inhibition of structural joint damage progression***

The primary endpoint of the inhibition of joint damage progression at Week 52 was met. A statistically significant difference between the CZP+MTX group and the PBO+MTX group was demonstrated for the mTSS change from Baseline ($p<0.001$). Similar statistically significant effects were also demonstrated for the mTSS subcomponents ($p<0.001$ for the bone erosion score and $p=0.006$ for the joint space narrowing score), respectively. Sensitivity and other analyses also showed less progression in the mTSS, bone erosion, and joint space narrowing scores indicating a robust response and thus supported the outcome of the primary variable analysis. Results based on the PPS were similar to those using the FAS, indicating that the inclusion of subjects with protocol deviations did not bias the results.

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Analyses of nonprogression in joint damage, yearly progression, and rapid radiographic progression at Week 52 supported the results obtained for the primary analysis in showing the superiority of CZP+MTX treatment as compared to PBO+MTX. The results of the primary efficacy analysis, confirmed by the results of the nonprogression, yearly progression, and rapid radiographic progression analysis, demonstrate an effective and clinically relevant inhibition of structural joint damage progression in subjects with early RA and poor prognostic factors.

The results of the secondary variable analysis (mTSS) and subcomponents (bone erosion, and joint space narrowing score) at Week 24 confirm the results obtained for the primary variable analysis at Week 52. Statistical significance was demonstrated for the mTSS and the respective subcomponents at Week 24. The results of the nonprogression, and rapid radiographic progression analysis at Week 24 also support the robust outcome of the primary analysis.

***Treatment of signs and symptoms***

Clinical response assessed by DAS28(ESR) and ACR/EULAR remission criteria at Week 24 and Week 52 was evaluated as secondary endpoints. The percentage of subjects meeting DAS28(ESR) remission criteria was approximately 20% higher in the CZP+MTX group as compared to the PBO+MTX group. This difference between the treatment groups was maintained at Week 52 and statistical significance was achieved at both timepoints. At Week 24, the percentage of subjects meeting SDAI-based and Boolean-based ACR/EULAR remission criteria was approximately 15% to 20% higher in the CZP+MTX group as compared to the PBO+MTX group. This difference between the treatment groups was maintained at Week 52. Statistical significance was achieved for remission criteria at both timepoints.

Other analyses evaluating efficacy over time indicated both early improvements with CZP+MTX treatment and maintenance of efficacy over time.

- The DAS28(ESR) remission rate was higher in the CZP+MTX group as compared to the PBO+MTX group at all visits and as soon as Week 1, indicating a rapid onset of action in the CZP+MTX group. At Week 20, a plateau phase with stable DAS28(ESR) remission rates was reached in both treatment groups and differences between the treatment groups were maintained over time through Week 52.
- The SDAI-based and Boolean-based ACR/EULAR remission rates confirm the outcome obtained for the DAS28(ESR) remission rate. Both remission rates were higher in the CZP+MTX group as compared to the PBO+MTX group at all visits and the difference between the treatment groups was maintained through Week 52.

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- All changes from Baseline in the DAS28(ESR) score and the SDAI were greater in the CZP+MTX group as compared to the PBO+MTX group at all visits and as soon as Week 1. A plateau phase was reached at Week 20 for the DAS28(ESR) score and at approximately Week 16 for the SDAI and values remained stable until Week 52. Differences in the changes from Baseline between the treatment groups were maintained over time.
- All ACR responder rates were higher in the CZP+MTX group compared to the PBO+MTX group at all timepoints and as soon as Week 1; indicating a rapid onset of action in the CZP+MTX group. In both groups, the maximal effect was achieved at Week 12 (ACR20), Week 16 (ACR50) and Week 20 (ACR70) and the responder rates were maintained up to Week 52. A more pronounced effect of CZP+MTX treatment was seen with increasing response categories (ACR20: 10% to 15%, ACR50 15% to 20%, and ACR70 approximately 20%).
- Changes from Baseline in disease activity markers are generally more pronounced in the CZP+MTX group as compared to the PBO+MTX group for all markers except for MMP-3.

Taken together, these observations further support the results of the primary analysis, indicating that CZP treatment is clinically effective in the inhibition of structural damage progression and in reducing signs and symptoms in MTX-naïve subjects with early RA and poor prognostic factors.

***Subject reported outcomes***

The percentage of subjects who reported a negative impact of RA on labor productivity was lower in the CZP+MTX group as compared to the PBO+MTX group at Week 24 and Week 52 indicating an improvement of labor productivity in the CZP+MTX group.

***Subgroup analyses of primary and most key secondary endpoints***

Subgroup analyses were performed to evaluate the impact of demographic and other Baseline characteristics and to compare the efficacy in subpopulations to the general population.

With the exception of the MMP-3 <50ng/mL subgroup, all subgroups analyzed showed a consistently lower change from Baseline in mTSS with CZP+MTX treatment compared to PBO+MTX treatment, even for the subgroups with a positive interaction (Baseline CRP, Baseline mTSS, Baseline use of steroids, and Baseline SDAI; no interaction was observed with other subgroups). For subpopulations stratified by Baseline disease activity (eg, CRP, DAS28[ESR]), a clear trend towards a more pronounced difference between CZP+MTX vs PBO+MTX was seen with increasing disease severity. No effect was seen on the inhibition of structural damage progression regardless of the average MTX dose.

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Subgroup analyses of other key secondary variables (DAS28[ESR] remission, ACR/EULAR remission, mTSS nonprogression) were consistent with the results obtained for the subgroup analysis of the primary variable.

**Efficacy results: Post-Treatment Period and Total Period**

***Inhibition of structural joint damage progression***

In the Total Period (POST) population (ie, in subjects who completed the Double-Blind Period), mean changes from DB-BL for the mTSS at Week 104 (inhibition of joint damage progression after 1 year with MTX monotherapy) were low in subjects who received PBO+MTX treatment during the Double-Blind Period and even lower in subjects receiving CZP+MTX treatment. These effects were consistent for the mTSS, the bone erosion score, and the joint space narrowing score. Analyses of nonprogression in joint damage at Week 104 supported the results obtained for the mTSS in showing the advantage of CZP+MTX treatment as compared to MTX monotherapy.

In the Total Period (ALL) population, mean changes from DB-BL for the mTSS at Week 104 were lower in the CZP+MTX group as compared to the PBO+MTX group; this difference was statistically significant (p=0.001). Similar trends with lower changes from Baseline in the CZP+MTX group were observed for the mTSS subcomponents. Analyses of nonprogression and sustained nonprogression in joint damage at Week 104 supported the results obtained for the mTSS and showed the advantage of CZP+MTX treatment with higher nonprogression rates as compared to MTX monotherapy.

The results of the change from Baseline in mTSS supported by the results of the nonprogression and sustained nonprogression, demonstrate that a clinically relevant inhibition of structural joint damage progression in subjects with early RA and poor prognostic factors during the Double-Blind Period is maintained for up to 1 year after discontinuation of CZP administration. Inhibition of joint damage progression was maintained at a higher degree in subjects who received CZP+MTX treatment as compared to subjects who received PBO+MTX treatment during the Double-Blind Period.

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***Treatment of signs and symptoms***

The results of study variables evaluating signs and symptoms demonstrated a continued benefit in subjects with both treatments; however, some loss of treatment effects after stopping CZP administration was seen for the CZP+MTX group and not for the PBO+MTX group as expected since MTX monotherapy was continued for both treatment groups.

- The percentage of subjects in the Total Period (POST) population meeting remission criteria (DAS28[ESR], ACR/EULAR [SDAI-based and Boolean-based], and HAQ-DI remission rates) decreased in the CZP+MTX to MTX group from Week 52 through around Week 68 and remained stable thereafter; the percentage of subjects in remission in the PBO+MTX to MTX group remained relatively stable from Week 52 onwards. Similar observations were seen for ACR20, ACR50, and ACR70 response rates. Changes from Baseline in DAS28(ESR), SDAI, and disease activity markers at Week 104 indicated that some treatment benefit was maintained for up to 1 year after discontinuation of CZP administration.
- The percentage of subjects in the Total Period (ALL) population meeting remission criteria at Week 52 was approximately 20% to 25% higher in in the CZP+MTX group as compared to the PBO+MTX group for the DAS28(ESR) and ACR/EULAR (SDAI-based and Boolean-based) remission rates. After Week 52, the percentage of subjects with remission in the PBO+MTX group remained almost stable until Week 104; the percentages in the CZP+MTX group decreased from Week 52 to Week 68 and remained on a relatively stable level thereafter until Week 104. The advantage of the CZP+MTX group compared to the PBO+MTX group was maintained throughout the Post-Treatment Period until Week 104. The same trend was observed for the DAS28(ESR) sustained remission.

***Subgroup analyses***

All subgroups analyzed showed a consistently lower change from Baseline in mTSS at Week 104 with CZP+MTX treatment compared to PBO+MTX treatment. Similar results were observed in subgroup analyses of DAS28(ESR) remission, DAS28(ESR) sustained remission, mTSS nonprogression, and mTSS sustained nonprogression.

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**Efficacy results: Rescue-Treatment Period**

After Week 0, changes from RESC-BL led to lower DAS28(ESR) and SDAI scores over time, thus indicating lower disease activity and early clinical response to CZP treatment from Week 4 onwards.

All subjects including Re-treated subjects (ie, subjects who received CZP+MTX in the Double-Blind Period and who switched to rescue treatment during the Post-Treatment Period) demonstrated a rapid clinical response upon CZP re-treatment.

***Overall efficacy conclusions***

Certolizumab pegol demonstrated robust efficacy for the inhibition of joint damage progression (mTSS) and the improvement of signs and symptoms (DAS28[ESR] and ACR/EULAR remission, ACR20, ACR50, and ACR70 remission, and disease activity markers) at Week 24 and Week 52 in MTX-naïve subjects with early RA and poor prognostic factors. There were clinically relevant differences between the CZP+MTX group and the PBO+MTX group. There is a clear benefit of the co-administration of CZP with MTX in MTX-naïve subjects with early RA and poor prognostic factors as first-line therapy.

The robust efficacy which CZP demonstrated for the inhibition of joint damage progression (mTSS) and the improvement of signs and symptoms during the Double-Blind Period was maintained over time until the end of the study at Week 104.

The follow-on analyses showed that the efficacy of CZP+MTX treatment is maintained for up to 1 year after stopping CZP in subjects who were in LDA after the initial 1-year Double-Blind Period. After 1 year of follow-on MTX monotherapy treatment, inhibition of joint damage progression was maintained at a higher degree in subjects who received CZP+MTX treatment as compared to subjects who received PBO+MTX treatment during the Double-Blind Period.

Similarly, continued clinical benefit in signs and symptoms was observed after stopping CZP treatment. Some loss of response in the CZP+MTX to MTX group reflects the need of some subjects to remain on CZP treatment to maintain clinical benefit.

Changes from RESC-BL led to lower DAS28(ESR) and SDAI scores over time, thus indicating the efficacy of CZP treatment in subjects who were not in LDA at RESC-BL including instances of flare. A rapid clinical response was seen in case of CZP re treatment.

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**Pharmacokinetics/pharmacodynamics results:**

- Overall, highest geometric mean CZP plasma concentrations were reached after the initial CZP loading dose phase; plasma levels declined thereafter, but remained on a stable level during the Double-Blind Period.
- Overall, the percentage of subjects who tested positive for anti-CZP antibodies at least once was higher during the Total Period including the Follow-Up Visit as compared to the Double-Blind Period excluding the Follow-Up Visit. The majority of anti-CZP antibody positive subjects were tested positive only at the Follow-up Visit or Week 60 (10 weeks after the final CZP administration) for the Total Period.
- Subjects who were positive for anti-CZP antibodies had lower geometric mean plasma concentrations at all visits from Week 6 (Double-Blind Period) or Week 4 (Total Period) onwards as compared to subjects who were negative for anti-CZP antibodies, as anticipated.
- During the Rescue Treatment Period, plasma concentrations in subjects in the PBO+MTX (to MTX) to CZP+MTX group and the CZP+MTX to MTX to CZP+MTX group (Re-treated subjects) were similar and generally lower as compared to CZP plasma concentrations in subjects who received CZP+MTX continuously during the course of the study (CZP+MTX to CZP+MTX group).
- During the Rescue Treatment Period, the percentage of subjects who were anti-CZP antibody positive was higher in re-treated subjects (CZP+MTX to MTX to CZP+MTX group) as compared to subjects in the PBO+MTX to (MTX) to CZP+MTX group and subjects in the CZP+MTX to CZP+MTX group.

**Safety results (Double-Blind Period):**

***Exposure***

The study population was representative of the targeted patient population (ie, MTX-naïve subjects with moderate to severe RA, early onset of disease, and poor prognosis factors). A total of 159 subjects were exposed to the study medication and received CZP 200mg Q2W in combination with MTX and 157 subjects received placebo in combination with MTX. The mean duration of exposure was 308.6 days in the CZP+MTX group and 265.1 days in the PBO+MTX group, with the shorter duration in the PBO+MTX group reflecting the time at which subjects switched to rescue treatment.

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***Adverse events***

Incidences of treatment-emergent adverse events (TEAEs) during the Double-Blind Period were generally similar in both treatment groups. Overall, 153 subjects (96.2%) in the CZP+MTX group and 148 subjects (94.3%) in the PBO+MTX group reported at least 1 TEAE during the Double-Blind Period. Treatment-emergent AEs were most commonly reported in the System Organ Class (SOC) of Infections and infestations (CZP+MTX group: 61.0%, PBO+MTX group: 55.4%), Gastrointestinal disorders (CZP+MTX group: 50.3%; PBO+MTX group: 52.9%), Skin and subcutaneous tissue disorders (CZP+MTX group: 33.3%; PBO+MTX group: 25.5%), Hepatobiliary disorders (CZP+MTX group: 37.1%; PBO+MTX group: 36.3%), Investigations (CZP+MTX group: 19.5%; PBO+MTX group: 14.0%), and Respiratory, thoracic and mediastinal disorders (CZP+MTX group: 16.4%; PBO+MTX group: 16.6%). Percentages were comparable in all of these most commonly reported SOCs with the exception of the Infection and infestations, Investigations, and the Skin and subcutaneous tissue disorder SOCs. Incidences of the most common TEAEs by preferred term (PT) were generally similar in both treatment groups except for nasopharyngitis (CZP+MTX group: 35.8%; PBO+MTX group: 29.3%) and nausea (CZP+MTX group: 22.0%; PBO+MTX group: 15.9%).

The incidence of TEAEs by time of occurrence (intervals of exposure) were generally stable or decreased with longer exposure intervals and particularly in the SOCs Gastrointestinal disorders, Infections and infestations, Hepatobiliary disorders, and General disorders and administration site conditions. No differences between treatment groups at any interval of exposure were observed.

No differences in the pattern of TEAEs in anti-CZP antibody-positive subjects as compared to the anti-CZP negative subjects were observed; however, these findings need to be interpreted with caution given the small number of subjects who were positive for anti-CZP antibodies and the transient nature of anti-CZP antibody positivity in 8 subjects.

In both treatment groups, more subjects reported TEAEs while receiving an MTX dose in the highest dose range (>12 to 16mg/week) as compared to the lower MTX dose ranges (0 to 8mg/week and >8 to 12mg/week) for the following SOCs: Gastrointestinal disorders, Hepatobiliary disorders, Infections and infestations (CZP+MTX group only), and Respiratory, thoracic and mediastinal disorders. No obvious trend was observed for any other SOC in any of the treatment groups. Results of analyses by MTX dose at AE onset should be interpreted with caution due to the variability in the MTX dose range, the short duration of exposure to MTX 0 to 8mg/week per study design (4 weeks), and since not all subjects received the highest MTX dose range (>12 to 16mg/week).

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The majority of the TEAEs were mild to moderate in intensity. Only a few subjects had severe TEAEs (CZP+MTX group: 4 subjects [2.5%]; PBO+MTX group: 8 subjects [5.1%].

The majority of subjects in both treatment groups reported TEAEs that were considered to be related to the study drug in the opinion of the Investigator (CZP+MTX: 71.1%, PBO+MTX: 66.9%). Incidences of drug-related TEAEs were comparable in both treatment groups except for the SOC Investigations (CZP+MTX group: 12.6%, PBO+MTX group: 7.6%) and the PTs nasopharyngitis (CZP+MTX group: 22.6%, PBO+MTX group: 16.6%) and cell markers increased (CZP+MTX group: 5.0%, PBO+MTX group: no subjects).

Overall, 13 subjects (8.2%) in the CZP+MTX group and 14 subjects (8.9%) in the PBO+MTX group reported serious adverse events (SAEs). Incidences of SAEs were comparable in both treatment groups. As expected, Infections and infestations was the most frequently reported SOC with 5 subjects (3.1%) in the CZP+MTX group and 7 subjects (4.5%) in the PBO+MTX group. The only SAEs reported in more than 1 subject per treatment group were pneumocystis jiroveci pneumonia (CZP+MTX group: 3 subjects [1.9%], PBO+MTX group: 2 subjects [1.3%]), pneumonia bacterial (CZP+MTX group: 1 subject [0.6%], PBO+MTX group: 2 subject [1.3%]), and interstitial lung disease (CZP+MTX group: 2 subjects [1.3%], PBO+MTX group: 1 subject [0.6%]).

Incidences of TEAEs leading to study drug discontinuation were low and similar in both treatment groups (CZP+MTX group: 5.7%; PBO+MTX group: 4.5%).The most frequent TEAEs leading to discontinuation of the study were reported in the Respiratory, thoracic and mediastinal disorders SOC (CZP+MTX group: [3.1%], PBO+MTX group: [1.3%]).

No deaths or pregnancies occurred during the reporting period of the study. No TEAEs resulting in an infection induced by a pathogen in a biological product or the study drug was reported.

***Adverse events of interest***

Anti-tumor necrosis factor alpha (anti-TNFα) medications are known to carry an increased risk of infections as well as MTX. The overall incidence of infections by SOC was slightly higher in the CZP+MTX group (61.0%) as compared to the PBO+MTX group (55.4%); however, incidence rates were higher in the PBO+MTX group compared to the CZP+MTX group (123.63 vs 114.64, respectively), indicating that there was no increase in the risk of infections with CZP treatment. The majority of TEAEs were related to the respiratory tract: nasopharyngitis (CZP+MTX group: 35.8%; PBO+MTX group: 29.3%), pharyngitis (CZP+MTX group: 10.1%; PBO+MTX group: 7.6%), bronchitis (CZP+MTX group: 6.3%, PBO+MTX group: 5.7%), upper respiratory tract infection (CZP+MTX group: 5.0%; PBO+MTX group: 6.4%), and pneumonia

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bacterial (CZP+MTX group: 2.5%; PBO+MTX group: 1.3%).
The overall incidence of serious infections was comparable in both treatment groups (CZP+MTX group: 5 subjects [3.1%]; PBO+MTX group: 7 subjects [4.5%]), with IRs of 3.70 and 6.08 per 100 patient-years, respectively. The most frequent serious infections were related to the respiratory tract: pneumocystis jiroveci pneumonia (CZP+MTX group: 1.9%; PBO+MTX group: 1.3%) and pneumonia bacterial (CZP+MTX group: 0.6%; PBO+MTX group: 1.3%). All other serious infections were reported in only 1 subject (0.6%) per treatment group.

No other SAEs of opportunistic infections besides pneumocystis jiroveci pneumonia and fungal meningitis were reported. Serious pneumocystis jiroveci pneumonia infections were reported at an MTX dose at onset of >12 to 16mg/week in the CZP+MTX group and at MTX doses of 10 and 16mg/week in the PBO+MTX group. In addition, 2 nonserious opportunistic infections were reported in the PBO+MTX group (pneumocystis jiroveci pneumonia [at an MTX dose of 12mg/week] and oesophageal candidiasis [at an MTX dose of 16mg/week at AE onset] in 1 subject each).

No cases of tuberculosis were reported during the Double-Blind Period.
Pneumonia (except interstitial pneumonia) was reported in 7 subjects (4.4%) in the CZP+MTX group and in 8 subjects (5.1%) in the PBO+MTX group. The most frequently reported TEAEs were pneumonia bacterial (CZP+MTX group: 4 subjects [2.5%], PBO+MTX group: 2 subjects [1.3%] and pneumocystis jiroveci pneumonia (3 subjects [1.9%] in both treatment groups).

One subject in the CZP+MTX group had a positive Hepatitis B DNA assay at 57 days after the start of study medication.

One malignancy of cervix carcinoma was reported in 1 subject (0.6%) in the CZP+MTX group.

There were no events of special interest, in particular no cardiac disorders, vascular disorders, or autoimmune disorders of ≥2% by PT. No events of congestive heart failure, demyelinating disorders, lupus or lupus-like syndrome, serious bleeding events, or serious skin reactions including psoriasis were reported.

The most frequent neurological disorders were headache (4.4% in the CZP+MTX group and 3.2% in the PBO+MTX group) and dizziness (2.5% in the CZP+MTX group and 0.6% in the PBO+MTX group), respectively. Two SAEs were reported: 1 TEAE of migraine in the CZP+MTX group and 1 TEAE of altered state of consciousness in the PBO+MTX group (0.6% each).

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The percentage of subjects with injection site reactions by PT was comparable in both treatment groups with no events reported in more than 2 subjects each. Events included administration site reactions, injection site reactions, injection site induration, and injection site haemorrhage.

Overall, a higher percentage of subjects in the CZP+MTX group (3.1%) reported a TEAE of interstitial lung disease as compared to the PBO+MTX group (0.6%).

The incidence of hepatic disorders was similar in both treatment groups (CZP+MTX group: 42.8%; PBO+MTX group: 44.6%). No subject fulfilled the Hy's law criteria.

Because RA0096 was the first study combining CZP with high doses of MTX, and because the population was MTX-naïve, additional analyses by MTX dose were performed. Due to the variability in the MTX dose received, that not all subjects received the highest MTX dose range (MTX >12 to 16mg/week), and that the duration of exposure to MTX 0 to 8mg/week was short by study design (4 weeks), the results should be interpreted with caution. However, it appears that there is more risk of hepatic disorders in the highest MTX group (>12 to 16mg/week) as compared to the lower MTX dose range groups. It also appears that there is more risk of an infection, serious infections, and pneumonia (except interstitial pneumonia), hematopoietic cytopenias, nausea, vomiting and decreased appetite, and stomatitis in the higher MTX dose range group as compared to the lower MTX dose range groups, even though fewer events were reported in some categories. The number of subjects with interstitial lung disease is too small to draw conclusions. Percentages of subjects reporting any AEs of interest at any MTX dose were comparable in both treatment groups.

No TEAEs of aplasia or pancytopenia were reported during the Double-Blind Period. Percentages of subjects with TEAEs of granulocytopenia, leukopenia, lymphopenia, white blood cell count decreased, and lymphocyte count decreased were similar in both treatment groups.

***Clinical laboratory evaluations and vital signs***

Mean CRP values were elevated to approximately 2.5 to 3-fold the upper limit of normal (ULN) values at Screening and Baseline, as expected in this population as a sign of chronic inflammation, and decreased in both treatment groups thereafter. The improvement of mean CRP values occurred more rapidly in the CZP+MTX group starting as early as in Week 1 (0.21mg/dL) and values below ULN were maintained until Week 52.

Mean hematology values at Screening and Baseline were generally similar in both treatment groups. The mean white blood cell (WBC) count decreased from Week 1 onwards in both treatment groups and there was a tendency towards a slight decrease over time for mean red blood cell (RBC) counts and platelet counts in both treatment groups; however, mean

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hematology values (WBC, RBC, hemoglobin, hematocrit, and platelets) remained within the normal ranges for all parameters and visits.

Mean biochemistry values at Screening and Baseline were generally similar in both treatment groups. Mean and median changes over time were small. Mean biochemistry values remained within the normal range at all times with the exception of creatine kinase (CK) values in the CZP+MTX group at Week 36. The median CK value at this visit was within the normal range.

No new safety-related adverse changes in hematology and biochemistry values, urinalysis values, vital signs, or body weight were observed.

**Safety results: Post-Treatment Period and Total Period**

***Exposure***

Subjects were not exposed to CZP during the Post-Treatment Period.

***Adverse events***

During the Post-Treatment Period (Week 52 to 104), approximately 3 quarters of subjects in the All Subjects group reported at least 1 AE. The majority of AEs were mild to moderate in intensity and not considered to be related to study drug. Overall, 8 subjects (4.5%) reported SAEs. Neoplasms benign, malignant and unspecified (incl cysts and polyps) and Renal and urinary disorders were the most frequently reported SOCs with 3 subjects (1.7%) and 2 subjects (1.1%) reporting SAEs, respectively. One SAE of cervix carcinoma with an AE onset ≤70 days after the final study drug dose was the only AE leading to study discontinuation. A few SAEs were reported >70 days after the final study drug dose: coronary artery stenosis, benign anorectal neoplasm, nephrolithiasis, renal artery stenosis, pulmonary fibrosis, Meniere's disease, pneumonia chlamydial, glomus tumour, and subarachnoid haemorrhage.

During the Total Period (Week 0 to 104), the percentage of subjects reporting at least 1 AE was similar in the CZP+MTX group (96.9%) and the PBO+MTX group (95.5%), respectively. The incidence of SAEs (10.7% vs 11.5%), severe AEs (4.4% vs 5.7%), AEs leading to discontinuation (6.3% vs 4.5%), and drug-related AEs (73.0% vs 67.5%) was also comparable in the CZP+MTX group and the PBO+MTX group, respectively. The majority of the AEs were mild to moderate in intensity.

One death due to cervix carcinoma was reported after the Safety Follow-up Visit more than 1 year after the AE onset.

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***Adverse events of interest***

During the Post-Treatment Period (Week 52 to 104), 41.9% of the subjects reported at least 1 infection. No severe infections and no infections leading to withdrawal of the study drug were reported. A serious infection of pneumonia chlamydial was reported in 1 subject in the PBO+MTX to MTX group with an onset >70 days after the final study drug dose. The incidence of pneumonia (except interstitial pneumonia) was 1.7%; 1 AE of pneumonia (except interstitial pneumonia) in the CZP+MTX to MTX group and 2 AEs in the PBO+MTX to MTX group were reported with an onset >70 days after the final study drug dose. No cases of viral hepatitis, tuberculosis, and pneumocystis jiroveci pneumonia were reported. One SAE of cervix carcinoma was reported in the CZP+MTX to MTX group with an AE onset ≤70 days after the final study drug dose and 1 AE of subarachnoid haemorrhage was reported in the PBO+MTX to MTX group with an AE onset >70 days after the final study drug dose. The overall incidence of hepatic disorders (Standard MedDRA Query) was 11.1% in the CZP+MTX to MTX group and 12.7% in the PBO+MTX to MTX group. Three of these AEs of hepatic disorders in both groups were reported with an onset >70 days after the final study drug dose. Two subjects in the CZP+MTX to MTX group reported AEs of interstitial lung disease with an onset >70 days after the final study drug dose.

There were few events of cardiac disorders, vascular disorders, or autoimmune disorders. No events of congestive heart failure, demyelinating disorders, lupus or lupus-like syndrome, and serious skin reactions including psoriasis were reported. The most frequent neurological disorder was headache.

***Clinical laboratory evaluations and vital signs***

There was no obvious shift pattern or trend for hematology, biochemistry, and urinalysis laboratory parameters or vital signs.

**Safety results: Rescue Treatment Period**

***Exposure***

A total of 151 subjects received rescue treatment with CZP+MTX up to Week 104.

***Adverse events***

More than 90% of subjects receiving rescue treatment reported at least 1 TEAE during the Rescue Treatment Period. The majority of TEAEs were mild to moderate in intensity. Few subjects (4.6%) had severe TEAEs and approximately two thirds of TEAEs were considered to be related to study drug. Eighteen subjects (11.9%) reported SAEs with Infections and

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infestations (4.0%) and Neoplasms benign, malignant and unspecified (incl cysts and polyps) (2.6%) being the most frequently reported SOCs. Eight subjects (5.3%) discontinued rescue treatment due to TEAEs with Neoplasms benign, malignant and unspecified (incl cysts and polyps) (2.0%) and Musculoskeletal and connective tissue disorders (1.3%) being the most frequently reported SOCs.

More than 90% of re treated subjects reported at least 1 TEAE during the Rescue Treatment Period. The majority of TEAEs were mild to moderate in intensity and approximately two thirds of TEAEs were considered to be related to study drug. There were no SAEs, severe TEAEs, or TEAEs leading to study drug discontinuation.

***Adverse events of interest***

Overall, 67.5% of subjects receiving rescue treatment reported TEAEs in the Infections and infestations SOC with the majority being related to the respiratory tract. Six subjects (4.0%) reported AEs of serious infections: lung abscess, peritonsillar abscess, pneumocystis jiroveci pneumonia, pyelonephritis acute, sepsis, and tuberculous pleurisy (1 subject each). No other SAEs of opportunistic infections were reported. One SAE of subarachnoid haemorrhage was reported. Breast cancer, colon cancer, lymphoproliferative disorder, and thyroid cancer were reported in 1 subject each.

Overall, 57.1% of re-treated subjects reported TEAEs in the Infections and infestations SOC with the majority being related to the respiratory tract. There were no serious or opportunistic infections and no malignancies. One mild TEAE of pustular psoriasis was reported.

No cases of viral hepatitis, events of congestive heart failure, demyelinating disorders, lupus or lupus-like syndrome, interstitial lung disease, and no SAEs in the Hepatobiliary disorders SOC were reported during the Rescue Treatment Period. There were few events of cardiac disorders, vascular disorders, and injection site reactions.

***Clinical laboratory evaluations and vital signs***

There was no obvious shift pattern or trend for hematology, biochemistry, and urinalysis laboratory parameters and vital signs.

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***Overall safety conclusions***

RA0096 is the first study conducted in Japan with an anti-TNF agent in MTX-naïve subjects receiving a high dose of MTX (up to 16mg/week).

No new safety concerns were identified for CZP during the course of the study that have not been previously observed in RA or in other geographic regions.

**Conclusions:**

Overall, with a robust efficacy and an acceptable safety profile, this adequate and well-controlled study confirms the clinical benefit of a 1-year CZP treatment concomitant with MTX as compared to MTX monotherapy. In addition, this benefit of CZP treatment was maintained up to another year even after discontinuation of CZP treatment. These results indicate the usefulness of early intervention with CZP for MTX-naïve subjects with early RA who have poor prognostic factors.

**Report date:** 14 Aug 2015