These Clinical Study Results are provided for informational purposes only.

The study listed may include approved and non-approved uses, formulations or treatment regimens. It is not intended to promote any product or indication and is not intended to replace the advice of a health care professional. The results reported in any single clinical trial may not reflect the overall results obtained across the product development. Only a physician can determine if a specific product is the appropriate treatment for a particular patient. If you have questions, please consult a health care professional. Before prescribing any product, healthcare professionals should consult prescribing information for the product approved in their country.

2 STUDY SYNOPSIS

Name of Sponsor/Company: Biogen Idec Inc.	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: CNF1010	**Name of Active Ingredient:** 17-(allylamino)-17-demethoxygeldanamycin [17-AAG]	**Study Indication:** Chronic Lymphocytic Leukemia

Title of Study:
A Phase 1, Multi-Center, Open-Label, Dose-Escalation, Pharmacodynamic Study of Intravenously Administered CNF1010 (17-(allylamino)-17-demethoxygeldanamycin [17-AAG]) in Patients with ZAP-70 Positive B-Cell Chronic Lymphocytic Leukemia (CLL)

Principal Investigators:

- [redacted] US
- [redacted] US
- [redacted] US
- [redacted] US
- [redacted] US

Study Period: Date of first subject treatment: 23 May 2005 Date of study completion (last subject visit): 11 June 2007	**Phase of Development:** 1

Study Objectives:
To determine the following for CNF1010 when administered intravenously twice weekly for 3 weeks during 4-week cycles:

1. Minimal biologically active dose (MBAD)
2. Safety and toxicity profile
3. Pharmacokinetics (PK)
4. Pharmacodynamics (PD)
5. Clinical and Hematological response
6. Recommended Phase 2 dose

Study Design:
This was an open-label, dose-escalation, multicenter study to evaluate the effects of CNF1010 on pharmacodynamic markers and hematologic response in subjects with ZAP-70 positive B-cell CLL.

Approximately 26 subjects were to be enrolled into the following 4 sequential dose cohorts: 50 mg/m^2, 100 mg/m^2, 150 mg/m^2, and 200 mg/m^2. The starting dose of 50 mg/m^2 was chosen based on previous clinical studies. Subjects were to receive CNF1010 on Days 1, 4, 8, 11, 15, and 18 of each 28-day cycle. Treatment cycles were to be repeated every 28 days in the absence of disease progression or unacceptable toxicity. Intra-subject dose escalation was to be implemented at the end of each cycle during the dose-escalation phase of the study, in the absence of toxicity. Enrollment was to begin with a single subject who was at the 50 mg/m^2 dose level. If a dose limiting toxicity (DLT) was observed, an additional 5 subjects were to be added at that dose level. A DLT was defined as any treatment-related Grade 4 absolute neutrophil count, decrease in platelets, or hemoglobin; Grade ≥3 non-hematological toxicity (except nausea and vomiting) that did not resolve within 7 days, or cardiac arrhythmia Grade 3 of any duration. Three additional subjects were to be treated at each subsequent dose starting with 100 mg/m^2, and subjects were to be added that had started at lower doses. If a DLT was observed in 1 of 3 subjects, 3 additional subjects were to be enrolled at that dose. Dose escalation was to proceed according to this scheme until the MBAD was reached or dose escalation was stopped due to ≥2 subjects experiencing a DLT in the first cycle of treatment. MBAD was defined as the dose at which at least 4 of 6 subjects demonstrated a 60% decrease in ZAP-70 expression in circulating CLL cells. Fifteen additional subjects were to be treated at the MBAD. Individual subject dose escalation did not affect the decision rules for dose cohort escalation.

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Number of Subjects (Planned and Analyzed):

Planned: Approximately 26 subjects.

Enrolled: 10 subjects.

Analyzed: 10 subjects in the All Enrolled population, 10 subjects in the Safety population, and 8 subjects in the Pharmacokinetic population.

Study Population:

Inclusion criteria:

1. Diagnosis of B-cell CLL including
   - Lymphocytosis of ≥5000 monoclonal B-cells/μL co-expressing ≥1 B-cell marker (CD19, CD20, or CD23) and CD5 in peripheral blood AND
   - ≤55% prolymphocytes AND
   - Bone marrow with ≥30% mononuclear cells being lymphocytes.
2. ZAP-70 positive CLL (defined as expression of ZAP-70 detected by flow cytometry in more than 20% of leukemia cells)
3. Intermediate or high risk, poor prognosis CLL refractory to fludarabine-based therapy, as defined by one of the following:
   - Disease progression following 2 cycles of fludarabine OR
   - Failure to achieve partial response (PR) or complete response (CR) after at least 2 cycles OR
   - No response to treatment or stable disease after at least 2 cycles of fludarabine OR
   - Disease progression after chemotherapy treatment after fludarabine-based therapy OR
   - CLL subjects intolerant to fludarabine-based therapy (intolerance is defined as the development of any serious medical condition occurring after exposure to fludarabine, which would restrict further use of the agent as treatment for the subject's CLL [i.e., autoimmune hemolytic anemia, myelosuppression, hypersensitivity])
4. Indication for treatment as defined by the National Cancer Institute Working Group (NCIWG) Guidelines:
   - Massive or progressive splenomegaly OR
   - Massive lymph nodes, nodal clusters, or progressive lymphadenopathy OR
   - Grade 2 or 3 fatigue OR
   - Fever ≥100.5°F or night sweats for greater than 2 weeks without documented infection OR
   - Presence of weight loss ≥10% over the preceding 6 months OR
   - Progressive lymphocytosis with an increase of ≥50% over a 2-month period or an anticipated doubling time of less than 6 months.
5. Males and females 18 years of age and older.
6. Laboratory parameters as specified below:
   - Hematologic: Hemoglobin ≥10 g/dL (may be post-transfusion); platelet count ≥50 × 10^3/mm^3.
   - Hepatic: T. Bili <2 × ULN, and ALT and AST <2 × ULN.
   - Renal: Creatinine ≤2 × ULN.
7. ECOG Performance Score ≤2.
8. Anticipated survival of at least 3 months.
9. For men and women of child-producing potential, use of effective contraceptive methods during the study and for one month following treatment.
10. Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agreement to abide by the study restrictions and return for the required assessments.

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Exclusion criteria:

1. Pregnant or nursing women.
2. Class III or IV cardiac disease defined by the New York Heart Association Functional Classification (Protocol Appendix B) and/or left ventricular ejection fraction <40%.
3. Subjects with a history of prior radiation that potentially included the heart in the field (e.g., mantle).
4. History of myocardial infarction or active ischemic heart disease within 6 months of study entry.
5. History of arrhythmia (including atrial fibrillation, multifocal premature ventriclular contractions, ventricular bigeminy or trigeminy, ventricular tachycardia) or a requirement for antiarrhythmics (including digoxin).
6. Baseline QTc ≥450 msec for men and ≥470 msec for women in the absence of correctable electrolyte imbalance.
7. Poorly controlled angina.
8. Congenital long QT syndrome or first degree relative with unexplained sudden death under 40 years of age.
9. Presence of left bundle branch block.
10. Treatment with chemotherapy, monoclonal antibody, or radiotherapy within 28 days prior to entering the study.
11. Severe or debilitating pulmonary disease (dyspnea at rest, significant shortness of breath, chronic obstructive pulmonary disease [COPD]).
12. Participation in any investigational drug study within 28 days prior to CNF1010 administration. (Subject has recovered from all acute effects of previously administered investigational agents).
13. Presence of active malignancy with the exception of basal cell carcinoma.
14. Active symptomatic fungal, bacterial and/or viral infection including active HIV or viral (A, B, or C) hepatitis.
15. Known allergy to soy.
16. Requirement for concomitant therapy with drugs that alter metabolism by cytochrome P450 3A4 except low dose warfarin for implanted device patency.
17. Requirement for concomitant therapy with drugs that prolong or may prolong QTc interval.
18. Any illness or condition that in the opinion of the Investigator may affect safety of treatment or evaluation of any of the study endpoints.

Study Treatment, Dose, Mode of Administration, Lot Number(s):

CNF1010 was administered by intravenous infusion over a 1-hour period.

Doses administered (dependent on cohort assignment) were 50 mg/m^2, 100 mg/m^2, 150 mg/m^2, and 200 mg/m^2.

Lot numbers of CNF1010 used during the study were [redacted].

Duration of Treatment and Follow-Up:

Treatment period: Subjects received CNF1010 on Days 1, 4, 8, 11, 15, and 18 of each cycle. Treatment was repeated every 28 days in the absence of disease progression or unacceptable toxicity.

Follow-up period: Subjects were monitored for adverse events (AEs) for 30 days after the last dose of study treatment or until resolution of AEs, whichever was longer.

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Criteria for Evaluation:

Safety: Safety evaluation included physical examinations, vital sign measurements, weight, ECOG Performance Status, concomitant medication and procedures, AEs, serious adverse events (SAEs), hematology, serum chemistry, urinalysis, 12-lead electrocardiogram (ECG). The Safety population (all enrolled subjects who received any part of an infusion of CNF1010) was used for the analysis of safety endpoints.

Efficacy: Clinical and hematological response was determined by the Investigator using the Revised National Cancer Institute–Sponsored Working Group Guidelines, listed in the Protocol (Section 5.6.1).

Pharmacokinetics: The plasma PK profiles of 17-(allylamino)-17-demethoxygeldanamycin (17-AAG) and 17-(amino)-17-demethoxygeldanamycin (17-AG) were determined in all subjects entered in the study. PK parameters for 17-AAG and 17-AG included area under the serum concentration time curve extrapolated to infinity ($AUC_{0\text{-}inf}$), terminal-phase half-life ($t_{1/2}$), total body clearance (CL), time to achieve maximum concentration (t_{max}), volume of distribution (Vd), and maximum concentration (C_{max}). The PK population (all enrolled subjects who received any part of an infusion of CNF1010 and who had at least 3 measurable plasma concentrations of 17-AAG on Day 1 of Cycle 1) was used for the analysis of PK endpoints.

Pharmacodynamics: The PD endpoints for the study were measurements of ZAP-70, PARP (poly[ADP-ribose]polymerase [autoantibody]), and Hsp70 levels using western blot. However, due to technical variability, including variability in sample handling, and lack of assay reproducibility, the PD assays were deemed non-evaluable and results invalid. Therefore, no PD results are reported.

Statistical Methods:

Descriptive statistics for continuous endpoints included the N, mean, standard deviation, median, minimum, and maximum. For categorical endpoints, descriptive statistics included the number and percentage of subjects with data in each category.

Subject Disposition: The number and percentage of subjects who enrolled, received study drug, completed the study, or discontinued from the study for any reason was summarized by dose cohort. The number and percentage of subjects in each analysis population was also summarized by dose cohort. Additionally, the number of subjects in each dose cohort was summarized by study site. The All Enrolled population was used for the subject disposition summary.

Extent of exposure: The Safety population was used for the extent of exposure summary. The cumulative number of doses received was summarized by dose cohort. The total dose of CNF1010 was summarized by dose cohort. This summary included the number of treatment cycles, planned dose, actual dose received, and the ratio of actual to planned dose by dose cohort.

Safety: The incidence of AEs was summarized by system organ class (SOC) and preferred term within an SOC, as well as by severity and relationship to study drug for each dose cohort in the Safety population. Hematology, clinical chemistry parameters, and vital signs from baseline to the end of the study were summarized by change from baseline to minimum, maximum, and last post-baseline values and percent change from baseline to minimum, maximum, and last post-baseline values by dose cohort.

Pharmacokinetics: PK parameters of both 17-AAG and 17-AG were calculated using non-compartmental methods. PK parameters were summarized by each dose level on Day 1 of each treatment cycle by means of descriptive statistics. For t_{max} only the median was provided.

Efficacy: Best overall response was summarized by dose cohort. For the 3 subjects who dose-escalated, the dose cohort the subject was assigned to for his or her final intravenous infusion of CNF1010 was used to summarize best overall response.

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Results:

Of the 10 subjects in the All Enrolled population, 1 subject (10%) completed less than one 28-day treatment cycle. All subjects discontinued from the study: 8 (80%) due to disease progression and 2 (20%) due to an AE**.**

Demographics and baseline disease characteristics:

- The majority of the subjects were White (8 of 10; 80%) with a mean age of 66.8 years (minimum 56 years, maximum 75 years).
- Seven subjects (70%) had ECOG Performance Status of 1, 2 subjects (20%) had ECOG Performance Status of 0, and 1 subject (10%) had ECOG Performance Status of 2.
- All subjects had received prior chemotherapy or radiation. Best response to prior chemotherapy or radiation was as follows: complete response, 8 subjects (80%); partial response, 1 subject (10%); stable disease, 1 subject (10%); and progressive disease, 0 subjects (0%).
- Nine subjects (90%) had Cardiac Status of I at baseline, and 1 subject (10%) had Cardiac Status of II.

Extent of exposure:

- The Safety population completed a median of 1 treatment cycle (minimum 1 cycle, maximum 6 cycles). The median CNF1010 doses received at each dose level were as follows: 50 mg/m^2, 6 doses; 100 mg/m^2, 9.5 doses; 150 mg/m^2, 5.5 doses; and 200 mg/m^2, 18 doses.
- Three subjects had their dose escalated during the study and no subjects had a dose reduction.

Safety:

- No DLTs were experienced by subjects.
- 9 of 10 subjects (90%) in the Safety population experienced at least 1 AE.
- 4 of 10 subjects (40%) in the Safety population experienced at least 1 NCI Common Terminology Criteria for Adverse Events (CTCAE) (Version 3) Grade 3 and/or Grade 4 AE.
- 7 of 10 subjects (70%) in the Safety population experienced at least 1 treatment-related AE.
- 3 of 10 subjects (30%) experienced at least 1 Grade 3 treatment-related AE, and no subject experienced a Grade 4 treatment-related AE.
- 2 of 10 patients withdrew from the study due to the adverse events of elevated GGT, nausea, and fatigue.
- The most common (incidence ≥20%) treatment-related AEs were: nausea and diarrhea (30% each) and fatigue, edema, bradycardia, and dizziness (20% each).
- Grade 3 treatment-related AEs were diarrhea, bilirubin conjugated increased, GGT increased, and platelet count decreased.
- Hemoglobin and platelets were generally decreased in all dose groups, but the decreases did not appear to be dose dependent.

Pharmacokinetics:

- The pharmacokinetics of 17-AAG and 17-AG at the dose levels tested were nearly linear, as judged by the dose-proportional increases in C_{max} and $AUC_{0\text{-}inf}$.
- Median clearance of 17-AAG ranged from 27.75 to 32.50 $L/hr/m^2$ and median terminal half-life ranged from 3.26 to 3.78 hours.

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Conclusion(s):

- The MTD of CNF1010 has not been established in a CLL subject population.
- Liver function abnormalities, thrombocytopenia, and anemia are possibly associated with CNF1010 administration.
- The most common treatment-related adverse events were nausea and diarrhea (30% each).
- The safety profile of CNF1010 in CLL is similar to that observed for CNF1010 in solid tumor patients.
- As expected, maximum concentration of 17-AAG occurred at the end of the one hour infusion. Plasma exposure of the metabolite 17-AG showed greater variability than its parent, 17-AAG.
- Treatment with CNF1010 did not appear to cause a significant hematologic or clinical response, with the best response (per Revised NCI-WG Guidelines) being stable disease in 2 of 10 subjects (20%): Subject 1204 received CNF1010 at 100 mg/m^2 for the duration of the study and Subject 1302 began CNF1010 at 100 mg/m^2 and escalated to 150 mg/m^2.
- The safety profile of CNF1010 in CLL appears similar to that observed for CNF1010 in advanced solid tumor patients. At this time, the CNF1010 clinical program is no longer being pursued by Biogen Idec due to 1) the toxicity profile of the drug observed in the parallel Phase 1 study of CNF1010 in solid tumors (CNF101-ST-04002) where significant hepatotoxicity was observed, and 2) the ongoing development of second-generation Hsp90 inhibitor molecules in this and other indications.

Publication(s) Based on the Study:
None.

Date of Report: 02 June 2008