RA0028, 2009-013758-33

CLINICAL STUDY REPORT SYNOPSIS

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

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Sponsor:

UCB Pharma S.A.

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Official study title:

Multicenter study with a 16-week double-blind, placebo-controlled (during the initial 2 weeks) randomized period, followed by a 24-week open-label extension to assess magnetic resonance image-verified early response to certolizumab pegol in subjects with active rheumatoid arthritis

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Title of study: Multicenter study with a 16-week double-blind, placebo-controlled (during the initial 2 weeks) randomized period, followed by a 24-week open-label extension to assess magnetic resonance image-verified early response to certolizumab pegol in subjects with active rheumatoid arthritis

Investigators: This was a multicenter study with a total of 10 investigators for the Double-Blind (DB) Period and 9 Investigators for the Open-Label Extension (OLE) Period.

Study sites: This was a multicenter study with subjects enrolling at 10 sites during the DB Period and 9 sites during the OLE Period.

Publications (references): None

Studied period: Approximately 2 years and 5 months **First subject enrolled:** 06 Dec 2010 **Last subject completed:** 02 May 2013	**Phase of development:** Phase 3b

Objectives: The primary objective of this study was to identify the first time point the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Rheumatoid Arthritis-Magnetic Resonance Imaging Scoring System (RAMRIS) score for the activity of synovitis was statistically significantly reduced compared to Baseline in response to certolizumab pegol (CZP) therapy.

The secondary objectives of this study were:

- To identify the efficacy of CZP on synovitis in dynamic magnetic resonance imaging (MRI) parameters of initial rate of enhancement (IRE), maximum enhancement (ME), and number of voxels (Nvox) with Plateau and Washout pattern
- Correlation of reduction of synovitis as measured by MRI at Week 16 with:
    - European League Against Rheumatism (EULAR) response
    - American College of Rheumatology 20%, 50%, and 70% response criteria (ACR20, ACR50, and ACR70)
    - Disease Activity Score-28 joint count (DAS28) response
    - X-ray changes in bone mineral density

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- Change from Baseline for the OMERACT RAMRIS synovitis scores at Week 1 and Week 2 were analyzed and compared between treatment groups (CZP versus placebo [PBO])
- Assessment of clinical response during DB and OLE Periods

The exploratory objectives of this study were to examine the efficacy of CZP with regards to bone edema (osteitis) and bone erosion and to further characterize the process of bone erosion.

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

Methodology: This was a Phase 3b multicenter, randomized, double-blind, PBO-controlled study. Eligible subjects were randomized (2:1 ratio) at Baseline to receive either:

- CZP 400mg (2 injections of 200mg) at Weeks 0, 2, and 4, followed by CZP 200mg and PBO at Week 6 and CZP 200mg at Weeks 8, 10, 12, 14, and 16, or
- PBO at Day 0 (2 injections) and then CZP 400mg at Weeks 2, 4, and 6 followed by CZP 200mg at Weeks 8, 10, 12, 14, and 16.

After Week 16, subjects were given the opportunity to enter the OLE Period and receive CZP 200mg every 2 weeks (Q2W) for 6 months.

The contrast enhanced MRI of one hand and wrist was taken for all enrolled subjects at Baseline (Day 0), Weeks 1, 2, 4, 8, and 16 before the injection of study medication. All the MRIs were analyzed by an experienced reader who was blinded to subject identity, study treatment, and time point. The digital x-ray radiogrammetries (DXRs) were performed at Baseline, Week 16, and at the Withdrawal Visit (only if subject withdrew before Week 16). All DXRs were read centrally.

Study medication was administered by a hospital study nurse during the DB Period. During the OLE Period, home-based self-administration was allowed for the subjects having appropriate storage conditions and those who were able to self-administer.

All subjects not continuing directly on to commercial CZP completed a Safety Follow-Up (SFU) assessment via telephone contact 10 weeks after the last dose of study medication.

Number of subjects (planned and analyzed): A sample size of 36 subjects was planned to be randomized (24 in the CZP group and 12 in the PBO+CZP group). A total of 45 subjects were enrolled in the study and 41 subjects were randomized into the DB Period (28 subjects in the CZP group and 13 subjects in the PBO+CZP).

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Diagnosis and main criteria for inclusion: Subjects had to be at least 18 years of age, have a diagnosis of adult–onset rheumatoid arthritis (RA) of at least 3 months duration, but no longer than 15 years as defined by the 1987 ACR classification criteria, and have active RA disease as defined by the following:

- ≥1 tender joint and ≥1 swollen joint (at Baseline) in the joint area imaged, which was 1 wrist and hand (metacarpophalangeals [MCP] 2 to 5); and
- ≥3 tender joints (28 joint count) at Baseline; and
- ≥3 swollen joints (28 joint count) at Baseline

Subjects must have been on disease-modifying antirheumatic drug (DMARD) therapy for at least 12 weeks, and the dose and route of administration had to be stable for at least 8 weeks prior to Baseline.

Test product, doses and mode of administration, batch numbers: Certolizumab pegol was supplied as a sterile solution in a 1mL single-use glass prefilled syringe (PFS). Each syringe contained 200mg/mL of CZP per mL in sodium acetate buffer and sodium chloride.

The following CZP bulk batch numbers were used in the study:

[redacted]

The following CZP investigational medicinal product (IMP) batch product numbers were used in the study:

[redacted]

Duration of treatment: The study duration per subject was approximately 14 months including a 1-month Screening Period, a 4-month DB Period (including an initial 2-week PBO-controlled period), a 6-month OLE Period, and a 2.5-month SFU Period with a SFU phone contact performed 10 weeks after the last dose of study drug administration.

Reference therapy, dose(s) and mode of administration, batch number(s): Placebo (0.9% saline) was supplied as a sterile solution in a 1mL for single-use glass PFS.

The following PBO bulk batch numbers were used in the study:

[redacted]

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Name of active ingredient: Certolizumab pegol	**Page:** Not applicable	

The following PBO IMP batch product numbers were used in the study:

[redacted]

Criteria for evaluation:

Efficacy: The primary efficacy variable was the change from Baseline (Day 0) in OMERACT RAMRIS synovitis score measured with MRI (gadolinium-containing contrast agent) of 1 hand and wrist at Weeks 1, 2, 4, 8, and 16.

The secondary efficacy variables were:

- Dynamic MRI parameters of IRE, ME, and Nvox at Day 0 and Weeks 1, 2, 4, 8, and 16 during the DB Period.
- EULAR response at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 during the DB Period, then every 8 weeks during the OLE Period, and at the Completion/Withdrawal Visit.
- ACR20, ACR50, and ACR70 at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 during the DB Period, then every 8 weeks during the OLE Period, and at the Completion/Withdrawal Visit.
- Change from Baseline in DAS28(C-reactive protein [CRP]) at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 during the DB Period, then every 8 weeks during the OLE Period, and at the Completion/Withdrawal Visit.
- DAS28(CRP) remission status at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 during the DB Period, then every 8 weeks during the OLE Period, and at the Completion/Withdrawal Visit.
- Change from Baseline in bone mineral density (g/cm^2) as measured by DXR at Week 16.
- Change from Baseline in ACR components: tender joints and swollen joints, and Health Assessment Questionnaire–Disability Index (HAQ-DI) at Weeks 1, 2, 4, 6, 8, 10, 12, 14, and 16 during the DB Period, then every 8 weeks during the OLE Period, and at the Completion/Withdrawal Visit.
- Ratio to Baseline for CRP at Weeks 2, 4, 6, 8, 10, 12, 14, and 16 during the DB Period, then every 8 weeks during the OLE Period, and at the Completion/Withdrawal Visit.

The exploratory variables were:

- Change from Baseline in the MRI bone edema (osteitis) scores at Weeks 1, 2, 4, 8, and 16.
- Change from Baseline in the MRI bone erosion scores at Weeks 1, 2, 4, 8, and 16.

Name of company: UCB Pharma	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
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Safety: Safety variables assessed were adverse events (AEs), vital signs, and measurements of laboratory parameters.

Statistical methods: Summary statistics consisted of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation (SD), minimum, and maximum) were tabulated. All statistical tests were carried out as 2-tailed at the 5% level of significance, unless otherwise stated.

The primary efficacy variable was the change from Baseline (Day 0) in the OMERACT RAMRIS synovitis score (hereafter referred to as synovitis score) measured with gadolinium enhanced MRI of one hand and wrist at Weeks 1, 2, 4, 8, and 16.

The Full Analysis Set (FAS) population was used to conduct analysis of the primary efficacy variable.

The permutations test for matched pairs data was used to analyze the primary efficacy variable, defined as change from Baseline for synovitis scores at the following time points: Weeks 1, 2, 4, 8, and 16, within the CZP treatment group. In order to determine the earliest time point at which a significant change occurred, testing was conducted in a sequential fashion beginning with the Week 16 Visit. If the test at Week 16 was statistically significant, then the Week 8 time point was analyzed. If the Week 8 time point was statistically significant, then the Week 4 time point was analyzed. Testing was continued in this manner until a nonsignificant result was obtained. Once a nonsignificant result was obtained, no further testing was allowed. The time point, which corresponded to the last statistically significant result, was declared the earliest time point at which the synovitis scores were significantly different from Baseline.

Missing data were imputed using last observation carried forward (LOCF) for the primary analysis.

As a secondary analysis of the primary efficacy variable, the change from Baseline for the synovitis scores at Week 1 and Week 2 was compared between treatment groups (CZP versus PBO [PBO portion of the PBO+CZP treatment group]) using the Wilcoxon rank-sum test. The Hodges-Lehmann estimate for median difference (for independent samples) and 95% confidence interval (CI) were computed and displayed for Week 1 and Week 2.

The following supportive and sensitivity analyses for the primary efficacy variable were planned:

- If 10% or more of the FAS subjects in the CZP treatment group were excluded from the Per-Protocol Set (PPS) due to important protocol deviations, the analysis of the primary efficacy variable was to be repeated on the PPS; however, this analysis did not need to be performed.

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

- The primary efficacy analysis and the secondary analyses described above were repeated using observed cases (ie, without imputation of missing data).
- In order to assess the monotonicity of the change from Baseline synovitis score used in the primary efficacy analysis, individual profile plots were produced over time for the change from Baseline synovitis score.

The Safety Set (SS) was used for all safety analyses during the DB Period and the OLE Safety Set (OLE-SS) for the OLE Period.

Summary and conclusions:

Subject disposition: A total of 45 subjects were enrolled in the study and 41 subjects were randomized into the DB Period (28 subjects in the CZP group and 13 subjects in the PBO+CZP). Four subjects were not randomized in the study due to reasons of ineligibility (1 subject), withdrawn consent (1 subject) and other reasons (2 subjects). The majority of subjects (24 subjects [85.7%] in the CZP group and 12 subjects [92.3%] in the PBO+CZP group) completed the DB Period. Four subjects (14.3%) in the CZP group discontinued during the DB Period due to AEs (3 subjects [10.7%]) or lack of efficacy (1 subject [3.6%]) and 1 subject (7.7%) in the PBO+CZP group discontinued during the DB Period due to withdrawn consent. Of note, 1 subject discontinued the DB Period due to an AE reported prior to administration of study medication. All subjects who completed the DB Period also completed the OLE Period.

Efficacy results:

RA0028 was conducted in order to identify the first time point at which the OMERACT RAMRIS score for the activity of synovitis was statistically significantly reduced compared with Baseline in response to CZP therapy. In order to establish this initial time point, the primary analysis of the study was the change from Baseline (Day 0) in the synovitis score in the CZP group at Weeks 1, 2, 4, 8, and 16 (LOCF). The secondary analysis (of the primary efficacy variable) was the change from Baseline in synovitis scores at Weeks 1 and 2 between treatment groups (ie, CZP vs PBO [ie, the PBO portion of the PBO+CZP group]; LOCF).

Despite the relatively small sample size (N=27), the difficulties in differentiating through blinded reading 6 time points simultaneously, and the fact that variability in the MRI results was introduced since MRI examinations were conducted across different investigational sites, a statistically significant change from Baseline in the median synovitis score was observed at Week 16 in the CZP group (-1.5 [95% CI: -3.0, 0.0]; p=0.049). Although there was a decrease from Baseline in the median synovitis score at Week 8 (-1.0 [95% CI: -3.0, 1.0]), this decrease was not significant (p=0.206); therefore, further statistical testing of earlier time points was

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precluded. The results of the primary analysis of the primary efficacy variable were confirmed using observed cases (ie, without imputation of missing data). A statistically significant change from Baseline in the median bone edema score (an exploratory efficacy variable) was also observed in the CZP group at Week 16 (-2.5 [95% CI: -5.0, 0.0]; p=0.031), providing additional evidence of the efficacy of CZP in reducing inflammation.

Statistically significant differences between the CZP and PBO+CZP groups in the change from Baseline in the median synovitis score at Week 1 and Week 2 (ie, the secondary analysis of the primary efficacy variable) were not observed, which can possibly be attributed to the relatively small sample size coupled with the short (2-week) PBO-controlled portion of the DB Period.

The same analyses as those performed for the primary efficacy variable were repeated for the dynamic MRI variables (IRE, ME, and Nvox with Plateau and Washout pattern) on proximal interphalangeal (PIP) joints 2 to 5, MCP joints 2 to 5, and PIP+MCP joints 2 to 5 combined. The dynamic MRI variables were included in RA0028 as secondary endpoints to support the primary endpoint and were investigative in nature. The ability to demonstrate the efficacy of CZP based on these variables was affected by the same challenges that impacted the synovitis data. Despite these challenges, the efficacy of CZP in reducing inflammation was demonstrated by the observations of statistically significant changes from Baseline at Week 16 in the CZP group for PIP joints 2 to 5 in median IRE (-0.0093 [95% CI: -0.0190, -0.0015]; p=0.024) and median ME (-0.3315 [95% CI: -0.7755, -0.0170]; p=0.021), and for MCP joints 2 to 5 and PIP+MCP joints 2 to 5 combined in median Nvox with Plateau and Washout pattern (-235.0 [95% CI: -879.0, 23.5]; p=0.025 and -421.5 [95% CI: -1542.5, -47.0]; p=0.015, respectively). Statistically significant changes were not observed at Week 8; therefore, further statistical testing of earlier time points was precluded.

For all RAMRIS parameters (synovitis, bone erosion, and bone edema) as well as dynamic MRI variables (ME, IRE, and Nvox), very good intrareader reliability (intraclass correlation [ICC] >0.90) was observed, indicating that the data from the study were consistently scored by the single reader.

Treatment with CZP generally resulted in notable improvements from Baseline in all clinical outcome measurements (EULAR response; ACR20, ACR50, ACR70 responses; DAS28[CRP] response; and DAS28[CRP] remission) as well as the individual ACR components (swollen joint count [SJC], tender joint count [TJC], HAQ-DI, and CRP) beginning as early as Week 1. The demonstration of the early onset of the efficacy of CZP on clinical outcome measurements and individual ACR components is similar to the results that have been consistently observed in prior CZP studies. During the first 2 weeks of the DB Period (during which time a direct comparison

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Name of finished product: Cimzia	**Volume:** Not applicable	
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between the CZP and PBO treatments can be made), larger numerical improvements from Baseline across the clinical outcome measurements and individual ACR components, except for ACR70, were observed in the CZP group compared with the PBO+CZP group. In the CZP group, increasingly larger improvements from Baseline, relative to Week 2, across each of the clinical outcome measurements and individual ACR components were observed during the remainder of the 16-week DB Period, and these improvements were consistently maintained throughout the 24-week OLE Period. In the PBO+CZP group, once subjects began to receive CZP at Week 2, increasingly larger improvements from Baseline, similar to those seen in the CZP group at earlier time points, were observed during the DB Period, and these improvements were also consistently maintained throughout the OLE Period.

Statistically significant correlations between the change from Baseline to Week 16 in the synovitis score and the clinical outcome measurements (EULAR response, ACR20, ACR50, and ACR70 responses, DAS28[CRP] response, and bone mineral density) at Week 16 were not observed in either the CZP or PBO+CZP group.

Safety results:

Treatment with CZP during the DB and OLE Periods in this study resulted in a safety profile that was consistent with both the expected profile in subjects with RA receiving an antitumor necrosis factor α (TNFα) agent and with the safety profile in previous studies of CZP. No new safety concerns were identified during this study.

- During the DB Period, 26 subjects (65.0%) reported at least 1 treatment-emergent AE (TEAE) while on CZP at any time. The 3 most commonly reported TEAEs by preferred term (PT) were nasopharyngitis, oral herpes, and oropharyngeal pain. During the OLE Period, 25 subjects (69.4%) reported at least 1 TEAE. The 3 most commonly reported TEAEs by PT were nasopharyngitis, urinary tract infection, and cough.
- All TEAEs reported by subjects in the DB and OLE Periods were mild or moderate in intensity, with the exception of a severe serious AE (SAE) of coronary artery disease reported by 1 subject (2.5%) in the CZP group during the DB Period and severe SAEs of tonsillectomy and postprocedural hemorrhage reported by 1 subject (2.8%) during the OLE Period.
- Thirteen subjects (32.5%) reported at least 1 TEAE considered by the Investigator to be related to study medication while on CZP at Any Time during the DB Period. The most commonly reported drug-related TEAEs by PT during the DB Period were injection site pain, injection site discoloration, injection site swelling, and oral herpes. During the OLE Period,

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8 subjects (22.2%) overall reported at least 1 TEAE considered by the Investigator to be related to study medication. No TEAE by PT was reported by more than 1 subject overall during the OLE Period.

- No deaths were reported during the study. Two subjects (5.0%), both in the CZP group, reported treatment-emergent SAEs during the DB Period (sensory loss and coronary artery disease reported by 1 subject each). During the OLE Period, 2 subjects (5.6%) reported treatment-emergent SAEs (bladder cancer and bladder transitional cell carcinoma stage I reported by 1 subject and tonsillectomy and postprocedural hemorrhage reported by 1 subject).
- Two subjects (5.0%) discontinued during the DB Period due to treatment-emergent SAEs (sensory loss and coronary artery disease). No subjects discontinued during the OLE Period due to TEAEs.
- The incidences of AEs in the categories of interest (injection reactions, serious infections and other infections of interest, malignancies, cardiac, vascular, autoimmune, neurological, serious bleeding, bone marrow dysplasia, and serious skin reactions) did not reveal any unexpected findings or suggest any new safety concerns.
- There were no pregnancies reported during the DB or OLE Periods.
- No clinically important deleterious effects or unexpected findings were observed for hematology variables, biochemistry variables, or vital signs. There were no notable treatment-related patterns in systolic or diastolic BP increases during either the DB or OLE Periods.
- There were no clinically relevant findings on urinalysis during the DB or OLE Periods. In addition, any abnormalities noted during physical examination were not considered clinically significant.

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Conclusions:

- In this first study with multiple MRIs following the initiation of biological therapy, CZP statistically significantly reduced the OMERACT RAMRIS synovitis (primary endpoint) and bone edema (exploratory endpoint) scores as measured by MRI at Week 16. The inability to detect a significant reduction in the synovitis and bone edema scores earlier than Week 16 is likely due to the small sample size, the technical challenges of reading 6 time points simultaneously, and the variability in MRI results since examinations were conducted across different sites.
- Statistically significant results from a number of the dynamic MRI efficacy variables at Week 16 (median IRE and median ME for PIP joints 2 to 5, and median Nvox with Plateau and Washout pattern for MCP joints 2 to 5 and PIP+MCP joints 2 to 5 combined) provided further evidence of the efficacy of CZP in reducing inflammation.
- Beginning as early as Week 1, treatment with CZP resulted in notable improvements from Baseline in all clinical outcome measurements and individual ACR components assessed in this study, and these improvements consistently increased through the end of the 16-week DB Period and then were maintained through the end of the 24-week OLE Period.
- The safety profile, including the type and incidence of TEAEs, was consistent with that expected in subjects with RA receiving an anti-TNFα agent and with previous studies of CZP and no new safety concerns were identified during this study.
- Overall, the results from this study provide essential information on the optimal timing of conducting MRI examinations and the required sample size needed for subsequent larger clinical trials of CZP with MRI examinations using OMERACT RAMRIS scoring and dynamic MRI parameters.

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