CLINICAL STUDY REPORT

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of CCX354-C in Subjects with Rheumatoid Arthritis Partially Responsive to Methotrexate Therapy

Protocol Number:	CL004_354
EudraCT Number:	2010-019964-36
Kendle Study Number:	039730
Investigational Product:	CCX354-C
Indication:	Rheumatoid arthritis
Phase:	II
Study Initiation Date:	31 August 2010
Study Completion Date:	07 July 2011
Principal or Co-ordinating Investigator:	Prof. PP. Tak, MD, PhD
Sponsor:	ChemoCentryx, Inc. Mountain View CA 94043 USA
Date of Report:	21 November 2011
Version of Report:	Final 1.0 CSR

GCP Statement: This study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.

1 Study Synopsis

Name of Sponsor/Company: ChemoCentryx, Inc.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Investigational Product: CCX354-C	Volume:	
Name of Active Ingredient: CCX354-C	Page:	

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of CCX354-C in Subjects with Rheumatoid Arthritis Partially Responsive to Methotrexate Therapy

Coordinating Investigator: Prof PP. Tak, MD, PhD.

Study Centers: A total of 55 study centers were selected for participation in this study. Among these, 45 study centers in 8 countries recruited and screened subjects and of these, 44 study centers randomized subjects: 3 centers in Belgium (1 center did not randomize any subjects); 6 centers in the Czech Republic; 3 centers in Germany; 6 centers in Hungary; 1 center in the Netherlands; 11 centers in Poland; 9 centers in Romania; and 6 centers in Ukraine.

Publication (Reference):]None	**Phase of Development:** II

Studied Period: 31 August 2010 to 07 July 2011

Objectives: The primary objective of the study was to evaluate the safety and tolerability of CCX354-C in subjects with rheumatoid arthritis (RA) who had an inadequate response to methotrexate treatment.

The secondary objectives of the study were to evaluate the efficacy of CCX354-C compared with placebo based on: Change from baseline in RA Disease Activity Score 28-C-reactive protein (DAS28-CRP); proportion of subjects achieving American College of Rheumatology (ACR) 20, 50, and 70 response criteria; proportion of subjects achieving a DAS28-CRP value less than 2.6 (remission), and proportion of subjects achieving a DAS28-CRP value less than 3.2 (low disease activity).

The tertiary objectives of the study were: To compare the proportion of subjects achieving the minimally clinically important difference (MCID) (0.22 units) change in Health Assessment Questionnaire-Disability Index (HAQ-DI) across treatment groups; to compare the change from baseline in DAS28-Erythrocyte Sedimentation Rate (ESR) across treatment groups; to compare the change from baseline in the components of the DAS28 and ACR scores, including the swollen joint count (SJC), tender/painful joint count (TJC), subject assessment of RA, subject assessment of pain, physician assessment of RA, HAQ-DI, serum C-reactive protein (CRP) concentration, and ESR across treatment groups; to compare the change from baseline in the duration of morning stiffness across treatment groups; to determine the plasma concentrations of CCX354 in subjects with active RA; and to determine the effect of CCX354-C treatment compared with placebo on bone metabolism and inflammation markers.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel group study in approximately 150 subjects with RA who had an inadequate response to methotrexate therapy. Three groups of approximately 50 subjects were randomized (1:1:1):

- Group 1: Placebo twice-daily (BID) for 12 weeks.
- Group 2: 100 mg BID CCX354-C for 12 weeks.
- Group 3: 200 mg once-daily (QD) CCX354-C (in the morning) and placebo QD (in the evening) for 12 weeks.

Subjects were stratified based on prior biologic therapy use or not, and based on current systemic glucocorticosteroid use or not, and were then randomized to one of the 3 treatment groups. Prior biologic therapy included any anti-tumor necrosis factor (TNF) antagonist such as etanercept, infliximab, adalimumab, certolizumab, golimumab, or anakinra, rituximab, abatacept, ocrelizumab, tocilizumab, or any other approved protein-based therapy for RA.

All subjects had to be on methotrexate (7.5 to 25 mg/week) for at least 16 weeks and on a stable dose of methotrexate for at least 8 weeks before randomization, and had to continue to take their regular methotrexate dose in addition to study treatment over the course of the study. All subjects were required to take supplemental folic acid or folinic acid of at least 5 mg per week for the duration of the study.

Subjects participating in this study visited the study center for screening procedures on Day 1 and Weeks 1, 2, 4, 8, 12, and 16. At these visits, RA disease assessments were made, and blood samples were collected for safety, pharmacokinetic (PK), and pharmacodynamic (PD) measurements. Subjects were terminated from the study at the Week 16 follow-up visit.

Number of Subjects (Planned and Analyzed): It was planned that approximately 150 subjects would be randomized in this study. Three groups of approximately 50 subjects were to be randomized (1:1:1) to either placebo BID for 12 weeks; 100 mg BID CCX354-C for 12 weeks; or 200 mg QD CCX354-C (in the morning) and placebo QD (in the evening) for 12 weeks.

The actual subjects disposition is included in the table below:

	Placebo (N=54) n (%)	**100mg BID CCX354-C (N=53) n (%)**	**200mg QD CCX354-C (N=52) n (%)**	**Total (N=159) n (%)**
Number of subjects randomized	54 (100.0)	53 (100.0)	52 (100.0)	159 (100.0)
Number of subjects completed	45 (83.3)	41 (77.4)	45 (86.5)	131 (82.4)
Number of subjects discontinued early	9 (16.7)	12 (22.6)	7 (13.5)	28 (17.6)
Reason for early termination from study:				
Adverse event	2 (22.2)	6 (50.0)	0	8 (28.6)
Consent withdrawn	2 (22.2)	3 (25.0)	4 (57.1)	9 (32.1)
Lost to follow up	0	0	0	0

Protocol violation	1 (11.1)	0	1 (14.3)	2 (7.1)
Investigator decision	0	0	0	0
Sponsor Decision	4 (44.4)	3 (25.0)	2(28.6)	9 (32.1)
Other	0	0	0	0

Diagnosis and Main Criteria for Inclusion:

- Male or female subjects, aged 18 to 75 years inclusive, with functional class I to III RA based on ACR criteria for at least 3 months before screening; wheel-chair bound subjects or those with irreversible disease were not eligible.
- Subjects must have had active RA, defined by a minimum of 8 swollen joints and 8 tender/painful joints (based on 66/68 joint count) at screening.
- Serum CRP above 5 mg/L at screening.
- Must have been on methotrexate (7.5 to 25 mg/week) taken orally, subcutaneously, or intramuscularly for ≥16 weeks and on a stable dose for ≥8 weeks before randomization.
- If on hydroxychloroquine, must have been on a stable dose for ≥16 weeks before randomization.
- If taking non-steroidal anti-inflammatory drugs (NSAIDs), must have been on stable doses for ≥2 weeks before randomization.
- If taking oral corticosteroids, subjects must not have taken more than 10 mg/day of prednisone or equivalent, and must have been on a stable dose for ≥4 weeks before randomization.
- Willing and able to give written informed consent and to comply with the requirements of the study protocol.
- Negative result of the human immunodeficiency virus (HIV) screen, hepatitis B screen, and hepatitis C screen.
- Judged to be otherwise healthy by the investigator, based on medical history, physical examination (including electrocardiogram [ECG]), and clinical laboratory assessments.

Test Product, Dose and Mode of Administration, Batch Number: The test product was CCX354-C. Subjects randomized to receive 100 mg BID CCX354-C took one 100 mg CCX354-C tablet and one placebo tablet in the morning, and one 100 mg CCX354-C tablet in the evening. Subjects randomized to receive 200 mg QD CCX354-C took two 100 mg CCX354-C tablets in the morning and one placebo tablet in the evening. All doses of CCX354-C were administered orally.

Batch numbers: CCX354-C Film Coated Tablets, 100 mg: 1) Lot W006131 exp. Nov 2010; 2) Lot W009029 exp. Feb 2011; 3) Lot W009285 exp. date Oct 2011

Duration of Treatment: 84 days.

Reference Therapy, Dose and Mode of Administration, Batch Number: The reference therapy was placebo. Subjects randomized to receive placebo took 2 placebo tablets in the morning and one placebo tablet in the evening. All doses of placebo were

administered orally. Batch numbers: Placebo for CCX CCX354-C Film Coated Tablets: 1) Lot W0066132 exp. date Nov 2011; 2) Lot W009112 exp. date Aug. 2012
Criteria for Evaluation:
Efficacy: The following procedures were performed at screening and Day 1 (pre-dose), and at Weeks 1, 2, 4, 8, 12, and 16 to derive DAS28-CRP (primary efficacy measure), the ACR responses, and DAS28-ESR: • An SJC of 66 joints and TJC of 68 joints. • Subject's assessment of his/her pain due to RA using a 100 mm visual analog scale (VAS). • Subject's assessment of his/her RA disease activity using a 100 mm VAS. • Physician's assessment of the subject's RA disease activity using a 100 mm VAS. • Subject completion of HAQ-DI. • Serum CRP. • ESR (to calculate DAS28-ESR and ACR scores using ESR instead of CRP). The subject was also asked about the average duration of morning stiffness (in minutes) over the previous week, from waking to maximum improvement, s/he experienced before each of the study visits.
Pharmacokinetics: A 6-mL blood sample for CCX354 and metabolite(s) assessment was collected at Day 1 (pre-dose) and Weeks 1, 2, 4, 8, and 12.
Pharmacodynamics: Concentrations of the bone metabolism markers serum C-telopeptide (CTx), intact parathyroid hormone (iPTH), osteocalcin, and procollagen Type I N-terminal propeptide (PINP) were assessed at Day 1 (pre-dose) and Weeks 1, 4, 12, and 16. Blood samples were collected at each time point for these assays. Plasma samples collected for PK could also be used to assess levels of markers of inflammation such as interleukin-6 (IL-6), TNF, soluble interleukin-2 receptor (sIL-2R), matrix metalloproteinase-3 (MMP-3), macrophage inflammatory protein-1 alpha (MIP-1α), and monocyte chemotactic protein-1 (MCP-1), and cartilage degradation, such as collagen Type II CTx.
Safety: Safety assessments included adverse event (AE) incidence, laboratory evaluations, vital sign parameters, physical examination, and ECG abnormalities.

Statistical Methods:

Efficacy Endpoints

1. Change from baseline to Week 12 in DAS28-CRP.
2. ACR20, ACR50, and ACR70 Response at Week 12.
3. Proportion of subjects achieving a DAS28-CRP score less than 2.6 (remission) at Week 12.
4. Proportion of subjects achieving a DAS28-CRP score less than 3.2 (low disease activity) at Week 12.
5. Proportion of subjects achieving the MCID of 0.22 in HAQ-DI at Week 12.
6. Change from baseline to Week 12 in DAS28-ESR.
7. Change from baseline to Week 12 in the components of the DAS28 and ACR, including the SJC, the TJC, the subject's assessment of RA (VAS), the subject's assessment of pain (VAS), the physician's assessment of the subject's RA (VAS), the HAQ-DI, CRP, and ESR.
8. Change from baseline to Week 12 in duration of morning stiffness.

Efficacy as determined by these endpoints was also assessed at other timepoints, Weeks 1, 2, 4, 8, and 16.

The main efficacy hypothesis in this study was that at least one dose of CCX354-C would result in a statistically significant reduction in DAS28-CRP compared with placebo at Week 12. This hypothesis was tested using linear contrasts of an analysis of covariance (ANCOVA) model with treatment group as a factor and baseline DAS28-CRP and the 2 baseline stratification factors (prior biologic use and concomitant corticosteroid use) as covariates. All statistical testing was 2-sided and Dunnett's adjustment was used to control the Type I error rate at α=0.05. When testing fixed effects, the Kenward-Roger method was used to set the denominator degrees of freedom. The main efficacy analysis was performed in the intent to treat (ITT) Population, by region and overall.

In addition, a sensitivity analysis was used to assess the effect of dropouts on the conclusions derived from the primary ANCOVA model, by region and overall.

Changes from baseline to Week 12 and all other timepoints were summarized descriptively including 95% confidence intervals (CIs) for changes from baseline within each treatment group, by region and overall. Similar ANCOVA models or non-parametric methods, if relevant, with appropriate baseline variables were used to compare treatment groups, by region and overall.

In addition, changes from baseline to Week 12 and all other timepoints were summarized descriptively including 95% CIs for changes from baseline within each treatment group,

for each stratification factor.

The other continuous variable efficacy endpoints, ie, change from baseline to each timepoint in DAS28 and ACR components, including the 28 and 66 SJC, the 28 and 68 TJC, the subject's assessment of RA (VAS), the subject's assessment of pain (VAS), the physician assessment of the subject's RA (VAS), the HAQ-DI, CRP, and ESR, as well as the DAS28-ESR and duration of morning stiffness, were analyzed in a similar manner as the DAS28-CRP, but not by region or stratification factor.

The categorical variables, ie, ACR20, ACR50, ACR70, DAS28-CRP <2.6, DAS28-CRP <3.2, and HAQ-DI MCID at each timepoint were summarized by treatment group, by region, and overall. They were also analyzed by Cochran-Mantel-Haenszel (CMH) chi-square testing, incorporating the 2 baseline stratification factors, separately for each pairwise treatment comparison with placebo, for the ITT population, by region and overall. Differences in proportions between each active treatment group and placebo and 95% CIs for these differences were presented.

In addition, the categorical variables ACR20, ACR50, and ACR70 at each timepoint were summarized by treatment group, for each stratification factor.

Due to a study treatment importation issue in the Ukraine, a sensitivity analysis was conducted at each timepoint to exclude subjects from Ukraine who were withdrawn early from the study because of this issue.

Pharmacokinetics

CCX354, CCX354-M11, and possible other metabolite concentration results, PK parameter estimation, statistical analyses for PK parameters, and production of tables, listings, and figures for PK parameters were performed by the sponsor.

Only sparse plasma concentration data for CCX354, CCX354-M11, and possible other metabolites were available from subjects participating in this study since only one sample was taken at each study visit. Data were listed by treatment group, subject, visit, and time of sample collection relative to the previous dose of CCX354-C. Data could also be summarized descriptively by treatment group using the arithmetic mean, standard deviation (SD), median, minimum, and maximum. Data from all subjects in a treatment group were combined in a scatterplot of plasma CCX354 vs. time since last dose. These data could be used to determine how the overall PK profile compared to the profile in subjects with stable RA, as well as the PK profile in healthy volunteers from previous CCX354-C studies. If feasible, the data could be used to assess the dose-response relationship based on the efficacy and PD parameters, and, if feasible, population PK analysis could be performed.

Details are provided in separate reports that are included as an appendix to this clinical study report.

Pharmacodynamics

Analyses were performed to evaluate whether there were any differences between either of the 2 CCX354-C groups and placebo in percentage changes from baseline in the bone metabolism markers CTx, iPTH, osteocalcin, and PINP. The change and percentage change from baseline in CTx, iPTH, osteocalcin, and PINP were summarized and analyzed in a similar manner as the methodology for the primary efficacy endpoint.

Actual values and percentage change from baseline values were listed by treatment group, subject number, and visit, and summarized by treatment group.

Safety

Summary statistics were calculated for all safety parameters using the safety population. No inferential statistical analysis was performed on safety parameters.

All clinical safety and tolerability data were listed by treatment group and subject number.

Summary – Conclusions:

Efficacy Results: Overall, the 200 mg CCX354-C QD dose group showed evidence of biologic activity of CCX354-C, while the 100 mg BID dose was not as effective. More specifically, the CCX354-C 200 mg QD group showed a statistically significant Week 12 ACR20 response compared to placebo (delta 25.8%; p=0.014) in subjects eligible at Screening and Day 1 (pre-dose). CCX354-C 200 mg QD showed a higher Week 12 ACR20 response compared to placebo (delta 21.7%; p=0.059) in subjects naïve to biologic agents (subjects who had not previously used biologics). CCX354-C 200 mg QD decreased CRP significantly (p=0.023) compared to placebo at Week 12. Data from other RA efficacy measures were consistent with a greater treatment effect of 200 mg QD CCX354-C compared to placebo: ESR and TJC were significantly different from placebo at certain timepoints. DAS28, SJC, Subject's Assessment of RA and Pain, Physician Assessment of RA, and HAQ-DI showed numerically greater improvement in CCX354-C vs. placebo. Bone turnover markers CTx, PINP, and osteocalcin showed statistically significant treatment effects supporting the bone anti-resorptive efficacy of CCX354-C in RA. Data from exploratory analyses confirm that the 200 mg QD dose was the most efficacious dose.

Safety Results: Regarding the primary objective, safety and tolerability assessment of CCX354-C, review of the safety data indicated that in general, CCX354-C was well tolerated and safe.

- The 4 serious adverse events (SAEs) that were observed in the 100 mg BID group were not considered related to CCX354-C and did not show a systemic pattern. The event of "angina pectoris" was not confirmed as having a cardiac origin, the syncope case was considered related to a vasovagal reaction due to blood draw, the case of psychomotor epilepsy occurred during the study drug free follow-up period, and the case of myocardial infarction occurred in an elderly subject with a history of hypertension. It is of note that there were no SAEs in the 200 mg QD group.
- Regarding withdrawals due to the AEs, there were none reported in the 200 mg

QD group. 7 subjects were withdrawn due to AEs in the 100 mg BID group; 2 withdrew due to GI AEs: ie, nausea, abdominal pain, vomiting (subject 401002) and diarrhea, nausea and vomiting (subject 613002). Apart from this, there did not appear to be a systematic trend in the AE profile leading to subject discontinuation.

- The most common AEs reported in subjects receiving CCX354-C were headache, nasopharyngitis, and nausea.
- With regard to laboratory parameters, a systematic review of all laboratory parameters indicates that CCX354-C does not appear to cause hepatic, renal, metabolic, or hematologic safety issues.
- There were no significant effects of CCX354-C treatment on vital signs, physical exam findings, or ECG measurements.

Conclusion: CCX354-C 200 mg QD showed evidence of biologic and clinical activity in this Phase 2 study in subjects with moderate to severe RA, partially responsive to methotrexate. CCX354-C appeared safe and well tolerated in study participants. Further study of this CCR1 blocker in RA is justified.

Date of Report: 28 October 2011