SGS Life Science Services

A Randomized, Double-Blind, Placebo-Controlled, Phase II Study Testing CCX282-B in the Treatment of Celiac Disease

Test drug	CCX282-B
Protocol number	ChemoCentryx, Inc. CL009_282 SGS Life Science Services 7819
Development phase	Phase II
Indication	Celiac Disease
GCP statement	This study was performed in compliance with the current version of the declaration of Helsinki and with the ICH note for guidance on good clinical practice (CPMP/ICH/135/95), including the archiving of essential documents.

Study period	12-Oct-2007 to 26-Jun-2008
Date of the report (version)	08-Feb-2010 (Final)
Author(s)	E. Van Bavel, SGS Life Science Services, Generaal De Wittelaan 19A bus 5, 2800 Mechelen (Belgium)
Sponsor	ChemoCentryx, Inc.
Sponsor representative	P. Bekker, 850 Maude Avenue, Mountain View, CA 94043, USA
Principal investigator	M-L Lähdeaho, MD Finn-Medi Research Ltd. Biokatu 10, Tampere 33520, Finland

2. SYNOPSIS

Name of sponsor: ChemoCentryx, Inc.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: CCX282-B	**Page:**	

Title of study:	A Randomized, Double-Blind, Placebo-Controlled, Phase II Study Testing CCX282-B in the Treatment of Celiac Disease	
Investigators:	Principal investigator: M-L Lähdeaho, MD	
Study center:	Finn-Medi Tutkimus oy, Biokatu 10, Tampere 33520, Finland	
Publication (reference):	None	
Study period:	From 12-Oct-2007 to 26-Jun-2008	**Phase of development:** Phase II

Objectives:

Primary:

The primary objective of this study was to evaluate the effect of CCX282-B compared to placebo on the small intestinal mucosal morphology (measured as villous height/crypt depth ratio) of biopsy specimens taken from subjects with celiac disease on a longstanding gluten-free diet, before and after gluten exposure.

Secondary:

Secondary objectives of this study included evaluation of CCX282-B compared to placebo on small intestinal mucosal inflammation, gluten-induced celiac-type serology, symptom scores, malabsorption parameters, and safety and tolerability profiles. [redacted]

Name of sponsor: ChemoCentryx, Inc.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: CCX282-B	**Page:**	

Methodology:

This randomized, double-blind, placebo-controlled, parallel group, Phase II, proof-of-concept study planned to enroll a total of approximately 90 adult volunteer subjects with biopsy-proven celiac disease who had been established on a gluten-free diet for 2 years or more.

All subjects were to undergo screening procedures to determine eligibility for the study. An oesophago-gastro-duodenoscopy (OGD) was to be performed in order to obtain baseline (i.e., pregluten exposure) small intestinal mucosal biopsy specimens. Directly after OGD, subjects were to be randomized to either the CCX282-B or placebo group (randomization ratio 1.5:1, CCX282- B: placebo). For the first 7 days after randomization, subjects were to receive either CCX282-B or placebo while continuing with a strict gluten-free diet. From the eighth day after randomization, all subjects also were to start ingesting a foodstuff that contained a tightly controlled amount of gluten. The original gluten dose was 5 g (2.5 g twice daily); this was reduced to 1.25 g (0.625 g twice daily) mid-way through the study. Apart from this controlled gluten exposure, subjects were instructed to continue on their normal strict gluten-free diet. Concomitant dosing of study medication and gluten was to be continued for a 12-week period. At Study Day 91 the gluten containing foodstuff and study medication were to be stopped, a post-gluten exposure mucosal biopsy was to be obtained, and subjects were to continue their normal gluten-free diet. Any subjects who dropped out during the 12-week gluten exposure period due to clinical symptoms were encouraged to still undergo an OGD examination to determine whether gluten-induced mucosal deterioration was likely to have been the cause of the clinical symptoms. All subjects were to have a safety follow-up visit 4 weeks after the end of their gluten and CCX282-B/placebo dosing period. Subjects were recruited through one trial center and all histological and serological measurements were performed at this center.

Number of subjects:

Ninety adult celiac subjects, established on a gluten-free diet for over 2 years, were planned to be entered into the study, 54 for CCX282-B and 36 for placebo.

Forty-one and 26 subjects were actually randomized to CCX282-B and placebo, respectively, of which 17 subjects each completed the study.

Diagnosis and main criteria for inclusion:

- Male or female, between 18 and 75 years of age.
- The subject had an established diagnosis of celiac disease based on prior medical records.
- The subject had been following a strict gluten-free diet at least 24 months prior to Visit 1 and was anti-tissue transglutaminase antibody negative (tested using the rapid on-site whole blood Biocard™ Celiac-Test, ANIBiotech, Vantaa, Finland).
- Subjects able to provide written Informed Consent and willing and able to comply with study procedures.
- Subjects of childbearing potential or female partners of childbearing potential could participate if adequate contraception was used during and for at least the 4 weeks after any administration of study medication.

Name of sponsor: ChemoCentryx, Inc.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: CCX282-B	**Page:**	

Main criteria for exclusion:

- The subject was pregnant, trying to become pregnant, or breast-feeding.
- The subject had any known liver disease, or an abnormality in one or more liver function test results (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, gamma glutamyl transferase [GGT], bilirubin, lactate dehydrogenase [LDH]). (This criterion was added with amendment #2.)
- The subject had a known sensitivity to any of the components of the CCX282-B formulation (microcrystalline cellulose, polyvinyl pyrrolidone, sodium lauryl sulphate, colloidal silicon dioxide, crospovidone, or sodium stearyl fumarate).
- Use of a tumor necrosis factor [TNF] inhibitor, natalizumab, or any immunosuppressants during the 12 weeks prior to study randomization, and use of steroids during the 4 weeks prior to randomization (Visit 2).
- History or presence of illicit drug use and/or alcohol abuse within a year of study entry.
- History or presence of any medical or psychiatric condition or disease, or laboratory abnormality that, in the opinion of the Investigator, could place the subject at unacceptable risk for study participation and completion.
- The subject had either a medical history of tuberculosis or currently active tuberculosis.
- History of any form of cancer within 5 years prior to study entry, with the exception of basal cell or squamous cell skin cancer, cervical carcinoma in situ, or breast carcinoma in situ that had been excised or resected completely and was without evidence of recurrence or metastasis.
- The subject had a history of infection requiring intravenous antibiotics, a serious local infection (e.g., cellulitis or abscess), systemic infection (e.g., pneumonia or septicemia), or gastrointestinal infection within 12 weeks of randomization.
- Known immunoglobulin E [IgE]-mediated atopy or allergy or anaphylactic reactions to gluten or other ingredients in the gluten containing foodstuff.

Test product, dose and mode of administration, batch number:

Study medication was supplied in bottles. Each bottle contained 30 hard gelatin capsules filled with 250 mg CCX282-B. Subjects received study medication on Visit 2 (Study Day 0) and Visit 3 (Study Day 35). Subjects randomized to the 250 mg CCX282-B twice daily group took one 250 mg CCX282-B capsule orally every morning and every evening, approximately 12 hours after the morning dose.

The first dose of study medication was administered while the subject was at the study center. The study drug was taken with approximately 240 mL of water. There were no restrictions on dosing of study medication with regard to food consumption. Gluten exposure was only started following a one week run-in period with study medication. The gluten dose was decreased from 5 to 1.25 g daily in January 2008.

The batch number of CCX282-B used was C6I02681.

Name of sponsor: ChemoCentryx, Inc.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: CCX282-B	**Page:**	

Reference product, dose and mode of administration, batch number:

Study medication was supplied in bottles. Each bottle contained 30 hard gelatin capsules filled with placebo. Subjects received study medication on Visit 2 (Study Day 0) and Visit 3 (Study Day 35). The placebo and CCX282-B capsules were identical in appearance. Subjects randomized to the placebo group took one placebo capsule orally every morning and every evening, approximately 12 hours after the morning dose.

The first dose of study medication was administered while the subject was at the study center. The study drug was taken with approximately 240 mL of water. There were no restrictions on dosing of study medication with regard to food consumption. Gluten exposure was only started following a one week run-in period with study medication. The gluten dose was decreased from 5 to 1.25 g daily in January 2008.

The batch numbers of placebo used was C6I03791.

Duration of treatment:

Subjects were screened within the 21 days prior to their entry into the study. Subjects self-administered an oral dose of study medication twice daily for up to 13 consecutive weeks.

Name of sponsor: ChemoCentryx, Inc.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: CCX282-B	**Page:**	

Criteria for evaluation:

Efficacy Assessments:

- An OGD and biopsy for small bowel histology was performed on Visit 2.
- Repeat OGD and biopsy for small bowel histology within 7 days before or 3 days after Visit 4 (Study Day 91) or within 5 days after premature termination.
- Anti-Endomysial, Anti-Tissue Transglutaminase, and Anti-Gliadin Peptide Antibodies were determined on Visit 2 (prior to administration of the first dose of study medication), Visit 3 (Study Day 35), and at the time of repeat OGD.
- Peripheral blood CCR9+ T cell levels were determined on Visit 2 (before administration of the first dose of study medication), on Visit 3, and at the time of repeat OGD.
- SF-36v2™ Health Survey and Gastrointestinal Symptom Rating Scale questionnaires were collected on Study Day 1 (prior to administration of the first dose of study medication) and at the time of repeat OGD. Only validated translations of the instruments were used in the study.
- Daily assessment of stool output.
- Visual Analog Scale was used to measure gluten-induced ill health as an exploratory assessment.

Efficacy Endpoints:

The primary efficacy endpoint was the measurement of villous-height to crypt-depth ratio at baseline and at time of repeat OGD (Study Day 91). It was hypothesized that the active drug, CCX282-B, would attenuate the gluten-induced mucosal deterioration.

A particularly important set of secondary endpoints were the quantitation of mucosal inflammation through measurement of the following intraepithelial lymphocyte cell densities:

(1) CD3+ T cells;

(2) αβ+ and (3) γδ+ T cell receptor-bearing intraepithelial lymphocytes;

(3) aberrant up-regulation of mucosal HLA DR (as an exploratory endpoint).

Other secondary endpoints for the gluten exposure period included:

(1) the change from baseline in gluten-induced serum antibody levels;

(2) the incidence of celiac disease symptoms;

(3) change in quality of life;

(4) change in stool output quantity and quality;

(5) change in blood malabsorption parameters;

(6) change in peripheral blood CCR9+ receptor status.

[redacted]

Name of sponsor: ChemoCentryx, Inc.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: CCX282-B	**Page:**	

Pharmacokinetic Assessments:

Plasma samples for population pharmacokinetic (PK) analysis were collected on Visit 2 (Study Day 0), Visit 3 (Study Day 35), at the time of repeat OGD, and at the time of any early termination. For each PK sampling, the times of the following events were recorded: (1) the most recent meal; (2) study drug dosing prior to PK sample collection; and (3) PK sample collection.

Safety Assessments:

Safety assessments were performed at each visit to the study center. Safety was evaluated by periodic physical examinations, assessments of vital signs, clinical laboratory tests (including blood chemistry, hematology, and urinalysis), an electrocardiogram (ECG) at Screening (to include QTc interval duration), and monitoring of adverse events (AEs).

Liver function tests were performed at regular intervals over the duration of the study, with any abnormal results followed up according to strict guidelines. Malabsorption parameters consisting of serum iron, serum ionized calcium and erythrocyte folic acid levels were measured at each visit to the study center.

Subjects were followed for safety for up to 4 weeks after receiving their final dose of study medication and at the end of this time a safety follow-up visit was also performed.

Statistical methods:

Linear regression, Cochran-Mantel-Haenszel chi-square tests, student's t-test, Fisher's exact test, intent-to-treat analysis, and per-protocol analysis.

Name of sponsor: ChemoCentryx, Inc.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: CCX282-B	**Page:**	

Summary of results:

Efficacy:

Results of the ITT population are presented. In general, similar results were obtained in the PP population.

Mean Vh/Cd ratio values were lower (i.e., worse) at Study Day 91 compared to baseline in both the CCX282-B and placebo group. In the CCX282-B group, the geometric mean (95% CI) Vh/Cd ratio decreased from 2.5 (2.2-2.9) at baseline to 0.8 (0.6-1.0) at Study Day 91. In the placebo group, the geometric mean (95% CI) Vh/Cd ratio decreased from 2.8 (2.6-3.1) at baseline to 1.4 (1.0-2.1) at Study Day 91. The Study Day 91/baseline Vh/Cd ratio was 0.32 and 0.49 in the CCX282-B and placebo groups, respectively ($p = 0.048$). The majority of subjects had Vh/Cd < 2.5 (i.e., not desirable) at Study Day 91: 34 (87%) subjects in the CCX282-B group and 15 (65%) subjects in the placebo group. The difference between the CCX282-B and placebo group was not statistically significant.

No statistically significant differences in CD3+ lymphocytes, αβ+ cells, or γδ+ cells were observed between the CCX282-B and placebo group. No statistically significant differences in anti-tTG, anti-gliadin peptide, and anti-endomysial antibody titers were observed between the CCX282-B and placebo group.

At Study Day 91, an enhanced (i.e., abnormal) expression in HLA-DR was observed for the majority of subjects in the CCX282-B and placebo group. No statistically significant difference was observed between both groups. Lower IgA deposit densities were observed for subjects in the placebo group compared to the CCX282-B group ($p = 0.040$).

The GSRS total score and the SF-36v2 subscale scores indicate severity of gastrointestinal symptoms and health-related quality of life, respectively. No statistically significant differences between the CCX282-B and placebo group in changes from baseline to Study Day 91 were observed, except for the physical functioning score (SF-36v2 subscale, $p = 0.0093$) that was in favor of the placebo group. Subjects also monitored their stool output number and fecal consistency daily. A statistically significant difference between the CCX282-B and placebo group in change from baseline to Study Day 91 in mean days with hard lumps was observed in favor of the CCX282-B group ($p = 0.0013$).

Pharmacokinetics:

Plasma concentrations of CCX282 and its metabolites were similar to those observed in normal healthy volunteers as well as in subjects enrolled in Crohn's disease studies.

Name of sponsor: ChemoCentryx, Inc.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: CCX282-B	**Page:**	

Safety:

Adverse Events

Overall, 40 (98%) subjects in the CCX282-B group and 25 (96%) subjects in the placebo group had at least one treatment-emergent adverse event (TEAE). The most commonly reported TEAEs (> 33% of the subjects in any treatment group) were AST increased (30 [73%] subjects in the CCX282-B and 11 [42%] subjects in the placebo group), ALT increased (29 [71%] and 7 [27%] subjects, respectively), abdominal distension (13 [32%] and 13 [50%] subjects, respectively), flatulence (17 [41%] and 12 [46%] subjects, respectively), and nausea (16 [39%] and 12 [46%] subjects, respectively), diarrhea (8 [20%] and 12 [46%] subjects, respectively), and dyspepsia (18 [44%] and 3 [12%] subjects, respectively).

None of the subjects died during the trial. Serious AEs were reported for 9 (22.0%) subjects in the CCX282-B group. These were all related to increased hepatic transaminases. One of these cases was reported as a suspected unexpected serious adverse reaction (SUSAR). The transaminase increases were typically not associated with liver function impairment, and were reversible upon study drug and/or gluten withdrawal. No SAEs were reported for the placebo group. Eighteen (44%) subjects in the CCX282-B group and 8 (31%) subjects in the placebo group discontinued study medication due to an AE.

Most TEAEs were mild or moderate in severity. Severe TEAEs were reported for 10 (24%) and 6 (23%) subjects in the CCX282-B and placebo group, respectively.

Treatment-related TEAEs were reported for 40 (98%) subjects in the CCX282-B group and 24 (92%) subjects in the placebo group. Of the most commonly reported TEAEs, all cases of AST increased, ALT increased, dyspepsia, abdominal distension, and flatulence were considered treatment-related by the Investigator.

The highest incidence of AEs associated with gluten ingestion were reported for abdominal distension (13 [32%] subjects in the CCX282-B group and 13 [50%] subjects in the placebo group), diarrhea (8 [20%] and 12 [46%] subjects, respectively), and abdominal pain (13 [32%] and 7 [27%] subjects, respectively). Abdominal discomfort, vomiting, and anorexia were reported for at most 8% of subjects in either treatment group. No TEAEs of bloating were reported. One subject (SUB-NUR-002) had an episode of severe pruritic rash during the study resulting in withdrawal of gluten and study drug.

Laboratory Parameters

The majority of laboratory parameters did not show meaningful differences between treatment groups regarding mean laboratory values over the course of the study. ALT, AST, GGT, and LDH mean changes over time were higher in the CCX282-B group compared to placebo. However, bilirubin changes were not different between groups.

Name of sponsor: ChemoCentryx, Inc.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: CCX282-B	**Page:**	

Safety Results, Continued:

Regarding shifts from baseline, most laboratory parameters did not show meaningful differences between treatment groups, except for the following laboratory parameters. Shifts from normal at Screening to abnormally high at Study Day 35 occurred in ALT (14 [40%] subjects in the CCX282-B group compared to 2 [10%] in the placebo group), AST (18 [51%] vs. 2 [10%] subjects), LDH (4 [11%] vs. 0 subjects), and eosinophils (%) (5 [14%] vs. 1 [5%] subject); shifts from normal at Screening to abnormally low at Study Day 35 occurred in phosphorus (3 [9%] subjects in the CCX282-B group compared to 4 [20%] subjects in the placebo group) and serum calcium (6 [17%] vs. 2 [10%] subjects; shifts from normal at Screening to abnormally high at Study Day 91 occurred in ALT (23 [56%] subjects in the CCX282-B group compared to 3 [12%] in the placebo group), AST (22 [54%] vs. 6 [24%] subjects), LDH (8 [20%] vs. 2 [8%] subjects), and eosinophils (%) (3 [7%] vs. 3 [12%] subjects; shifts from normal at Screening to abnormally low at Study Day 91 occurred in phosphorus (4 [10%] subjects in the CCX282-B group compared to 5 [20%] subjects in the placebo group).

Concerning malabsorption, ionized calcium below normal was observed for 5 (12%) subjects in the CCX282-B group and 1 (4%) subjects in the placebo group. Iron below and above normal was observed for 4 (10%) and 2 (5%) subjects, respectively, in the CCX282-B group. No abnormalities related to iron were observed in the placebo group. Red blood cell folic acid below normal was observed for 4 (10%) subjects in the CCX282-B group and in none of the subjects in the placebo group; values above normal were observed for 1 (2%) and 2 (8%) subjects, respectively.

Laboratory abnormalities most frequently reported as an AE were AST increased (30 [73%] subjects in the CCX282-B and 11 [42%] subjects in the placebo group), ALT increased (29 [71%] and 7 [27%] subjects, respectively), lipase increased (12 [29%] and 6 [23%] subjects, respectively), eosinophil count increased and GGT increased (6 [15%] and 2 [8%] subjects each, respectively), blood folate decreased (6 [15%] and 0 subjects, respectively), and blood phosphorus decreased (5 [12%] and 8 [31%] subjects, respectively).

One subject of the CCX282-B group had an AE related to urinalysis, i.e., blood urine present.

Vital Signs, Body Weight, and Physical Examination

Changes in vital sign parameters, body weight, and BMI were generally small, and were not considered clinically relevant.

No AEs related to vital signs or body weight were reported.

Name of sponsor: ChemoCentryx, Inc.	**Individual study table referring to module 5 of the dossier**	**(For national authority use only)**
Name of finished product: NA	**Volume:**	
Name of active ingredient: CCX282-B	**Page:**	

Conclusions:

In conclusion, CCX282-B did not show a treatment benefit in individuals with celiac disease who are challenged with gluten. However, there was evidence of a pharmacologic effect of CCX282-B treatment in this setting. Vh/Cd ratio decreases and hepatic transaminase increases were observed in both groups, but more so in the CCX282-B group compared to placebo. It is documented that hepatic transaminases are elevated in approximately 40% of newly diagnosed adult subjects with celiac disease. Other studies demonstrated that withdrawal of gluten from the diet results in normalization of hypertransaminasemia in the majority of subjects, supporting a causal link with gluten intake. Therefore, the gluten challenge fundamentally underlies these increases in hepatic transaminases. CCX282-B treatment in other settings, i.e., Crohn's disease, has not been associated with hepatic transaminase increases. Gastrointestinal epithelial infiltration of lymphocytes and serologic changes were not statistically different between treatment groups. Mucosal IgA deposits were stronger in CCX282-B compared to placebo.

Date of the report: 08-Feb-2010 (Final)