1. 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: CCX140-B	Volume:	
Name of Active Ingredient: CCX140-B	Page:	
Title of Study: A Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Effect of CCX140-B on Albuminuria in Subjects with Type 2 Diabetes Mellitus		
Principal or Coordinating Investigator: J. Burggraaf, MD, PhD		
Study Centers: Centre for Human Clinical Research, Leiden, The Netherlands		
Publication (Reference): None	**Phase of Development:** 2	
Studied Period: 10 months		

Objectives: The primary efficacy objective of this study was to evaluate the effect of CCX140-B treatment on urinary albumin excretion in subjects with type 2 diabetes mellitus (T2DM) with albuminuria.
The primary safety objective of this study was to evaluate the safety and tolerability of CCX140-B in subjects with T2DM with albuminuria.
The secondary objectives of this study were:
1. To evaluate the effect of CCX140-B on hemoglobin A1c (HbA1c);
2. To evaluate the pharmacokinetic (PK) profile of CCX140-B in subjects with T2DM with albuminuria;
3. To evaluate the effect of CCX140-B on renal function as measured by urinary creatinine excretion, serum creatinine, creatinine clearance, blood urea nitrogen (BUN), and phosphorus (P); and
4. To evaluate the effect of CCX140-B on urinary MCP-1:creatinine ratio, and other serum and urinary markers of renal function and inflammation.

Methodology: The target was to enroll 20 male or female subjects in this randomized, double-blind, placebo controlled, Phase 2a study. Not more than 24 subjects were to be enrolled. Subjects were randomized 1:1 to one of two treatment groups:

- Group A: Placebo once daily (N=10)
- Group B: CCX140-B 10 mg once daily (N=10)

Study medication was taken as follows by study subjects:

- Group A: Four placebo capsules once daily in the morning for 84 days;
- Group B: Four 2.5 mg CCX140-B capsules once daily in the morning for 84 days.

All subjects took study medication in the morning, with or without food, for 84 consecutive days. Following the 84-day dosing period, there was a 28-day follow-up period. The screening period was up to 21 days. All potential study subjects had to sign written informed consent before any study screening procedures. During the screening period, a first morning urine sample collected on 2 separate days was analyzed for albuminuria. Eligible subjects had to have a urinary albumin:creatinine ratio (ACR) of 100 to 3000 mg/g creatinine, inclusive, on both study days.Not more than 50% of subjects were to have an average ACR of 100 to 300 mg/g creatinine to ensure that most subjects had macroalbuminuria. The other screening procedures included collection of demographic information and medical history, physical examination, ECG, vital signs, blood chemistry, hematology, urinalysis, viral and TB screening, pregnancy testing (for all female subjects of childbearing potential) and concomitant medication use. Subjects checked into the study center on Day -1 and stayed overnight through the morning of Day 3. Subjects then visited the study center on Day 8 and checked into the study center on Day 14 and stayed through the morning of Day 15. Subjects visited the study center on Days 29 and 57, and again checked into the study center on Day 84 and stayed through the morning of Day 85. Subjects visited the study center on Day 113 for the final study visit. Subjects took study medication once daily starting on Day 1 for 84 days continuously. All study procedures are presented in a schedule, see Section 12.1. Study days 29, 57, and 113 were to occur within a +/- 2-day window of the scheduled visit. Subjects were terminated from the study at the completion of the Study Day 113 visit. All subjects had to be on a stable dose of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for at least 8 weeks prior to screening. It was also attempted to keep doses of other anti-hypertensives, anti-diabetic medications, and lipid-lowering

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medications fixed throughout the study period in order to prevent undue influence of changes in these medications on the efficacy measurements. To the extent possible, any adverse events that were deemed study drug-related and were ongoing at discharge were followed-up to resolution or until a determination was made that the unresolved event was stable.

Number of Subjects (Planned and Analyzed): The target number of subjects was 20. Not more than 24 subjects were to be enrolled. It was allowed to replace subjects who discontinued during the first 14 days of taking study medication to ensure that sufficient data were available for safety, PK and efficacy assessments. However, this did not occur.

Diagnosis and Main Criteria for Inclusion:

1. Male or female, aged 18-75 years inclusive, with documented previously diagnosed type 2 diabetes mellitus (per American Diabetes Association [ADA] criteria);
2. Albumin:creatinine ratio (ACR) of 100 to 3000 mg/g creatinine, inclusive, based on two values obtained from two first morning urine samples taken on two separate days during the screening period; both ACR values had to be 100 to 3000 mg/g creatinine, inclusive;
3. Estimated glomerular filtration rate based on serum creatinine (eGFR, determined by Modification of Diet in Renal Disease [MDRD] equation) of ≥ 25 mL/min.
4. All subjects had to be on a stable dose of an ACE inhibitor or ARB for at least 8 weeks prior to screening. The dose of these drugs had to be similar to or higher than the lowest labeled dose. Subjects were not allowed to be on both an ACE inhibitor and an ARB. Doses of any other anti-hypertension treatment had to be stable for at least 4 weeks prior to screening. Any oral anti-diabetic treatment had to be maintained at stable dose(s) for at least 8 weeks prior to screening. If receiving insulin, subjects had to be on insulin for at least 8 weeks prior to screening;
5. If taking any phosphate binders, cinacalcet, vitamin D or vitamin D analogues, subjects had to be on stable doses for at least 4 weeks prior to screening;
6. Fasting plasma glucose less than 270 mg/dL at screening;
7. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol;
8. Judged to be otherwise healthy by the Investigator, based on medical history, physical examination (including electrocardiogram [ECG]), and clinical laboratory assessments. Subjects with clinical laboratory values that were outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other abnormal clinical findings that were judged by the Investigator not to be of clinical significance, were allowed to enter into the study; and
9. Female subjects of childbearing potential, and male subjects with partners of childbearing potential, were allowed to participate if adequate contraception was used during, and for at least the four weeks after, any administration of study medication. Adequate contraception was defined as usage by at least one of the partners of a barrier method of contraception, together with usage by the female partner, commencing at least three months prior to Screening, of a stable regimen of any form of hormonal contraception or an intra-uterine device. Use of abstinence alone was not considered adequate. Use of a barrier method alone was considered adequate only if the male partner was vasectomized at least six months prior to Screening. Use of a double-barrier method of contraception was acceptable. Women of childbearing potential had to have a negative serum pregnancy test during the screening period and a negative urine pregnancy test on the day prior to the initial dosing.

Main Criteria for Exclusion:

1. Type 1 diabetes mellitus or history of diabetic ketoacidosis;
2. Previous renal transplant or known non-diabetic renal disease, except related to hypertension;
3. Has undergone renal dialysis at any time in the past;
4. Women who were pregnant or breastfeeding;
5. Body mass index (BMI) above 45.4 kg/m^2;
6. Received chronic (more than 7 days continuously) systemic glucocorticoid or other immunosuppressive treatment within 8 weeks of screening;
7. Use of bardoxolone, atrasentan or other endothelin antagonist within 8 weeks of

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screening;
8. Received chronic (more than 7 days continuously) NSAID treatment within 2 weeks of screening;
9. Cardiac failure (class III or IV), history of unstable angina, symptomatic coronary artery disease, myocardial infarction or stroke within 12 weeks of screening;
10. Poorly-controlled blood pressure (systolic blood pressure >155 or diastolic blood pressure >95, with blood pressure measured in the seated position after at least 5 minutes of rest);
11. History of hypersensitivity to ingredients of the placebo (tartrazine, microcrystalline cellulose, starch, or croscarmellose sodium);
12. History or presence of leukopenia (WBC count $<3.5 \times 10^9$/L);
13. History or presence of any form of cancer within the 5 years prior to randomization, with the exception of excised basal cell or squamous cell carcinoma of the skin, or cervical carcinoma *in situ* or breast carcinoma *in situ* that has been excised or resected completely and is without evidence of local recurrence or metastasis;
14. Presence of tuberculosis based on chest X rays, tuberculin skin test, QuantiFERON®-TB Gold test, or T-SPOT®. TB test was performed during screening; If screening test was performed and it is deemed positive due to previous vaccination or TB exposure, chest X rays had to be acquired to rule out TB;
15. Positive HBV, HCV, or HIV viral screening test;
16. History of gastrointestinal conditions that could interfere with study medication compliance, e.g., severe gastroparesis, with regurgitation of food or oral medication;
17. History of alcohol or illicit drug abuse;
18. Any infection requiring antibiotic treatment within 4 weeks of screening;
19. Hemoglobin less than 10 g/dL (or 6.18 mmol/L) at screening;
20. Evidence of hepatic disease; AST, ALT, or bilirubin > 2 x the upper limit of normal;
21. Clinically significant abnormal ECG during screening, e.g., QTc greater than 450 msec;
22. Participation in another clinical trial within 3 months prior to the start of this study or more than 4 times per year; and
23. History or presence of any medical condition or disease which, in the opinion of the Investigator, might place the subject at unacceptable risk for study participation.

Test Product, Dose and Mode of Administration: CCX140-B was administered via hard gelatin capsules containing 2.5 mg CCX140 (2.6 mg CCX140-B, the sodium salt of CCX140). The CCX140-B capsules were supplied to the study center in plastic bottles, each bottle containing 30 capsules. Subjects were asked to take the 4 capsules every morning, with or without a meal, for 84 days continuously. Capsules were taken with approximately 8 oz (240 mL) of water.

Duration of Treatment and Observation: Subjects were screened within 21 days prior to Study Day 1 (the first day of dosing). The treatment period was 84 days and all subjects were followed for 28 days after the dosing period. Subjects stayed overnight at the study center from Day -1 through the morning of Day 3, from Day 14 through the morning of Day 15, and again from Day 84 through the morning of Day 85. To the extent possible, any adverse events that were deemed study drug-related and were ongoing at discharge were followed-up to resolution or until a determination was made that the unresolved event was stable.

Criteria for Evaluation:

Safety Assessments: Safety was evaluated by periodic physical examinations and body system reviews, assessments of vital signs, routine clinical laboratory tests (including blood chemistry, hematology, and urinalysis), electrocardiographic (ECG) monitoring, and monitoring of adverse events.

Pharmacokinetic Assessments: Concentrations of CCX140 (and possible metabolites) were determined in plasma from 4.0-mL blood samples collected in K_2EDTA tubes at the following times:

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• Study Day 14:Hours 312 (prior to the 14th dose of study medication), 313, 314, 316, 320, 324
• Study Day 15: Hour 330 and 336
Representative urine samples (in 6 mL tubes) were taken from each of the 24-hour urine collections on Days -1, 1, 2, 14, and 84 for CCX140 and possible metabolite measurements.

Efficacy Assessments: Efficacy assessments included:
1. Change from baseline in 24-hour urinary albumin excretion;
2. Change from baseline in first morning urinary albumin:creatinine ratio;
3. Change from baseline in HbA1c;
4. Change from baseline in urinary MCP-1:creatinine ratio;
5. Change from baseline in urinary and plasma renal function and inflammation markers

Other assessments included change from baseline in renal function as measured by 24-hour urinary creatinine excretion, serum creatinine, creatinine clearance, BUN, and P, as well as glycemic control as measured by serum glucose and 24-hour urinary glucose. After a complete void, 24-hour urine samples were collected on Days -1, 1, 2, 14, and 84. Urine collection containers were kept in the refrigerator between collections. The volume of 24-hour urine collections from each day was determined and recorded, the total 24-hour urine collection was mixed thoroughly, and representative samples (4 x 6 mL) were taken for albumin, creatinine, MCP-1, glucose, as well as other renal function and inflammation marker measurements. First morning urine aliquots (2 x 6 mL) were taken from the first morning void urine samples on Days 1, 2, 3, 8, 14, 15, 29, 57, 84, 85, and 113 for albumin, creatinine, MCP-1, as well as other renal function and inflammation markers. All the urine samples were frozen and kept at -70 °C for subsequent analysis. Blood samples were collected for HbA1c measurement on Days -1, 1, 84, 85, and 113.

Blood samples were also collected on Days -1, 8, 15, 29, 57, 85, and 113 for renal function and inflammation markers. For these samples, 10 mL blood samples were collected and 4 x ~1 mL plasma aliquots were frozen and kept at -70 °C for shipment to ChemoCentryx for analysis. Plasma and urine markers could include transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), N-acetylglucosamine (NAG), β2 microglobulin, adiponectin, C-reactive protein (CRP), cystatin C, synaptopodin, neutrophil gelatinase-associated lipocalin (NGAL), liver-fatty acid-binding protein (LFABP), kidney injury molecule-1 (KIM-1), intact PTH, leptin, resistin, chemerin, retinol binding protein 4 (RBP-4), MCP-1 through 4, IL-1β, IL-6, and TNF-α.

Statistical Methods: ***Screening, compliance, safety and tolerability data***
All baseline subject characteristics of demographic data (age, height, weight, race), smoking status, medical history (abnormalities only), physical examination (abnormalities only), ECG, and concomitant medications at study entry were listed. Demographics were summarized by dose group. All clinical safety and tolerability data were listed for each subject and by treatment. Individual vital signs and individual differences from baseline in vital signs were listed by treatment and measurement time and summarized descriptively. ECG assessments were listed. Laboratory values outside the laboratory's normal ranges were listed separately, together with associated repeats and comments as to their clinical significance. All reported adverse events were coded using MedDRA and listed. Treatment-emergent adverse events were tabulated by treatment and by other categorical information of interest, and summarized. Laboratory data was also summarized by treatment group.

Pharmacokinetic analysis: Individual plasma concentrations of CCX140 (and possible metabolites) were listed, plotted, and summarized descriptively and graphically for subjects receiving 10 mg CCX140-B. The following parameters were determined for CCX140, and relevant metabolites where applicable:

- C_{max}: Maximum plasma concentration
- T_{max}: Time of maximum plasma concentration
- AUC_{0-t}: Area under the plasma concentration-time curve from Time 0 to Time t (time of last quantifiable plasma concentration)

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- AUC_{0-24}: Area under the plasma concentration-time curve from Time 0 to 24h

Efficacy analysis: Summary statistics were calculated for each of the efficacy parameters. For continuous variables, numbers, means, medians, ranges, and standard deviations were calculated. Because of the relatively small size of the study, inferential statistical analyses were not considered to be appropriate.
Baseline was defined as the last value prior to starting study drug unless otherwise indicated. For 24-hour urinary albumin, urinary creatinine, creatinine clearance, and urinary glucose, baseline was the Day -1 value. For urinary ACR and MCP-1:creatinine ratio, baseline was the average of the two screening values plus the Day 1 (pre-dose) value. For serum creatinine, BUN, P, and glucose, baseline was the average of the Day -1 and Day 1 (pre-dose) values. For HbA1c, baseline was the average of the Day -1 and 1 (pre-dose) values, and Day 85 was the average of the Day 84 and 85 values.

Pharmacokinetic Results: Results are discussed in a separate ancillary report (see Section 14.2.2)

Efficacy: As no formal statistical analysis was performed in this study, discussion of efficacy results is descriptive based on summary statistics. Because of the relatively small sample size, considerable subject-to-subject variability, relatively low baseline albuminuria levels, and baseline differences between treatment groups, no definitive conclusions can be drawn. No obvious CCX140-B-induced changes in endpoint measures were observed when CCX140-B-treated patients were compared with placebo-treated subjects. In both the active and the placebo group, urinary albumin excretion and albumin/creatinine ratio remained relatively stable over time. The data suggest that serum glucose levels and HbA1c were slightly lower in the CCX140-B treated group.

Results: *Safety and tolerability*
No severe or serious adverse events occurred during the study. Daily oral administration of multiple doses (84) of 10 mg CCX140-B to patients with diabetic nephropathy was associated with mild and transient AEs, comparable to the AE's observed in the placebo group. No AE's were likely to be treatment related. Two subjects discontinued study drug due to AE's for safety reasons, however, in hindsight no treatment relation is suspected. There were no other clinically significant changes in laboratory parameters, vital signs or ECG recordings. In summary, these safety data indicate that treatment with 10 mg CCX140-B for 12 weeks is safe and well tolerated in this group of 10 patients with diabetic nephropathy.

Discussion/Conclusion: No severe or serious adverse events occurred during the study. Daily oral administration of 10 mg CCX140-B for 84 days to patients with diabetic nephropathy appeared to be well tolerated in general. The AE incidence was similar across the two dose groups. No AE's were likely to be treatment related. Two subjects discontinued study drug due to AE's for safety reasons, however, no treatment relation is suspected. There were no other clinically significant changes in laboratory parameters, vital signs or ECG recordings. No obvious CCX140-B-induced changes in renal endpoints measures were observed when CCX140-B-treated patients were compared to placebo-treated subjects. In summary, these data indicate that treatment with 10 mg CCX140-B for 12 weeks is safe and well tolerated in this group of 10 patients with diabetic nephropathy. Although some indications of improvement of outcome measures on an individual level can be detected, no clear overall efficacy signal is observed in this study. Sample size was rather small and treatment period relatively short to be able to detect improvement of this chronic condition. Therefore, increasing sample size and prolonging treatment might enhance the efficacy signal.

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