CLINICAL STUDY REPORT SYNOPSIS: RA0056

Name of company: UCB Pharma	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Olokizumab	**Volume:** Not applicable	
Name of active ingredient: CDP6038	**Page:** Not applicable	

Title of study: A randomized, double-blind, placebo-controlled, dose ranging study with an active comparator to evaluate the efficacy and safety of CDP6038 administered subcutaneously for 12 weeks to subjects with active rheumatoid arthritis having previously failed TNF-blocker therapy.

Investigator(s): A total of 64 Investigators randomized subjects in the study.

Study site(s): This was a multicenter study; 64 sites randomized subjects in the study.

Publication(s) (reference[s]): None at the time of reporting.

Studied period: approximately 19 months **First subject enrolled:** 23 Nov 2010 **Last subject completed:** 29 Jun 2012	**Phase of development:** Phase 2

Objective(s): The primary objective of this study was to evaluate the efficacy of olokizumab (OKZ; CDP6038) administered subcutaneously (sc) at various doses and dose administration frequencies relative to placebo.

The secondary objectives of this study were:

- To evaluate the safety of OKZ at various doses and dose frequencies relative to placebo
- To assess the pharmacokinetics (PK) and immunogenicity of repeated doses of OKZ
- To assess the dose- and exposure-response relationship of OKZ with efficacy

The exploratory objectives of this study were:

- To evaluate the efficacy of OKZ at various doses and dose administration frequencies relative to placebo as assessed by health outcomes endpoints
- To compare the efficacy (including health outcomes endpoints) and safety of OKZ with those of tocilizumab (TCZ)
- To explore the relationship of plasma proteomic biomarkers with clinical response

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Methodology: This was a Phase 2, dose-ranging, double-blind, placebo- and active-controlled, multicenter, factorial-design, randomized study to evaluate the efficacy and safety of OKZ administered by sc injection to subjects with moderately to severely active rheumatoid arthritis (RA) who had previously failed tumor necrosis factor (TNF)-blocker therapy.

Subjects must have entered the study on a stable dose (at least 6 weeks) of methotrexate (MTX) 12.5 to 25mg/week (unless dose-limited by documented toxicity for which doses as low as 10mg/week were permitted) and continued their current nonbiological treatment regimens for RA, unmodified until Week 12.

Eligible subjects were randomized to 1 of 9 treatment groups as described in the table below. The randomization was stratified according to the number of prior failed TNF-blockers (1 vs 2 or more) in order to enable design balance.

Description of treatment groups

Group	Treatment
1	OKZ 60mg sc q2w
2	OKZ 60mg sc q4w
3	OKZ 120mg sc q2w
4	OKZ 120mg sc q4w
5	OKZ 240mg sc q2w
6	OKZ 240mg sc q4w
7[a]	Placebo sc q2w
8[a]	Placebo sc q4w
9	Tocilizumab 8mg/kg iv q4w

iv=intravenous; OKZ=olokizumab; q2w=every 2 weeks; q4w=every 4 weeks; sc=subcutaneous

[a] Subjects in the q2w and q4w placebo groups received identical treatments.

Study medication was administered at the study site by qualified, study personnel at Weeks 0, 2, 4, 6, 8, and 10. To maintain blinding of the treatment assignment, every subject received an intravenous (iv) infusion every 4 weeks (q4w) and two-1.2mL sc injections every 2 weeks (q2w).

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Number of subjects (planned and analyzed): A sample size of 220 subjects (22 for each OKZ treatment group, 44 for placebo, and 44 for TCZ) was planned for this study. A total of 398 subjects were screened and 221 subjects were randomized into the 9 treatment groups (OKZ 60mg q4w: 23 subjects; OKZ 60mg q2w: 20 subjects; OKZ 120mg q4w: 23 subjects; OKZ 120mg q2w: 22 subjects; OKZ 240mg q4w: 22 subjects; OKZ 240mg q2w: 23 subjects; placebo q4w: 23 subjects; placebo q2w: 22 subjects; TCZ 8mg/kg q4w: 43 subjects).

Diagnosis and main criteria for inclusion: Subjects ≥18 years with a diagnosis of moderate to severely active adult-onset RA with an intolerance or inadequate response to treatment with no more than 2 licensed TNF-blockers.

Test product, dose(s) and mode of administration, batch number(s): Olokizumab solution for injection/infusion supplied as 1.6mL of OKZ study medication in a glass vial with a 1.2mL extractable volume at a concentration of 100mg/mL in the formulation buffer, containing 25mM sodium citrate, 90mM sodium chloride, 0.02% (w/v) polysorbate 80, pH 6.0, batch numbers: BX1004769, BX1004918, and BX1005178.

Duration of treatment: The study duration was up to 25 weeks; for subjects who entered the open-label extension study, RA0057, the study duration was up to 15 weeks.

Reference therapy, dose(s) and mode of administration, batch number(s):

Placebo solution for injection/infusion administered sc and iv containing 10mL of 0.9% sodium chloride preservative free for injection/infusion, batch numbers: 31016/1, BX1004955, BX1007506, and BX1007541 (31016/13).

Tocilizumab active comparator solution for iv infusion, batch numbers: 80mg: 31016/1, 31016/2, 31016/11, 3101613, BX1004956, BX1005288, and BX1007273; 200mg: 31016/1, 31016/2, BX1004957, and BX1005289; 400mg: 31016/1, 31016/2, 31016/12, BX1004958, and BX1005290.

Criteria for evaluation: Efficacy: The primary efficacy variable was the change from Baseline in the Disease Activity Score 28-joint count (C-reactive protein) (DAS28[CRP]) at Week 12 for OKZ and placebo.

The secondary efficacy variables were the American College of Rheumatology (ACR) 20%, 50%, and 70% response rates (ACR20, ACR50, and ACR70) at Week 12 for OKZ and placebo.

The following exploratory efficacy variables were assessed:

- Change from Baseline in DAS28(erythrocyte sedimentation rate [ESR]) at Week 4 and Week 12

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- ACR20, ACR50, and ACR70 response rates at Weeks 1, 2, 4, 6, 8, 10, and 12 (for TCZ)
- Change from Baseline in DAS28(CRP) at Weeks 1, 2, 4, 6, 8, 10, and 12 (for TCZ)
- Percentage of subjects with DAS28(CRP) <2.6 and with DAS28(CRP) ≤3.2 at Weeks 2, 4, 8, and 12
- Change from Baseline in Clinical Disease Activity Index (CDAI) and change from Baseline in Simplified Disease Activity Index (SDAI) at Weeks 1, 2, 4, 6, 8, 10, and 12
- ACR Core Set changes from Baseline at Weeks 1, 2, 4, 6, 8, 10, and 12 including the following components:
  - Tender/painful joint count (TJC; an assessment of 68 joints)
  - Swollen joint count (SJC; an assessment of 66 joints)
  - Patient's Assessment of Arthritis Pain - Visual Analog Scale (PAAP-VAS)
  - Patient's Global Assessment of Disease Activity, VAS (PtGADA)
  - Physician's Global Assessment of Disease Activity, VAS (PhGADA)
  - Value of acute phase reactants (ie, CRP)
  - Health Assessment Questionnaire-Disability Index (HAQ–DI)
- Change from Baseline in Bristol Rheumatoid Arthritis Fatigue-Multi-Dimensional Questionnaire (BRAF-MDQ) and BRAF Coping-Numeric Rating Scale (NRS) at Weeks 1, 2, 4, 8, 10, and 12
- Duration of early morning stiffness at Baseline and Weeks 1, 2, 4, 6, 8, 10, and 12
- Patient's Global Impression of Change (PGIC) at Weeks 4, 8, and 12
- Change from Baseline in Patient Acceptable Symptom State (PASS) scores at Weeks 1, 2, 4, 8, 10, and 12
- Health status as assessed by the EuroQoL-5 Dimensions Questionnaire (EQ-5D) at Baseline and Weeks 4, 8, and 12
- European League Against Rheumatism (EULAR) at Week 12

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Pharmacokinetics/pharmacodynamics:

Assuming a 2-compartment PK model (consistent with prior knowledge), the primary PK variables were:

- Absorption rate constant (Ka)
- Apparent clearance
- Apparent volumes of distribution (V/F) of the central and peripheral compartments, V1/F and V2/F (or V2/F and V3/F if Compartment 1 is defined as the depot compartment)
- Intercompartment clearance (Q)

Individual concentrations at the time of clinical observations (Ci) were derived from the PK model. They were used as the exposure measurement to assess the exposure-response relationship. The PK/pharmacodynamics (PD) models for dose- and exposure-response were described by the following primary PD variables:

- Dose leading to 50% of the maximum effect (D50) on DAS28(CRP)
- Exposure leading to 50% of the maximum effect on DAS28(CRP)
- Concentration leading to 50% of the maximum effect (EC50) on DAS28(CRP)
- Slope of concentration effect (γ) on DAS28(CRP)

In addition, anti-OKZ antibodies and the concentration of TCZ following repeated doses were assessed.

Exploratory biomarkers:

The exploratory biomarker variables included inflammation biomarkers (ie, chemokines, cytokines, and growth factors) measured at Baseline and Week 2 to explore the prediction of response/nonresponse.

Safety: Safety variables assessed included adverse events (AEs), laboratory parameters, immunological parameters, tuberculosis (TB) screening, physical examinations, electrocardiograms (ECGs), vital signs, and body weight.

Statistical methods: The primary efficacy variable was the change from Baseline in DAS28(CRP) at Week 12. Mixed model repeated measures methodology (Siddiqui et al, 2009; Mallinckrodt et al, 2003), using the variables treatment group, Baseline DAS28(CRP), prior failed TNF-blocker status, visit, and treatment group by visit, was used to evaluate and assess the

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dose-response relationship at Week 12. This model incorporated all available post-Baseline data at all visits through Week 12. Data from premature Withdrawal Visits (prior to Week 12) were recoded to the closest scheduled treatment period visit (after the last nonmissing visit value). Otherwise, no other imputation for missing data was done for the primary efficacy analysis.

Summary and conclusions:

Subject disposition: A total of 398 subjects were screened and 221 subjects were randomized to 9 treatment groups in this study. The majority of subjects overall (89.6%) and in each treatment group (range: 69.6% to 95.5%) completed the study and entered the open-label extension study RA0057 (86.0% of subjects overall; range: 69.6% to 95.5%). The percentage of subjects discontinuing the study was low in all treatment groups (range: 4.5% to 15.0%) with the exception of the OKZ 60mg q4w treatment group which had 30.4% of subjects discontinue, largely due to AEs (21.7%). The most frequently reported reasons for discontinuation overall were AEs (11 subjects [5.0%]) and consent withdrawn (6 subjects [2.7%]). All other reasons for discontinuation were reported by <1% of subjects overall.

Efficacy results:

The primary objective of this study, to evaluate the efficacy of OKZ administered sc at various doses and dose administration frequencies relative to placebo, was met.

- The primary efficacy variable in this study was the change from Baseline in the DAS28(CRP) at Week 12 for the OKZ and placebo treatment groups. Across all OKZ dose groups, a greater improvement in least squares (LS) mean DAS28(CRP) from Baseline at Week 12 was observed compared with the placebo groups, with the greatest improvement observed in the OKZ 240mg q2w group. The overall dose-response trend (across the q4w and q2w dosing frequencies) was highly statistically significant ($p<0.0001$).
- Additional supportive hypothesis testing for change from Baseline in DAS28(CRP) at Week 12 demonstrated that all dose group comparisons vs placebo were also statistically significant (60mg vs placebo; 120mg vs placebo; 240mg vs placebo; each $p\leq0.0001$). Comparisons of dosing frequency (q2w vs q4w) and dose by dose frequency interactions (q2w trend vs q4w trend) were not statistically significant.
- The secondary efficacy variables were ACR20, ACR50, and ACR70 at Week 12 for the OKZ and placebo treatment groups. The ACR20 and ACR50 estimated response rates at Week 12 were higher in all of the OKZ dose groups compared with the placebo groups. Very few subjects in any treatment group were ACR70 responders; however, those subjects that were

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ACR70 responders were all in OKZ treatment groups.

- At Week 4 and Week 12, improvements in DAS28(ESR) from Baseline were observed in all OKZ dose groups, which were greater than the placebo groups. The overall dose-response trend at Week 12 was highly statistically significant ($p<0.001$). In addition, all dose group comparisons versus placebo were also statistically significant (each $p<0.0001$).
- Analysis of DAS28(CRP) over time demonstrated a greater improvement in LS mean change from Baseline in DAS28(CRP) compared with the placebo groups across the OKZ dose groups at all time points (Weeks 1, 2, 4, 6, 8, 10 and 12).
- For all other exploratory efficacy variables (including Health Outcomes endpoints), results generally demonstrated trends towards improvement for all of the OKZ dose groups, which were greater than those observed in the placebo groups.

Pharmacokinetics/pharmacodynamics results:

- Olokizumab plasma concentrations increased with increasing dose (60mg vs 120mg vs 240mg).
- Analysis of plasma samples for anti-OKZ antibody (Ab) status was conducted, and 13 subjects in OKZ treatment groups were found to be anti-OKZ Ab positive. However, due to issues with the specificity of the assay, the true incidence of specific anti-OKZ antibodies were likely less than reported. Only 1 subject in the OKZ 120mg q4w group fits the profile of true immunogenicity.
- Pharmacokinetics of OKZ were adequately described by a 2-compartment model with first order absorption. The bioavailability of OKZ via sc administration was estimated to be 63% across the 3 studies evaluated (RA0056, RA0001, and RA0010).
- Suppression of CRP levels (as determined using a high sensitivity CRP assay) was observed as early as Week 1 and was sustained throughout the 12-week Treatment Period for the OKZ and TCZ dose groups.
- Marked and sustained suppression of CRP was observed regardless of OKZ dose.
- A concentration-effect relationship for DAS28(CRP) and exposure relationship for ACR20 was elucidated. The models were used to simulate dose-response curves for q2w and q4w regimens. A shallow dose-response curve was predicted for DAS28(CRP) <2.6 responders at Week 24 in contrast to ACR20, wherein a very steep response curve was predicted, and

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should be simultaneously considered when evaluating doses.

- Concentration-effect relationships were elucidated for the effects observed on absolute neutrophil counts, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and triglycerides, but effects were minimal, and were saturated across the doses explored.

Safety results:

Safety findings in RA0056 were consistent with the safety profile expected with this class of drug.

- There were no deaths reported in this study.
- Serious adverse events were reported by 3 subjects (15.0%) in the OKZ 60mg q2w group, 1 subject (4.5%) in the OKZ 60mg q4w group, 2 subjects (9.1%) in the OKZ 240mg q4w group, 2 subjects (9.1%) in the placebo q2w, 1 subject (4.5%) in the placebo q4w group, and 4 subjects (9.3%) in the TCZ 8mg/kg q4w group. Pneumonia was the only SAE was reported by more than 1 subject (1 subject in the OKZ 240mg q4w group and 1 subject in the TCZ 8mg/kg q4w group).
- A total of 12 subjects discontinued due to treatment-emergent adverse events (TEAEs) (5 subjects [22.7%] in the OKZ 60mg q4w group, 2 subjects [10%] in the OKZ 60mg q2w group, 1 subject [4.5%] in the OKZ 120mg q2w group, 2 subjects [8.7%] in the OKZ 240mg q2w group, 1 subject [4.5%] in the placebo q2w group, and 1 subject [2.3%] in the TCZ 8mg/kg q4w group). No TEAE preferred term (PT) leading to discontinuation was reported by more than 1 subject in any treatment group.
- Treatment-emergent AEs were reported by 17 subjects (77.3%) in the placebo q4w group, 19 subjects (86.4%) in the placebo q2w group, 18 subjects (81.8%) in the OKZ 60mg q4w group, 14 subjects (70.0%) in the OKZ 60mg q2w group, 20 subjects (87.0%) in the OKZ 120mg q4w group, 14 subjects (63.6%) in the OKZ 120mg q2w group, 19 subjects each in the OKZ 240mg q4w (86.4%) and OKZ 240mg q2w (82.6%) groups, and 37 subjects (86.0%) in the TCZ 8mg/kg q4w group.
- The TEAEs which occurred with the greatest incidence in any OKZ treatment group included: LFT abnormal, injection site reaction, injection site pruritus, ALT increased, and AST increased.
- Injection site reaction TEAEs were reported by a higher percentage of subjects in the OKZ treatment groups (8.7% to 39.1%) compared with the placebo groups (4.5% of subjects each)

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and TCZ 8mg/kg q4w group (4.7%), with the OKZ 240mg q2w group reporting the highest incidence (39.1%). Systemic injection reaction TEAEs were reported by relatively few subjects (12 TEAEs overall).

- The overall incidence of other TEAEs of interest was higher in the OKZ q4w groups (45.5% to 54.5%) compared with the OKZ q2w groups (35% to 40.9%). Within the system organ class (SOC) of Infections and infestations, the most frequently reported PTs were upper respiratory tract infection and urinary tract infection. Urinary tract infection was reported at a lower frequency (4.5% to 13.0%) in all active treatment groups compared with placebo (18.2% and 22.7%). Within the SOC of Investigations, the most frequently reported other TEAEs of interest were ALT increased and AST increased.
- No opportunistic infections were reported in the OKZ treatment groups, and only 5 serious infections were reported during the study (3 SAEs in the TCZ 8mg/kg group [cellulitis, abscess limb, and pneumonia] and 2 SAEs in the OKZ 240mg q4w group [pneumonia and perineal abscess]).
- Decreases in leukocytes, neutrophils, and platelets were observed following administration of OKZ at all dose levels, which plateaued by Week 4 and remained stable throughout the remainder of the treatment period. Only 1 subject in the TCZ 8mg/kg group had an AE of infection with an apparent temporal relationship to incidences of neutropenia.
- No subjects in any treatment group fulfilled the Hy's law criteria for drug-induced liver injury (ie, AST or ALT >3x the upper limit of normal [ULN] ***and*** bilirubin >2xULN). Elevations in ALT occurred in a total of 8 subjects with OKZ treatment, the majority of which were >3xULN. One subject in the OKZ 60mg q4w group had a >10xULN elevation in ALT. Few subjects reported elevations in AST of >3xULN or higher (3 subjects) or bilirubin >2xULN (1 subject) with OKZ treatment.
- Small increases from Baseline in median total cholesterol, low density lipoprotein cholesterol, and triglycerides were observed at Week 6 in each of the active treatment arms, including TCZ 8mg/kg q4w. The increases in these parameters were generally maintained at Week 12, with the exception of triglycerides which had returned to near Baseline values by Week 12.
- Reductions from Baseline in complements C3 and C4 were observed starting at Week 2 in each of the active treatment arms. The reductions in these parameters plateaued by Week 4 and remained stable through Week 12; despite the greater reductions from Baseline in the active treatment arms, median values for complements C3 and C4 generally remained within

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the normal range.

- Clinically significant urinalysis values were reported in ≤10.5% of subjects in any of the treatment groups across visits. No clinically relevant changes in vital signs or ECGs were noted for any treatment group.

Conclusions: Olokizumab demonstrated improvements in multiple efficacy variables (eg, DAS28, ACR, CDAI) compared with placebo, in subjects with moderate to severe RA who had previously failed TNF-blocker therapy, at all 3 dose levels tested (60mg, 120mg, and 240mg) and using a q4w or a q2w dosing regimen. Variability observed in the study, due to factors such as small sample size and inherent heterogeneity of the study population, led to added complexity in the interpretation of the data.

The safety profile following treatment with OKZ 60mg, 120mg, and 240mg q4w and q2w was in line with expectations for this class of drug, with an AE and laboratory test profile consistent with the use of interleukin-6 targeted therapy in subjects with moderate to severe RA.

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