2 SYNOPSIS

Name of Sponsor: ChemoCentryx, Inc.

Name of Finished Product: Chemokine receptor 2 antagonist CCX140-B

Name of Active Ingredient: CCX140-B

Title of Study: A Randomized, Double-Blind, Placebo- and Active-Controlled Study to Evaluate the Safety and Efficacy of CCX140-B in Subjects with Type 2 Diabetes Mellitus

Investigators: For the list of Investigators, see Appendix 16.1.4.

Study Sites: 32 sites in Australia, Czech Republic, Germany, Hungary, and New Zealand

Publication (reference): None

Study Period: 10 months

Initiation Date: 29 Jan 2010

Completion Date: 24 Nov 2010

Phase of Development: 2

Study Objectives:

Primary: The primary objective of this study was to evaluate the safety and tolerability of CCX140-B in subjects with type 2 diabetes mellitus (T2DM) based on subject incidence of adverse events.

Secondary: The secondary objectives of this study included evaluation of the effect of CCX140-B, compared to placebo, on the following parameters:

1. Fasting plasma glucose (FPG) concentrations;
2. Glucose tolerance, measured by an oral glucose tolerance test (OGTT);
3. Homeostasis model assessment of insulin resistance (HOMA-IR);
4. Fasting plasma insulin concentrations;
5. Glucose control based on hemoglobin A_{1c} (HbA_{1c}) and fasting plasma fructosamine concentrations;
6. Serum total adiponectin concentrations;
7. Plasma monocyte chemoattractant protein-1 (MCP-1) concentrations;
8. Serum high-sensitivity C-reactive protein (hsCRP) concentrations; and

9. Serum lipid concentrations, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and non-esterified fatty acids (NEFAs).

Other objectives included the following:

1. Evaluation of the safety of CCX140-B based on changes in safety laboratory parameters, vital signs, and physical examination findings;
2. Evaluation of the magnitude of effect of CCX140-B on safety and efficacy outcome parameters relative to the pioglitazone hydrochloride control group;
3. Assessment of the plasma concentration profile of CCX140 and possible metabolites in subjects with T2DM; and
4. Assessment of MCP-1 polymorphism on efficacy responses to CCX140-B treatment.

The pharmacokinetic (PK) samples were to be used to assess the effect of CCX140-B treatment on plasma cytokine concentrations, such as leptin, resistin, chemerin, retinol binding protein-4 (RBP-4), monocyte chemoattractant protein-2 (MCP-2), interleukin-1ß (IL-1ß), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α).

Methodology: Approximately 140 subjects with T2DM were to be enrolled. Eligible subjects were stratified based on MCP-1 polymorphism status as well as gender. Subjects were then randomized in a 1:1:2:1 ratio to 1 of 4 treatment groups: placebo once daily (N=28), pioglitazone hydrochloride 30 mg once daily (N=28), CCX140-B 5 mg once daily (N=56), or CCX140-B 10 mg once daily (N=28).

The placebo-controlled part of the study was double-blind, i.e., placebo capsules were identical in appearance to the CCX140-B capsules. The pioglitazone hydrochloride group was open-label.

Study medication was to be taken as follows by study subjects:

1. Group A: Four placebo capsules once daily in the morning for 28 days;
2. Group B: One pioglitazone hydrochloride 30 mg tablet once daily in the morning for 28 days;
3. Group C: Two 2.5 mg CCX140-B capsules plus 2 placebo capsules once daily in the morning for 28 days; or
4. Group D: Four 2.5 mg CCX140-B capsules once daily in the morning for 28 days.

All subjects were to take study medication as instructed on the days of visits to the study center. For the other study days, study medication was to be taken at home after an overnight fast of ≥10 hours. Following the 28-day dosing period, there was a 28-day follow-up period.

The screening period was up to 21 days. Eligible subjects were to visit the study center on Day 1 after an overnight fast of ≥10 hours for a physical examination, vital signs measurements, laboratory tests, an OGTT with time-matched glucose and insulin measurements, and randomization. Dosing started on Study Day 1 and

continued through Study Day 28. Subjects also were to visit the study center on Study Days 8, 15, 22, 29, 36, 43, and 57. At visits specified in the protocol, blood and urine samples were to be collected for efficacy measurements, serum chemistry, hematology, PK, and urinalysis measurements. Physical examinations, body system reviews, and vital signs assessments were to be performed. A telephone visit was to occur on Study Day 2. Concomitant medications and adverse event assessments were to be performed at every study visit. An OGTT was also to be performed on Study Day 29 after an overnight fast of ≥10 hours.

Duration of Treatment: 28 days

Number of Subjects:

Planned: 140

Screened: 293

Randomized to treatment: 159

Completed study: 152

Discontinued from study: 7

Diagnosis and Main Criteria for Inclusion: The study population included male and post-menopausal or surgically sterile female subjects, aged 18-70, inclusive, with T2DM. Subjects must have had a body mass index ≥25 mg/m^2 and <45 kg/m^2, HbA_{1c} of 6.5-10%, inclusive, FPG of 135-270 mg/dL, inclusive, and must have been on a stable dose of metformin for ≥8 weeks prior to randomization (no minimum dose specified). Subjects on lipid-lowering agents must have been on a stable dose for ≥4 weeks prior to randomization.

Investigational Product and Comparator Information:

CCX140-B 2.5 mg capsules: Lot number 043I0509

Placebo capsules to match CCX140-B capsules: Lot number 044I0509

Criteria for Evaluation:

Safety assessments: Safety assessments included adverse events, physical examination abnormalities, vital signs, and clinical laboratory tests (including chemistry, hematology, and urinalysis).

Efficacy assessments: Efficacy assessments included change from baseline in FPG concentration; OGTT profile; HOMA-IR; fasting plasma insulin concentration; HbA_{1c} and fasting plasma fructosamine concentrations; serum total adiponectin concentration; plasma MCP-1 concentration; serum hsCRP concentration; serum lipid concentration including TC, HDL-C, LDL-C, TG, and NEFAs; and estimated glomerular filtration rate.

Exploratory assessments, including change from baseline in plasma cytokine concentrations (leptin, resistin, chemerin, RBP-4, MCP-2, IL-1ß, IL-6, and TNF-α), may also have been assessed depending on the outcome of the other efficacy assessments.

Pharmacokinetic assessments: Concentrations of CCX140 and possible metabolites were determined in plasma from blood samples collected in ethylene diamine tetra-acetic acid tubes over the course of the study.

Statistical Methods:

Safety Analysis:

Safety was assessed using the incidence of adverse events, safety laboratory tests, clinically significant changes in physical examinations and 12-lead electrocardiograms (ECGs), and vital signs and body weight. Adverse events were coded using the Medical Dictionary for Regulatory Affairs (Version 12.0). The presence of pitting edema in both lower legs was assessed and scored using the guidelines listed in the protocol.

Efficacy Analysis:

The main efficacy hypothesis of interest was that at least one dose of CCX140-B would result in a statistically significant reduction in FPG compared to placebo at Study Day 29. This hypothesis was tested using linear contrasts of an analysis of covariance model with treatment group as a factor and baseline FPG as a covariate. All statistical testing was 2-sided, and Dunnett's adjustment was used to control the type I error rate at $\alpha=0.05$. The primary efficacy analysis was performed in the Intent-to-Treat Population. If the model was determined not to be appropriate due to non-normality of residuals, the Wilcoxon Rank Sum test was to be used to compare the CCX140-B dose groups to the placebo group.

Sensitivity analyses were performed to examine the effects due to dropouts and protocol deviations and subgroup analyses were performed to compare the treatment effects in various subgroups.

The OGTT glucose and insulin profiles were analyzed by comparing the data before treatment (Study Day 1) and after treatment (Study Day 29) at each time point of the profile. In addition, areas under the curve (AUCs) were calculated for each subject's profile before treatment (Study Day 1) and after treatment (Study Day 29). The changes across treatment groups were compared.

The rest of the efficacy variables were analyzed in a similar manner as FPG, i.e., based on change from baseline.

Pharmacokinetic Analysis:

Sparse sampling for CCX140 plasma concentration measurements was performed. Plasma concentration results were used to conduct PK analysis. An objective of these analyses was to evaluate whether the PK profile of subjects with T2DM was similar to the profile documented in healthy volunteers. An additional objective was to evaluate, if possible, the PK/pharmacodynamic (PD) relationship of CCX140-B

treatment. Changes from baseline in glucose, OGTT, HOMA-IR, insulin, total adiponectin, MCP-1, and hsCRP were to be used as potential PD markers.

Summary of Results:

Safety Results:

The study met its primary objective by showing that CCX140-B treatment was safe and well tolerated over 4 weeks of treatment in subjects with T2DM who were on a stable dose of metformin treatment. The overall incidence of treatment-emergent adverse events (TEAEs) was 25.8% in the placebo group, 25.8% in the pioglitazone hydrochloride 30 mg group, 34.9% in the CCX140-B 5 mg group, and 35.5% in the CCX140-B 10 mg group. Most TEAEs were mild or moderate in severity. No possibly related TEAE (preferred term) was experienced by more than 2 subjects in a treatment group.

No subject died during the study. No serious adverse events (SAEs) occurred in subjects receiving CCX140-B. One subject in the placebo group experienced an SAE of syncope, which was considered by the Investigator to be moderate in severity and probably not related to study medication.

Two subjects discontinued due to a TEAE. One subject in the CCX140-B 5 mg group experienced a TEAE of dyspepsia, which led to discontinuation of study medication. The TEAE was considered by the Investigator to be moderate in severity and possibly related to study medication. One subject in the CCX140-B 10 mg treatment group experienced a TEAE of gouty arthritis, which led to discontinuation of study medication. The subject had a medical history of gout. The TEAE was considered by the Investigator to be severe in intensity and probably not related to study medication.

Changes in safety laboratory parameters, vital signs, and ECGs were not clinically meaningful. No new safety issues were identified in this study.

Efficacy Results:

The FPG profiles over the course of the study indicate a CCX140-B dose-dependent decrease from baseline to Day 29, with larger decreases observed during the 4-week treatment period with 10 mg CCX140-B than 5 mg CCX140-B given once daily. The least-squares mean change from baseline to Day 29 (with the last observation carried forward) was -10.7, -21.4, -4.3, and -16.1 mg/dL in the placebo, pioglitazone hydrochloride 30 mg, CCX140-B 5 mg, and CCX140-B 10 mg groups, respectively. The placebo group decrease was larger than expected and is likely due to a 14 to 21 mg/dL higher baseline FPG in this group compared to the others. The decrease from baseline in FPG of 21.4 mg/dL with pioglitazone was in line with the anticipated decrease of 25 mg/dL over 4 weeks of treatment. Compared to placebo, the pioglitazone hydrochloride 30 mg and CCX140-B group decreases in FPG from baseline to Day 29 were not statistically different. The least-squares mean change from baseline in HbA_{1c} was -0.09%, -0.13%, -0.09%, and -0.23% ($p=0.045$ vs. placebo; Wilcoxon Rank Sum test) in the placebo, pioglitazone hydrochloride 30 mg, CCX140-B 5 mg, and CCX140-B 10 mg groups, respectively, indicating that the latter dose of CCX140-B improves glycemic control. The fructosamine levels also trended lower in the active dose groups compared to placebo, but did not reach

statistical significance for any treatment group compared to placebo. There were no detrimental effects of CCX140-B treatment on plasma MCP-1 or circulating monocyte levels. Treatment with CCX140-B for 28 days in this study was not associated with clinically or statistically significant changes from baseline to Study Day 29 with last observation carried forward in fasting plasma insulin, fasting HOMA-IR, the OGTT AUC, serum adiponectin, or hsCRP. This suggests that improving insulin sensitivity may not be the major driver of anti-glycemic effects of CCX140-B based on FPG and HbA_{1c} results. The pioglitazone hydrochloride 30 mg group showed the anticipated decrease in OGTT AUC and increase in serum adiponectin.

CCX140-B treatment did not negatively affect the serum lipid profiles (TC, HDL-C and LDL-C, TG, and NEFAs) over the 4-week treatment period. There was no significant effect of CCX140-B treatment on body weight, no evidence of hemodilution (based on hematocrit data) and no detrimental effect on renal function over the course of the study.

Pharmacokinetic Results:

Pharmacokinetic results are presented in the PK report (Appendix 16.1.13).

Conclusions: This clinical trial met its primary objective by demonstrating that treatment with CCX140-B was safe and well tolerated. No new safety issues were identified in this study. Even though the treatment period was only 4 weeks, FPG and HbA_{1c} results with CCX140-B treatment are encouraging. Longer-term studies are planned to further evaluate the safety and efficacy of CCX140-B.

Date of the Report: 17 March 2011